

CBER CMC BLA Review Memorandum

BLA STN 125700/0

**Nadofaragene firadenovec
ADSTILADRIN**

Bradley Dworak, Ph.D., Reviewer, CBER/OCBQ/DMPQ

Table of Contents

| | | |
|-------|---|------|
| I. | BLA STN NUMBER | iv |
| II. | APPLICANT NAME AND LICENSE NUMBER | iv |
| III. | PRODUCT NAME/PRODUCT TYPE | iv |
| IV. | GENERAL DESCRIPTION OF THE FINAL PRODUCT | iv |
| V. | MAJOR MILESTONES | iv |
| VI. | CMC/QUALITY REVIEW TEAM | v |
| VII. | SUBMISSION(S) REVIEWED | v |
| VIII. | Referenced REGULATORY SUBMISSIONS | v |
| IX. | REVIEWER SUMMARY AND RECOMMENDATION | vi |
| | RECOMMENDATION - Approval | vi |
| X. | SIGNATURE BLOCK | viii |
| XI. | 3.2.S DRUG SUBSTANCE | 9 |
| | 3.2.S.2 Manufacture | 9 |
| | 3.2.S.2.1 Manufacturer(s) | 9 |
| | 3.2.S.2.2 Description of Manufacturing Process | 11 |
| | <input type="checkbox"/> Batch Numbering, Pooling and Scale Definition | 11 |
| | <input type="checkbox"/> Storage and Shipping | 11 |
| | 3.2.S.2.3 Control of Materials | 13 |
| | <input type="checkbox"/> Control of raw materials not of biological origin | 13 |
| | 3.2.S.2.4 Controls of Critical Steps and Intermediates | 14 |
| | 3.2.S.2.5 Process Validation and/or Evaluation | 15 |
| | <input type="checkbox"/> Review Scope | 15 |
| | <input type="checkbox"/> Description | 15 |
| | <input type="checkbox"/> Manufacturing Dates for (b) (4) PPQ lots | 15 |
| | <input type="checkbox"/> List of Critical Equipment Utilized | 16 |
| | <input type="checkbox"/> Acceptance criteria | 16 |
| | <input type="checkbox"/> Results and Evaluation | 16 |
| | <input type="checkbox"/> Deviations | 16 |
| | 3.2.S.2.6 Manufacturing Process Development | 17 |
| | 3.2.S.4 Control of Drug Substance | 17 |
| | 3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s) | 17 |
| | 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures | 18 |
| | 3.2.S.4.4 Batch Analyses | 18 |
| | 3.2.S.5 Reference Standards or Materials | 19 |
| | 3.2.S.6 Container Closure System | 19 |
| | 3.2.S.7 Stability | 20 |
| | 3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data | 20 |
| | 3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment | 20 |
| XII. | 3.2.P DRUG PRODUCT | 20 |
| | 3.2.P.1 Description and Composition of the Drug Product | 20 |
| | 3.2.P.2.2 Drug Product | 21 |
| | <input type="checkbox"/> 3.2.P.2.2.1 Formulation Development | 21 |
| | <input type="checkbox"/> 3.2.P.2.2.2 Overages | 21 |
| | 3.2.P.2.4 Container Closure System | 21 |
| | <input type="checkbox"/> Primary packaging | 21 |
| | <input type="checkbox"/> Validation of Vial Integrity | 22 |
| | <input type="checkbox"/> Validation of (b) (4) method | 24 |
| | <input type="checkbox"/> Shipping Validation | 25 |
| | <input type="checkbox"/> QC sample preparation | 28 |
| | 3.2.P.2.5 Microbiological Attributes | 29 |
| | 3.2.P.3 Manufacture | 30 |
| | 3.2.P.3.1 Manufacturer(s) | 30 |
| | 3.2.P.3.2 Batch Formula | 31 |

| | |
|--|----|
| 3.2.P.3.3 Description of Manufacturing Process..... | 31 |
| 3.2.P.3.4 Controls of Critical Steps and Intermediates | 33 |
| <input type="checkbox"/> Strategies to control and mitigation of cross-contamination | 33 |
| <input type="checkbox"/> Critical process parameters (CPPs) and in-process controls (IPCs) | 34 |
| 3.2.P.3.5 Process Validation and/or Evaluation..... | 35 |
| <input type="checkbox"/> PPQ lot information | 36 |
| <input type="checkbox"/> Hold Times | 36 |
| <input type="checkbox"/> Preparation of Syn3NODA batches | 37 |
| <input type="checkbox"/> (b) (4) | 38 |
| <input type="checkbox"/> (b) (4) | 38 |
| <input type="checkbox"/> (b) (4) | 39 |
| <input type="checkbox"/> Visual inspection results..... | 40 |
| <input type="checkbox"/> Release specifications and results..... | 49 |
| <input type="checkbox"/> Cleaning validation | 49 |
| <input type="checkbox"/> Aseptic Filling Process Validation (Media Fills) | 49 |
| <input type="checkbox"/> Sterile Filter Validation | 54 |
| 3.2.P.4 Control of Excipients..... | 58 |
| 3.2.P.4.1 Specifications | 58 |
| 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures | 59 |
| 3.2.P.4.4 Justification of Specifications..... | 60 |
| 3.2.P.4.5 Excipients of Human or Animal Origin..... | 60 |
| 3.2.P.4.6 Novel Excipient..... | 60 |
| 3.2.P.5 Control of Drug Product..... | 60 |
| 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)..... | 60 |
| 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures | 60 |
| 3.2.P.5.4 Batch Analyses..... | 60 |
| 3.2.P.5.5 Characterization of Impurities..... | 61 |
| 3.2.P.6 Reference Standards or Materials | 62 |
| 3.2.P.7 Container Closure System..... | 62 |
| 3.2.P.8 Stability | 62 |
| 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data..... | 62 |
| <input type="checkbox"/> Description | 62 |
| <input type="checkbox"/> Results | 63 |
| 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment..... | 63 |
| XIII. 3.2.A APPENDICES..... | 63 |
| 3.2.A.1 Facilities and Equipment..... | 63 |
| EQUIPMENT RELATED | 64 |
| <input type="checkbox"/> (b) (4) Equipment List | 64 |
| <input type="checkbox"/> (b) (4) Equipment List | 65 |
| (b) (4) | 66 |
| (b) (4) | 66 |
| (b) (4) | 67 |
| (b) (4) | 67 |
| (b) (4) | 68 |
| (b) (4) | 74 |
| (b) (4) | 77 |
| (b) (4) | 77 |
| (b) (4) | 77 |
| (b) (4) | 79 |
| (b) (4) | 80 |
| (b) (4) | 82 |
| (b) (4) | 82 |
| Qualifications..... | 83 |
| <input type="checkbox"/> (b) (4) | 83 |

| | |
|---|-----|
| FACILITY RELATED | 85 |
| <input type="checkbox"/> Utilities | 85 |
| <input type="checkbox"/> HVAC | 87 |
| <input type="checkbox"/> Environmental Monitoring (b) (4) | 89 |
| <input type="checkbox"/> Facility Layout Diagrams | 96 |
| <input type="checkbox"/> Dedicated GMP Manufacturing Areas | 97 |
| <input type="checkbox"/> Validation Master Plan 2021 (b) (4) | 97 |
| CLEANING / PREVENTION OF CROSS CONTAMINATION | 100 |
| <input type="checkbox"/> Efficacy Testing | 100 |
| 3.2.A.2 Adventitious Agents Safety Evaluation | 104 |
| 3.2.A.3 Novel Excipients | 104 |
| XIV. 3.2.R Regional Information (USA) | 104 |
| Executed Batch Records | 104 |
| Method Validation Package | 104 |
| Combination Products | 105 |
| Comparability Protocols | 105 |
| XV. Environmental Assessment or Claim of Categorical Exclusion | 105 |
| XVI. Reference Product Designation Request | 105 |
| XVII. Labeling Review | 105 |
| Full Prescribing Information (PI) | 105 |
| Carton and Container Label | 105 |
| XVIII. Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints | 105 |
| XIX. Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5 | 106 |

I. BLA STN NUMBER

STN 125700/0

II. APPLICANT NAME AND LICENSE NUMBER

Ferring Pharmaceuticals A/S, License # 2222

III. PRODUCT NAME/PRODUCT TYPE

Non-proprietary/Proper/USAN: Nadofaragene firadenovec

Proprietary Name: ADSTILADRIN

IV. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: Viral Vector
- b. Dosage form: Suspension
- c. Strength/Potency: 3×10^{11} vp/mL
- d. Route of administration: Intravesical instillation
- e. Indication(s): High-grade, Bacillus Calmette-Guerin (BCG) unresponsive non-muscle invasive bladder cancer

V. MAJOR MILESTONES

- BLA 1st resubmission received on April 22, 2022
- Incomplete response sent on May 10, 2022
- BLA 2nd resubmission received on July 14, 2022
- Mid-cycle meeting on September 29, 2022

- PLI inspection conducted on September 19-23, 26-27, 2022
- PDUFA Date: December 27, 2022

VI. CMC/QUALITY REVIEW TEAM

| Reviewer/Affiliation | Section/Subject Matter |
|--|--|
| Bradley Dworak, Ph.D., CSO OCBQ/DMPQ/MBR1 | 3.2.S Drug Substance 3.2.P Drug Product 3.2.A.1 Facilities |

VII. SUBMISSION(S) REVIEWED

A list of amendments are as follows:

| Date Received | STN | Comments / Status |
|--------------------|-------------|---|
| June 30, 2022 | 125700/0/54 | BLA resubmission |
| July 21, 2022 | 125700/0/55 | Production schedule, Response to IR dated July 15, 2022 |
| July 22, 2022 | 125700/0/56 | (b) (4) inspection status, Responses to IRs dated July 20, 2022 |
| September 1, 2022 | 125700/0/59 | Shipping and CCIT, responses to IRs dated August 19, 2022 |
| September 7, 2022 | 125700/0/62 | DS storage, hold times, PQ of filling machine, shipping validation CCIT, responses to IRs dated August 24, 2022 |
| September 9, 2022 | 125700/0/63 | PLI preparation questions, Responses to IRs dated August 19, 2022 |
| September 16, 2022 | 125700/0/66 | EM data during PQ, response to IR dated September 9, 2022 |
| November 14, 2022 | 125700/0/77 | Visual inspection and AQL sample sizes to IRs dated November 2, 2022 |
| November 15, 2022 | 125700/0/78 | Related to performance qualification to labelling machine to IRs dated November 7, 2022 |
| December 1, 2022 | 125700/87 | Response to labeling qualification and AQL sample size |
| December 2, 2022 | 125700/91 | Response including an update to the manufacturing process and including labeling |

VIII. Referenced REGULATORY SUBMISSIONS

N/A

IX. REVIEWER SUMMARY AND RECOMMENDATION

Executive Summary

This BLA review covered drug substance manufacturing including process, storage, control of materials, control of critical steps, process validation, major equipment qualification, batch analysis, container closure system, and stability. This review also covered drug product manufacturing including container closure system, validation of vial integrity including the (b) (4) method, primary packaging, shipping validation, QC sample preparation, control of critical steps, critical process parameters and in-process controls, process validation including hold times, visual inspection, release specifications, cleaning validation, aseptic filling process validation, and sterile filter validation. Facility information was reviewed including major equipment qualifications including the primary labeler, filling machine qualification, laminar flow hoods and units, vial washing machine, depyrogenation tunnel, utensil washer, bioreactors, and freezers. Utilities were reviewed including the HVAC system. Environmental monitoring qualification was reviewed, including facility layout diagrams and flow paths, facility cleaning regimens, and preventing of cross contamination including cleaning efficacy studies.

A pre-inspection 704a Records Request was conducted in advance of the reinspection of FinVector was conducted to provide documentation including a list of deviations and non-conformances, OOSs, listing of major processing equipment and qualification details, lot and media fill history, personnel qualifications, utility trend reports, and organizational charts. The firm provided the information in eCTD sequence 0063. The review of the Records Request is documented in a separate memo uploaded to CBER Connect under STN 125700/0.

As part of the BLA CR response review, FinVector was re-inspected from September 19-27, 2022. At the end of the inspection, a Form 483 was issued with 6 observations related to the quality control practice of personnel verifying their own work, inadequate maintenance intervals of the (b) (4), planned departures from the handling of deviations, inadequate revalidation frequency of (b) (4) effectiveness, visible (b) (4), and missing performance qualification reports of the vial and (b) (4). The firm responded to the observations and the corrective actions were reviewed and found to be adequate. As part of the 2022 inspection and this review, the firm's updated responses addressing the observations from the pre-license inspection of FinVector from January 20-28, 2020, were found to be adequate.

RECOMMENDATION - Approval

Recommend approval of this resubmission pursuant to the amendments and agreement with the firm not to commercialize (b) (4) PPQ lots (see details below and

section 3.2.S.4.4), and not to release any lots deemed for commercialization until a satisfactory additional AQL sampling has been met according to updated procedures and increased sample population (see visual inspection results in section 3.2.P.3.5).

The first (b) (4) PPQ batches (b) (4) contain (b) (4) utilizing (b) (4), a major concern identified during the 2020 inspection. This was discussed with OTAT and DMPQ management on September 14, 2022. OTAT confirmed that the PPQ lots can be used to demonstrate process consistency. However, an agreement was made between OTAT and Ferring Pharmaceuticals not to distribute these PPQ lots for commercial use due to the inadequacy of quality control and safety risk. (b) (4) is the only viable PPQ lot for commercialization and must pass the updated AQL sampling procedure as mentioned above before release.

(b) (4) conducts sterility release testing for this product, and the site is included in the inspection waiver for this submission. To support the waiver, an untranslated inspection report was provided on November 30, 2022 via the CBER MRA contact.

(b) (4) conducted a GMP inspection of (b) (4). Among the observations included violations for unrestricted access to laboratory areas. The existence of new laboratory facilities was also noted. According to the report, on November 10, 2022, (b) (4) submitted corrective and preventive measures in response to the observations. A certificate of GMP compliance was issued by (b) (4) on November 23, 2022 according to the online (b) (4) database.

The observations and insights regarding the new laboratory spaces and unrestricted access are relevant to the review of the safety and risk profile of the product. Recommend adding (b) (4) to the OBPO inspection schedule with the inspectional consideration (see below) to ensure adequate facility controls are in place, and any corrective and preventive measures to address this issue have been resolved.

All other review issues have been adequately addressed in the amendments as responses to Information Requests.

Inspectional Consideration

Review compliance and adequate facility controls of any new and existing QC laboratory spaces at (b) (4). This would include appropriate personnel access restrictions are functioning appropriately, and that adequate boundaries are in place to separate office, manufacturing, and laboratory spaces. Review any associated CAPAs regarding compliance of access controls and boundaries of these spaces as mentioned above. CBER understands that the recommendation may or may not be taken (based

on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

X. SIGNATURE BLOCK

| Reviewer/Title/Affiliation | Concurrence | Signature and Date |
|--|--------------------|---------------------------|
| Bradley Dworak, Ph.D., CSO OCBQ/DMPQ/MBR1 | Concur | |
| Lori Peters, Branch Chief OCBQ/DMPQ | Concur | |
| Carolyn Renshaw, Division Director OCBQ/DMPQ | Concur | |

Review of CTD
Table of Contents

Module 3

XI. 3.2.S DRUG SUBSTANCE
3.2.S.2 Manufacture
3.2.S.2.1 Manufacturer(s)

All sites involved in the manufacture and testing of nadofaragene firadenovec drug substance, and their contracted responsibilities are listed in Table 1 below.

(b) (4)

10 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

Overall Reviewer's Assessment of Section 3.2.S.7

Reviewer Comment

This section is deferred to OTAT.

XII. 3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

ADSTILADRIN is indicated for the treatment of unresponsive non-muscle invasive bladder cancer. It consists of a sterile, clear to opalescent ready-to-use (RTU) suspension, supplied in a 20-mL extractable volume in four single-dose 30-mL vials for a single administration via intravesical instillation. The excipient Syn3 is included in the formulation and is a polyamide surfactant that facilitates cell transduction in the urothelium by the adenoviral vector.

ADSTILADRIN is stored at manufacturing and distribution sites below -60°C and shipped frozen below -60°C. It may be stored in pharmacy frozen below -20°C.

The composition of the drug product is as follows:

| Component | Reference to Quality Standard | Function | Target Concentration (per mL) |
|-----------|-------------------------------|----------|-------------------------------|
|-----------|-------------------------------|----------|-------------------------------|

| | | | |
|---|----------|----------------------|-----------|
| Nadofaragene firadenovec | In House | Drug substance | (b) (4) |
| Sodium dihydrogen phosphate dihydrate | (b) (4) | Buffer agent | (b) (4) |
| Tromethamine | (b) (4) | Buffer agent | (b) (4) |
| Glycerol (b) (4) | (b) (4) | Stabilizer | (b) (4) |
| Sucrose | (b) (4) | Stabilizer | (b) (4) |
| Magnesium chloride hexahydrate | (b) (4) | Stabilizer | 0.34 mg |
| Syn3 [N-(3-cholamidopropyl)-N-(3-lactobionamidopropyl)]-cholamide | In House | Surfactant | (b) (4) |
| Hydroxypropyl-beta-cyclodextrin | (b) (4) | Solubilizer for Syn3 | (b) (4) |
| Citric acid monohydrate | (b) (4) | Buffer agent | 0.01 mg |
| Tri-Sodium citrate dihydrate | (b) (4) | Buffer agent | 0.04 mg |
| Polysorbate 80 | (b) (4) | Surfactant | (b) (4) |
| Water for Injection | (b) (4) | Solvent | q.s. 1 mL |

3.2.P.2.2 Drug Product

□ 3.2.P.2.2.1 Formulation Development

Reviewer Comment

For the Phase 1, 2, and 3 clinical trials, the DP was supplied in (b) (4) vials, but then combined with a diluent and mixed with reconstituted Syn3 at the hospital pharmacy. For commercial supply, the firm developed an RTU presentation that includes the Syn3 in the presentation. The strength and composition remained unchanged.

Review of this section is ultimately deferred to OTAT.

□ 3.2.P.2.2.2 Overages

Not applicable

3.2.P.2.4 Container Closure System

□ Primary packaging

There are three elements to the primary packaging:

- Clear Type (b) (4) glass (b) (4) vials (nominal volume 20 mL) (b) (4)

- (b) (4) stoppers containing on bromobutyl rubber (b) (4)
The inner face is sealed with a (b) (4) and the external non-contact face is (b) (4).
- (b) (4) aluminum crimps with flip-off seal (b) (4)

The primary vials are (b) (4) at FinVector Oy. The product stoppers are purchased (b) (4) at FKD. The stoppers are (b) (4)

The product crimps are supplied sterile (b) (4)

□ **Validation** (b) (4)

6 pages have been determined to be not releasable: (b)(4)

(b) (4)

○ (b) (4)

• (b) (4)

3.2.P.2.5 Microbiological Attributes

Reviewer Comment

The drug product is manufactured and filled sterile. The Type (b) (4) glass vials are sealed with (b) (4) stoppers and secured with tamper-evident aluminum crimps. Suitability of this container closure was demonstrated using a (b) (4) test. During the 2020 review (see section 3.2.P.7) and the 2020 inspection (see EIR

section titled *Container Closure and Integrity Testing*) it was evident that the assay was inadequately qualified.

In the 2022 re-submission, the firm re-validated their CCIT testing and updated the SOP for the testing. The validation and CCIT results were reviewed in their appropriate sections. Therefore, the container closure system appears to be suitable for this drug product.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

| Facility | Responsibilities | Inspection History |
|--|--|---|
| FinVector Oy Microkatu 1S 70210 Kuopio Finland FEI: 3010227150 | <ul style="list-style-type: none"> sterile filtration aseptic filling visual inspection labeling packaging storage | 9/2022 – CBER PLI - VAI 1/2020 – CBER PLI - OAI |
| (b) (4) | sterility release testing as backup | (b) (4) – OPQO surveillance - VAI (b) (4) – OBPO surveillance - VAI |
| (b) (4) | <ul style="list-style-type: none"> Sterility release testing Endotoxin testing bacterial endotoxin (b) (4) | (b) (4) GMP inspection (b) (4) GMP inspection (b) (4) GMP inspection – VAI (b) (4) – CDER GMP inspection – NAI |
| (b) (4) | <ul style="list-style-type: none"> Excipient release testing (b) (4) in-process testing | No inspection history |
| (b) (4) | Excipient release testing | (b) (4) GMP surveillance – VAI (b) (4) - OPQO surveillance – VAI |

| Facility | Responsibilities | Inspection History |
|----------|------------------------------------|--|
| (b) (4) | | |
| (b) (4) | | |
| (b) (4) | Excipient release testing | (b) (4) – CDER PAI – VAI (b) (4) – CDER For Cause – OAI |
| (b) (4) | Primary packaging (b) (4) stoppers | (b) (4) – OPQO – directed inspection – NAI (b) (4) – OPQO – surveillance cGMP - NAI |

3.2.P.3.2 Batch Formula

Refer to table in DP composition above.

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2

Reviewer Comment

The information provided appears to be acceptable.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

(b) (4)

The process is summarized in the following steps (see Section 3.2.P.3.3 for additional details not provided here):

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

The date of manufacture of ADSTILADRIN DP is defined as the date of filling.

Further detail on the manufacturing steps can be found in Section 3.2.P.3.3.

Overall Reviewer's Assessment of Section 3.2.P.3.3

Reviewer Comment

The firm has adequately described the manufacturing process for drug product. This appears to be acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The in-process controls (IPCs) were selected with input from the risk assessment of the drug product (DP) manufacturing process as described in 3.2.P.2.3.

□ Strategies to control and mitigation of cross-contamination

Refer to Contamination Prevention, Cleaning and Disinfectant Efficacy section of EIR

Reviewer Comment

The firm has various mitigation strategies at different stages of the manufacturing process in order to minimize risk to product safety including proper gowning, cleaning programs, cleaning agents, disinfection agents, (b) (4) for material and personnel transfer, including a dedicated (b) (4) suite for filling of drug product. The measures were evaluated during the 2022 re-inspection as well. Therefore, this overall strategy appears to be acceptable.

❑ **Critical process parameters (CPPs) and in-process controls (IPCs)**

Listings of the associated CPP and IPCs for each of the manufacturing steps are as follows:

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.4:

Reviewer Comment

The firm has implemented sufficient in-process controls at critical stages in the DP manufacturing process, including bioburden limits, hold times, and minimum total particulates. Therefore, this appears acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

4 pages have been determined to be not releasable: (b)(4)

(b) (4)

All data (under DMPQ purview) are within specifications for the lots produced.

□ **Visual inspection results**

All DP vials were 100% visually inspected according to predefined defect categories. (These categories were defined in response to Observation 7A from FDA Form 483 from the 2020 inspection, see below). After the 100% visual inspection, FinVector conducted an acceptance quality limit (AQL) test on (b) (4) vials to confirm the effectiveness of the visual inspection. The acceptance criteria for AQL testing was based on a criticality assessment of the different defect types combined with a standard AQL sampling plan.

• **Results**

The results of the visual inspection and AQL are below:

(b) (4)

| |
|-------------------------|
| Reviewer Comment |
|-------------------------|

8 pages have been determined to be not releasable: (b)(4)

Reviewer Comment

These AQL and visual inspection limits were reviewed and appear to be acceptable.

❑ **Release specifications and results**

All (b) (4) DP lots met specifications for Endotoxin and Sterility. The endotoxin limit is (b) (4) and all results were (b) (4). All lots exhibited No Growth for sterility.

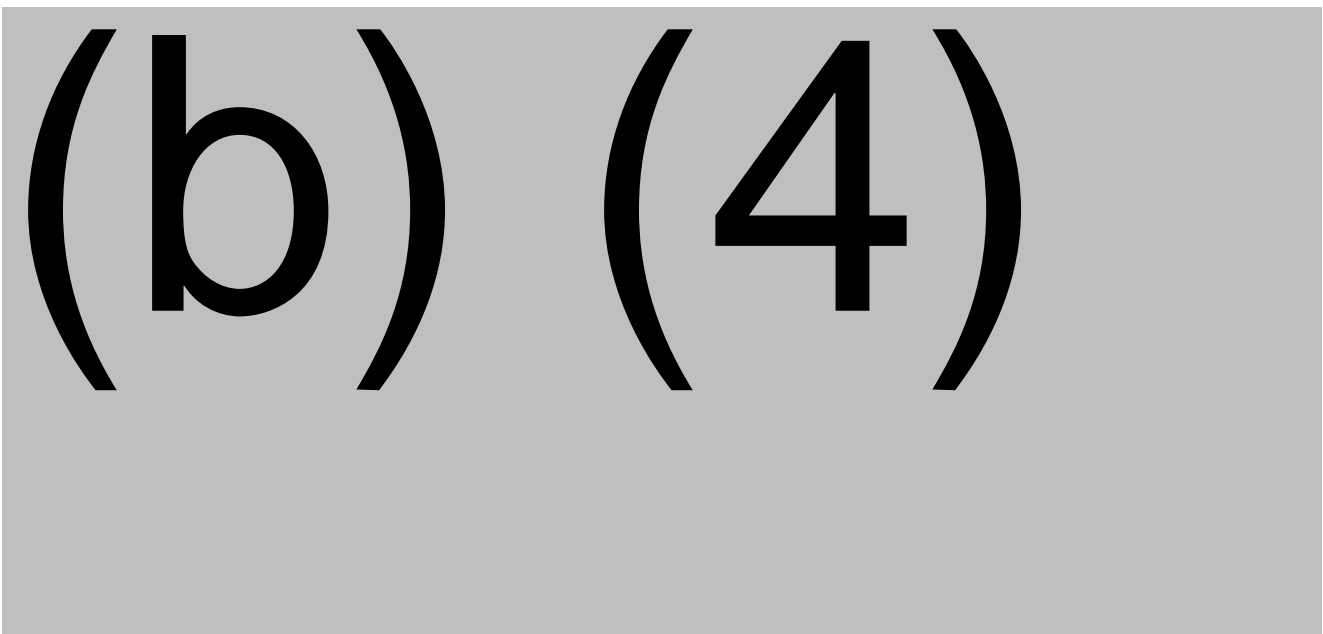


❑ **Cleaning validation**

All materials in direct product contact used for the manufacturing process of the DP are single use materials. Thus, no cleaning validation has been performed.

❑ **Aseptic Filling Process Validation (Media Fills)**

• **List of media fill runs**

(b) (4)



8 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.5

Reviewer Comment

(b) (4)

Therefore, this appears acceptable.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

Release specification for the active excipient Syn3 is below:

(b) (4)

(b) (4)

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Reviewer Comment

This section deferred to OTAT and/or DBSQC.

3.2.P.4.4 Justification of Specifications

Reviewer Comment

This section deferred to OTAT and/or DBSQC.

3.2.P.4.5 Excipients of Human or Animal Origin

Reviewer Comment

This section deferred to OTAT and/or DBSQC.

3.2.P.4.6 Novel Excipient

See novel excipient Syn3Noda in section 3.2.P.4.1

Overall Reviewer's Assessment of Section 3.2.P.4:

Deferred to OTAT and/or DBSQC.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Reviewer Comment

The specifications were reviewed and have not changed in this resubmission. The endotoxin spec of (b) (4) is deferred to the PO. The product is shipped sterile.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

These specifications under DMPQ purview appear to be acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Reviewer Comment

These procedures are deferred to OTAT and/or DBSQC.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

Deferred to OTAT and/or DBSQC.

3.2.P.5.4 Batch Analyses

A list of the PPQ batches are below:

(b) (4)

Reviewer Comment

(b) (4)

. Therefore, this appears acceptable.

3.2.P.5.5 Characterization of Impurities

No impurities identified.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

Deferred to OTAT.

3.2.P.6 Reference Standards or Materials

Refer to section 3.2.S.5 Reference Standards or Materials.

3.2.P.7 Container Closure System

Reviewer Comment

No changes have been made to the closure system in this resubmission.

Overall Reviewer's Assessment of Section 3.2.P.7:

Reviewer Comment

This is acceptable as there have been no changes to the original submission.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

☐ **Description**

The firm is proposing the following shelf-life and storage conditions are recommended for the drug product: (b) (4) months when stored below -60°C whereof up to 3 months at maximum -20 ± 5°C.

An overview of the batches used for stability studies is provided below:

(b) (4)

(b) (4)

(b) (4)

The stability program is as follows:

| Test/Time (months) | 0 | 3 | 6 | 9 | 12 | 18 |
|--|---|---|---|---|----|----|
| Sterility | x | - | - | - | - | - |
| Container closure integrity ^b | x | - | - | - | - | - |

(b) (4)

[b] Container closure integrity tested at T0 and end of stability for PPQ batches manufactured in 2020.

□ Results

All batches indicated Sterile at T=0 or T=6 months.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Review of this section is deferred to OTAT.

Overall Reviewer's Assessment of Section 3.2.P.8:

Reviewer Comment

The stability program is up to (b) (4) months, and includes (b) (4) batches currently on stability all indicating passing results for Sterility and CCIT at T=0. Therefore, this appears to be acceptable.

XIII. 3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

EQUIPMENT RELATED

□ (b) (4) Equipment List

A list of the main equipment used in the manufacture of (b) (4) DP in (b) (4) is as follows:

(b) (4)

(b) (4)

□ (b) (4) **Equipment List**

A list of the main equipment used in the manufacture of (b) (4) is as follows:

(b) (4)

34 pages have been determined to be not releasable: (b)(4)

CLEANING / PREVENTION OF CROSS CONTAMINATION


The cleaning regimen of the facilities was covered in the 2020 review and inspection. At the time, (b) (4) was considered a multi-product facility but at the time of the re-submission (b) (4) became product dedicated. Therefore, the risk of cross-contamination has been significantly reduced. Facility cleaning was reassessed in the 2022 Pre-License Inspection (PLI) inspection and found to be acceptable. In addition, (b) (4) was covered in the 2022 re-inspection (see 2022 EIR for further review).

□ Efficacy Testing


The firm conducted an efficacy test for new disinfection agents in accordance with QC-SUM-20-002v2.

• Disinfectants

Tested disinfectants in the study were (b) (4)



• (b) (4)



Additional test parameters can be found in the cleaning study report. An overview of the cleaning efficacy program can be seen from the figure below:



3 pages have been determined to be not releasable: (b)(4)

Reviewer Comment

All sections appear to be acceptable.

3.2.A.2 Adventitious Agents Safety Evaluation

(b) (4)

**Reviewer Comment**

This evaluation is deferred to the Product Office.

- **Viral Clearance Studies**

Not applicable

Overall Reviewer's Assessment of Section 3.2.A.2**Reviewer Comment**

The review of these materials is deferred to OTAT.

3.2.A.3 Novel Excipients**Reviewer Comment**

The review of these materials is deferred to OTAT.

XIV. 3.2.R Regional Information (USA)**Executed Batch Records****Reviewer Comment**

Executed batch records for the PPQ lots were provided in the submission.

Method Validation Package**Reviewer Comment**

The review of these materials is deferred to OTAT.

Combination Products

Not applicable.

Overall Reviewer's Assessment of Combination Products Section

Not applicable

Comparability Protocols

Not applicable.

Other eCTD Modules

Module 1

XV. Environmental Assessment or Claim of Categorical Exclusion**Reviewer Comment**

The review of these materials is deferred to OTAT.

XVI. Reference Product Designation Request**Reviewer Comment**

The review of these materials is deferred to OTAT.

XVII. Labeling Review**Full Prescribing Information (PI)****Reviewer Comment**

The review of these materials is deferred to OTAT.

Carton and Container Label**Reviewer Comment**

The review of these materials is deferred to OTAT.

Modules 4 and 5

XVIII. Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints**Reviewer Comment**

The review of these materials is deferred to OTAT.

XIX. Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5

Reviewer Comment

The review of these materials is deferred to OTAT.