

**CBER DMPQ CMC/Facility BLA Review Memorandum**

**BLA STN 125761/0**

**Anthrax Vaccine Adsorbed, Adjuvanted (CYFENDUS)**

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Kathleen Jones, Biologist, OCBQ/DMPQ/MRB1**

1. **BLA#:** STN 125761/0

2. **APPLICANT:** Emergent Product Development Gaithersburg, Inc, U.S. License Number 2089

3. **PRODUCT NAME/PRODUCT TYPE**

Anthrax Vaccine Adsorbed, Adjuvanted (CYFENDUS)

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

a. **Pharmacological category**

Vaccine

b. **Dosage form**

Suspension for injection

c. **Strength/Potency**

0.5 mL

d. **Route of administration**

Intramuscular

e. **Indication(s)**

Post-exposure prophylaxis (PEP) of disease following suspected or confirmed exposure to Bacillus anthracis in persons 18 - 65 years of age when administered in conjunction with recommended antibacterial regimen

5. **MAJOR MILESTONES**

Received, Part 2 of 2 (Rolling submission): April 20, 2022

Filing Action: June 19, 2022

PDUFA Action Due Date: July 20, 2023

6. **DMPQ CMC/FACILITY REVIEW TEAM**

| Reviewer/Affiliation                                 | Section/Subject Matter   |
|--|--|
| Kathleen Jones, Biologist,<br>OCBQ/DMPQ/MRB1         | <ul style="list-style-type: none"><li>3.2.S Drug Substance CPG 7909 (b) (4)</li></ul>  |
| Jared Greenleaf, CSO,<br>OCBQ/DMPQ/MRB1              | <ul style="list-style-type: none"><li>3.2.S Drug Substance AVA DS [EBOL]</li><li>3.2.A.1 Facilities and Equipment [EBOL]</li></ul> |
| Neetu Dahiya, Biological Reviewer,<br>OCBQ/DMPQ/MRB1 | <ul style="list-style-type: none"><li>3.2.P Drug Product AV7909 (b) (4)</li><li>3.2.A.1 Facilities and Equipment (b) (4)</li></ul> |

**7. SUBMISSION(S) REVIEWED**

| Date Received     | Submission      | Comments/ Status   |
|-------------------|-----------------|--|
| December 14, 2021 | STN 125761/0    | Part 1 of the rolling submission / Reviewed  |
| April 20, 2022    | STN 125761/0.3  | Part 2 of the rolling submission / Reviewed  |
| July 26, 2022     | STN 125761/0.8  | Response to an information request (IR) regarding leveraging from studies performed under BLA STN 103821 (BioThrax) / Reviewed |
| September 9, 2022 | STN 125761/0.16 | Response to an IR pertaining to the bioburden test method / Reviewed   |
| March 20, 2023    | STN 125761/0.37 | Removal of Emergent BioSolutions Inc. (b) (4) / Reviewed   |
| April 19, 2023    | STN 125761/0.45 | Minor BLA updates and updated stability data / Reviewed  |
| June 26, 2023     | STN 125761/0.55 | CPG 7909 sterile filter validation / Reviewed  |

**8. REVIEWER SUMMARY AND RECOMMENDATION****A. EXECUTIVE SUMMARY**

The Center for Biologics Evaluation and Research received a two-portion rolling Biologics License Application (BLA) for CYFENDUS under STN 125761/0 from Emergent Product Development Gaithersburg, Inc. (referred to as Emergent or the applicant) on 14 December 2022. The final portion of the rolling BLA was received on 20 April 2023.

CYFENDUS drug product (DP), also referred to as AV7909, is filled into a multidose vial. A single dose consists of (b) (4) of Anthrax Vaccine Adsorbed (AVA) drug substance (DS) and (b) (4) CPG 7909 adjuvant. The (b) (4) is made from cell-free filtrates of an avirulent nonencapsulated strain of *Bacillus anthracis* (b) (4)

(b) (4) containing formaldehyde and benzethonium chloride. The (b) (4), which is manufactured (b) (4), is used to formulate (b) (4) CYFENDUS and the previously licensed

BioThrax (Anthrax Vaccine Adsorbed, BLA STN 103821/5376). CPG 7909 adjuvant is a novel synthetic DNA molecule, 24 nucleotides in length with a phosphorothioate backbone. Additionally, CYFENDUS is (b) (4) as the previously licensed BioThrax.

CYFENDUS is administered as a post-exposure prophylaxis following suspected or confirmed exposure to *B. anthracis* in people 18 to 65 years of age. One 0.5 mL dose is injected into the deltoid muscle immediately, and another dose is administered two weeks later.

DMPQ waived inspections of the following facilities on 27 March 2023.

- Emergent BioDefense Operations Lansing LLC at 3500 N Martin Luther King Jr Blvd, Lansing, MI 48906 (FEI: 1873886) for DS and bulk drug product (BDP) manufacturing as well as drug product release testing
- (b) (4)

Based on the information submitted to BLA 125761/0 and in conjunction with the inspectional compliance history evaluations, the production process, facilities, equipment, and controls appear acceptable for the licensure of CYFENDUS™ and approval is recommended.

## B. RECOMMENDATION

### I. APPROVAL

Based on the information provided in this application and amendments, DMPQ recommends the approval of Anthrax Vaccine Adsorbed, Adjuvanted, which is manufactured at Emergent BioDefense Operations Lansing LLC at 3500 N Martin Luther King Jr Blvd, Lansing, MI 48906 and (b) (4) [REDACTED], with an inspectional recommendation below.

*Emergent BioDefense Operations Lansing LLC, (FEI: 1873886):*

- (b) (5) [REDACTED]

CBER understands the inspectional recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

### II. SIGNATURE BLOCK

| Reviewer/Title/Affiliation                           | Concurrence | Signature and Date |
|--|-------------|--------------------|
| Kathleen Jones, Biologist,<br>OCBQ/DMPQ/MRB1         | Concur      |                    |
| Jared Greenleaf, CSO,<br>OCBQ/DMPQ/MRB1              | Concur      |                    |
| Neetu Dahiya, Biological Reviewer,<br>OCBQ/DMPQ/MRB1 | Concur      |                    |
| Lori Peters, Branch Chief,<br>OCBQ/DMPQ/MRB1         | Concur      |                    |
| Carolyn Renshaw, Director,<br>OCBQ/DMPQ              | Concur      |                    |


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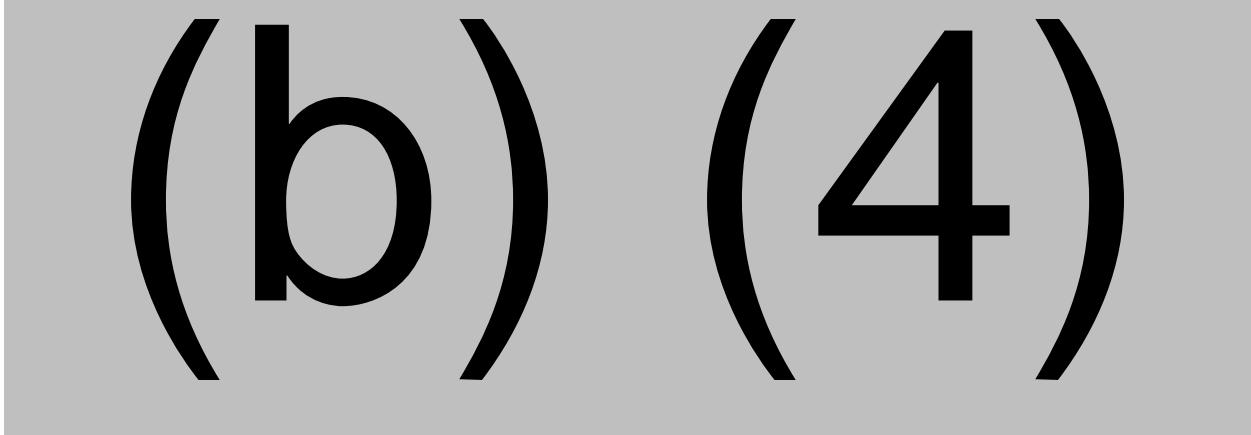
**Module 3**

**3.2.S DRUG SUBSTANCE [AVA DS]**


(b) (4)



**(b) (4)**



(b) (4)







(b) (4)

### 3.2.P DRUG PRODUCT [AV7909]

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

AV7909 drug product (DP) is a sterile, milky-white suspension supplied in a (b) (4) clear borosilicate multi-dose (b) (4) glass vial with a ready-to-sterilize rubber stopper for multi-puncture usage and a 20 mm flip-top aluminum seal. Each multi-dose vial is filled with approximately (b) (4) of AV7909 DP to ensure a sufficient volume to obtain 10 doses of 0.5 mL per vial. Each 0.5 mL dose of AV7909 DP contains (b) (4) of AVA DS and (b) (4) CPG 7909 adjuvant.

#### 3.2.P.2.5 Microbiological Attributes

AV7909 DP is a sterile product and increased sterility assurance is provided by 1) controlled aseptic manufacturing process validated with (b) (4) media fill batches, 2) addition of preservatives, formaldehyde and benzethonium chloride, to inhibit microbial growth, 3) integral container closure system, 4) sterility testing (b) (4), at release, and at expiry as part of the stability study, and 5) container closure integrity testing (CCIT) and (b) (4) testing at release and expiry as part of the stability study.

##### *Container closure integrity testing*

Container Closure integrity testing (CCIT) was performed using a (b) (4) test according to (b) (4) and test method (b) (4). The test samples and positive control (b) (4)

(b) (4)

(b) (4)

### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturer(s)

Table 1 in the submission (recreated below) lists the AV7909 manufacturing and testing facilities.

| Location  | Responsibility   |
|---|--|
| Emergent BioDefense Operations<br>Lansing LLC (EBOL)<br>3500 N. Martin Luther King Junior Blvd.<br>Lansing, MI 48906-9910, USA<br>FEI: 1873886<br>DUNS: 026489018 | <ul style="list-style-type: none"><li>• Manufacture of AV7909 bulk drug product prior to the filling step</li><li>• In-process control testing</li><li>• Inspection, packaging, and labeling of drug product</li><li>• Release testing of drug product</li></ul> |

| Location | Responsibility  |
|----------|---|
|          | <ul style="list-style-type: none"> <li>Disposition of drug product</li> <li>Stability testing of drug product (not including Container Closure Integrity Testing [CCIT], (b) (4) or Sterility)</li> </ul>   |
| (b) (4)  | <ul style="list-style-type: none"> <li>In-process control testing and release testing (sterility)</li> <li>Alternative site for Sterility testing of drug product (stability)</li> <li>Manufacture of drug product - filling step only</li> </ul> |
| (b) (4)  | <ul style="list-style-type: none"> <li>Stability testing of drug product (only CCIT and (b) (4))</li> <li>Alternative site for testing of Aluminum Content in drug product (release and stability)</li> </ul>                                     |

### 3.2.P.3.3 Description of Manufacturing Process

The AV7909 DP manufacturing process is comprised of (b) (4)

(b) (4)

- (b) (4)

### 3.2.P.3.4 Controls of Critical Steps and Intermediates

All AV7909 specifications are considered CQAs. Sterility (acceptance criteria: pass) according to (b) (4) is evaluated as an in-process control and as release test for AV7909 (b) (4) and AV7909 DP, respectively.

#### *Filter Integrity Testing – DP formulation and filling*

During manufacture of AV7909 DP, (b) (4) filters are used.

(b) (4)

Details of the (b) (4) is provided and reviewed under AVA DS.

#### *Visual inspection*

(b) (4) inspection is performed at the filling site, (b) (4) Final inspection is performed at EBOL where vials are inspected for the (b) (4)

(b) (4) are provided in Table 4 in Section 3.2.P.3.4 of the submission.

*Critical Process Parameters (CCPs)*

All process parameters for the AV7909 formulation and filtration stages were re-assessed for criticality using a failure mode and effects analysis (FMEA) process based on the data from PPQ studies and routine Strategic National Stockpile lot production. There were no additional CCPs identified for the formulation and filtration stages. The criticality of the filling process parameters was assessed by (b) (4) using their standard practices. Details of the CPPs for the filling process at (b) (4) and the justification for the range of the parameters is provided in Table 5 of Section 3.2.P.3.4 of the submission. Some CCPs at (b) (4) include:

- (b) (4)

**Reviewer's comment:** *The manufacture of sterile AV7909 DP is regulated by control of critical steps and intermediates. Sterility is performed as an (b) (4) control for AV7909 (b) (4) and a release test for AV7909 DP. (b) (4)*

*The filled DP is 100% visually inspected and an AQL inspection is performed. The information provided for control of critical steps and intermediates appears acceptable.*

**3.2.P.3.5 Process Validation and/or Evaluation**

(b) (4)



(b) (4)

### 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's comment:** The AV7909 DP specification and justification of specification with respect to microbial attributes are provided in Section 3.2.P.2.5

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

**Reviewer's comment:** Sterility is performed according to (b) (4) and the method validation is deferred to the DBSQC reviewer.

#### 3.2.P.5.4 Batch Analyses

(b) (4) PPQ lots (b) (4) (expanded processing times and filling at (b) (4) were manufactured at a batch size of (b) (4) at EBOL and filled at (b) (4). There was an (b) (4) for the PPQ. Sterility testing was performed as per (b) (4), and all (b) (4) lots met the specification i.e., pass for sterility.

**Reviewer's comment:**

The PPQ batches filled at (b) (4) met the sterility specification. The information appears acceptable.

### 3.2.P.7 Container Closure System

#### Primary packaging

The container closure system (CCS) for AV7909 consists of (b) (4) Plus borosilicate glass vials with an internal coating of (b) (4) supplied by (b) (4) 20 mm (b) (4) rubber stoppers made of (b) (4) and coated with (b) (4) on the outer top for lubricity supplied by (b) (4), and 20 mm flip-off aluminum seals with a plastic button supplied by (b) (4).

The vials are inspected and tested prior to release for filling and as part of the finished product inspection process. Specifications for the vials are listed in Table 2 of Section 3.2.P.7 CCS in the submission. The vials are cleaned, sterilized, and depyrogenated at the filling facility prior to use.

The stoppers are received ready for (b) (4). Specifications for the stoppers are listed in Table 3 of Section 3.2.P.7 CCS in the submission. The stoppers were tested by the manufacturer according to (b) (4) and evaluated for the following tests and acceptance criteria:

- (b) (4)

The results showed (b) (4) of (b) (4) no (b) (4) and no traces of the (b) (4) and met all the acceptance criteria as per (b) (4).

For the seal, no further processing is required after receipt. Specifications for the seal are listed in Table 4, Section 3.2.P.7 CCS of the submission.

#### *Secondary packaging*

The sealed vials are packaged with a leaflet inside a cardboard carton and individually packaged vials are grouped into a shipping carton, which holds 315 vials. The shipping cartons are packaged onto pallets and shipped in (b) (4).

**Reviewer's comment:** The container closure system was evaluated by CCIT as part of a simulated shipping study, which was performed under worst-case shipping conditions using (b) (4) testing, and during DP stability studies (Section 3.2.P.8, below). CCIT results appear to support the use of the CCS. The AV7909 DP is provided in a multi-dose vial. The stoppers met the acceptable criteria for the functionality tests (i.e., (b) (4)) as per (b) (4). The suitability of the stoppers for the multi-dose presentation of the DP appears acceptable. The information provided under DMPQ's purview appears acceptable.

The preparation (e.g., (b) (4)) of the CCS components is discussed in Section 3.2.A.1 for the (b) (4) facility below.

### **3.2.P.8 Stability**

The proposed shelf life of AV7909 DP is 48 months when stored at  $5 \pm 3^\circ\text{C}$ .

#### *Real-time stability study*

For real-time stability studies, (b) (4) PPQ lots, (b) (4) were placed on stability for (b) (4) at real-time conditions ( $5 \pm 3^\circ\text{C}$ ) in an (b) (4) position. Details of the different lots are provided in Table 1 of Section 3.2.P.8.1. The (b) (4) lots are evaluated at various timepoints (including release and expiry) for the following:

- Sterility: sterile and AME: effective, testing at T0, T6-month, T12-month, T24-month, T36-month, T48-month, (b) (4)
- Container closure integrity: no (b) (4), testing at T0, T3-month, T6-month, T9-month, T12-month, T18-month, T24-month, T36-month, and T48-month



The (b) (4) lots met the acceptance criteria listed above for up to the T24-month timepoint. All real-time stability studies are ongoing, and the data will be submitted in an annual report.

(b) (4)

(b) (4)

The post-approval stability protocol for AV7909 DP is provided in Section 3.2.P.8.2. The applicant will assess CCIT, AME, and sterility at the remaining timepoints. For each calendar year, the applicant committed to place one lot of AV7909 for post-approval stability testing.

**Reviewer's comment:** Based on the available real-time stability study data and completed accelerated stability study data, the proposed shelf-life of 48 months for AV7909 appears acceptable. Also, data appears to support the stability of the DP up to (b) (4) after the multi-dose vial has been initially punctured, up to (b) (4) when stored at  $5 \pm 3^{\circ}\text{C}$  during use.

### 3.2.A APPENDICES

#### 3.2.A.1 Facilities and Equipment [EBOL]

EBOL is a multiproduct facility that is used to manufacture AV7909 and BioThrax (BLA STN 103821). At EBOL, the manufacture of AVA DS and AV7909 BDP occurs in (b) (4), and the DP visual inspection and labeling occur in (b) (4). The (b) (4) that is used

to formulate AV7909 and BioThrax is manufactured in (b) (4). The addition of the CPG 7909 adjuvant to AVA DS during formulation to manufacture AV7909 is the main difference between AV7909 and BioThrax.

AV7909 (b) (4) is manufactured in (b) (4) processing room, (b) (4) (room (b) (4)), Grade (b) (4). Although the room is (b) (4) to the manufacture of AV7909 (b) (4), the product contact equipment consists of multiproduct (i.e., BioThrax) (b) (4) with the CPG 7909 adjuvant and filtration of the AV7909 BDP.

Product segregation between BioThrax and AV7909 is monitored by way of an identity test with specificity for (b) (4) CPG 7909. The method validation was provided in Section 3.2.P.5.3 of the submission, and the test was previously approved for BioThrax under STN 103821/5388 (approved May 16, 2017).

(b) (4)

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]



(b) (4)



**Overall reviewer's assessment of Section 3.2.A.1, EBOL:** The facility design, microbial contamination and cross-contamination controls, utilities, and equipment at EBOL appear acceptable to manufacture (b) (4) AV7909 BDP, especially because the manufacture of AVA <sup>(b) (4)</sup> uses the (b) (4) for AV7909 and BioThrax. The sterilization processes unique to AV7909 were supported by qualification studies specific to CPG 7909 and AV7909 <sup>(b) (4)</sup> loads that met acceptance criteria. <sup>(b) (4)</sup>

