

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA 125757/0

fecal microbiota spores, live-brpk; VOWST™

Miriam Ngundi, Reviewer, MRB1/DMPQ

1. **BLA#:** STN 125757/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Seres Therapeutics, Inc.; License No: Not available

3. **PRODUCT NAME/PRODUCT TYPE**

Non-proprietary/proper/USAN: fecal microbiota spores, live-brpk

Proprietary name: VOWST

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

a. Pharmacological category: Fecal Microbiota Transplantation (FMT)

b. Dose form: Spore suspension in a capsule

c. Strength/Potency: 1×10^6 to 3×10^7 spore colony forming units (SCFU) per capsule with a dose of 4 capsules each day ((b) (4) SCFU per daily dose)

d. Route of administration: Oral

e. Indication(s): To prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI)

5. **MAJOR MILESTONES**

Filing action date: October 25, 2022

Facility inspections:

- (b) (4) : Seres Therapeutics, Inc. in (b) (4) , MA
- December 12 – 14, 2022: Seres Therapeutics, Inc. in Cambridge, MA
- (b) (4)

PDUFA action date: April 26, 2023

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

Reviewer/Affiliation	Section/Subject Matter
Miriam Ngundi, OCBQ/DMPQ/MRB1	Reviewer, Inspector Drug substance (DS), drug product (DP), and facilities and equipment (3.2.S, 3.2.P, and 3.2.A.1)
Kathleen Jones, OCBQ/DMPQ/MRB1	Consult reviewer, Lead inspector

7. **INTER-CENTER CONSULTS REQUESTED**

None

8. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
08/26/2022	STN 125757/0.1	Final portion (Regional, Clinical, and CMC) of rolling submission / Reviewed

DMPQ review memo BLA 125757/0

Date Received	Submission	Comments/ Status
10/12/2022	Amendment STN 125757/0.9 Response to information request (IR) dated 09/28/2022	Donor collection and drug product release testing facilities / Reviewed
10/28/2022	Amendment STN 125757/0.12 Response to IR dated 10/07/2022	Shipping qualification and facilities and equipment / Reviewed
11/10/2022	Amendment STN 125757/0.14 Response to IR dated 11/01/2022	Testing performed at (b) (4) facility and manufacturing schedules for all facilities / Reviewed
11/30/2022	Amendment STN 125757/0.17 Response to Records Request dated 11/09/2022	Records request under section 704(a)(4) / Reviewed
12/06/2022	Amendment STN 125757/0.20 Response to IR dated 12/02/2022	Status of (b) (4) facility and testing performed at (b) (4) / Reviewed
12/16/2022	Amendment STN 125757/0.24 Response to IR dated 12/05/2022	Assays, donor screening tests, and updated manufacturers of DS / Reviewed section 3.2.S.2.1
12/30/2022	Amendment STN 125757/0.28 Response to IR dated 12/16/2022	Stability studies and the storage time/conditions of products / Reviewed
01/03/2023	Amendment STN 125757/0.30 Response to IR dated 12/15/2022	Shipping, process validation, container closure integrity testing, and Seres manufacturing facility at Cambridge – equipment, room classifications / Reviewed
01/12/2023	Amendment STN 125757/0.31 Response to IR dated 01/04/2023	Stability data / Reviewed
01/27/2023	Amendment STN 125757/0.34 Response to IR dated 01/12/2023	(b) (4) manufacturing facility - room classifications, utilities, contamination controls and equipment / Reviewed
01/30/2023	Amendment STN 125757/0.35 Update based on inspector's recommendation	Removal of the (b) (4) warehouse at (b) (4) / Reviewed
02/03/2023	Amendment STN 125757/0.36 Response to IR dated 01/12/2023	Product-contact equipment cleaning validation / Reviewed
02/17/2023	Amendment STN 125757/0.43 Response to PLI Form FDA 483	Responses to form FDA 483 list of observations / Reviewed

Date Received	Submission	Comments/ Status
03/24/2023	Amendment STN 125757/0.56 Response to IR dated 03/21/2023	Qualification of refrigerator used for (b) (4) / reviewed

9. Referenced REGULATORY SUBMISSIONS (e.g., IND, BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	White (b) (4) colorant (b) (4) component material for primary container closure (bottle)	Yes	I defer to Office of Vaccines Research and Review (OVR) for review of compatibility with product
DMF (b) (4)	(b) (4)	Closures, bottle caps	Yes	I defer to OVR for review of compatibility with product
DMF (b) (4)	(b) (4)	Polypropylene (b) (4) homopolymer component material for caps	Yes	I defer to OVR for review of compatibility with product
DMF (b) (4)	(b) (4)	(b) (4) White PP MB, component material for bottle caps	Yes	I defer to OVR for review of compatibility with product
DMF (b) (4)	(b) (4)	(b) (4) polyethylene resins, component material for bottle	Yes	I defer to OVR for review of compatibility with product
DMF (b) (4)	(b) (4)	Plastic bottles	Yes	I defer to OVR for review of compatibility with product
DMF (b) (4)	(b) (4)	Foil liner (b) (4) component material for cap	Yes	I defer to OVR for review of compatibility with product

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The Center for Biologics Evaluation and Research received a two-portion rolling Biologics License Application (BLA) for VOWST under STN 125757/0 from Seres Therapeutics, Inc. (referred to as Seres or the applicant) on May 24, 2022. The final portion of the rolling BLA was received on August 26, 2022.

VOWST drug product (DP) consists of Firmicutes bacterial spores purified from stool collected from qualified human donors, formulated in 88% to 96% w/w glycerol in saline, and encapsulated for oral administration. Each capsule contains 1×10^6 to 3×10^7 SCFU.

The product is dosed orally at 4 capsules each day for 3 consecutive days ((b) (4) SCFU per daily dose).

Donor human stool (referred to as donor-sourced material, DSM) is collected, sampled, and stored at donation collection facilities (DCFs). The DSM is then shipped to Seres Therapeutics, Inc. in Cambridge, MA, where it is stored prior to being qualified and released as starting raw material (SRM) for the manufacture of (b) (4) intermediate. (b) (4) is shipped to (b) (4) for further manufacture of the drug substance (DS) and DP.

DMPQ conducted the following pre-license inspections (PLIs) with the outcomes as indicated:

- Seres Therapeutics, Inc. at (b) (4) MA (referred to as Seres (b) (4)) – (b) (4) (No Action Indicated (NAI))
- Seres Therapeutics, Inc. at 200 Sidney St., Cambridge MA (referred to as Seres Cambridge) – December 12 – 14, 2022 (NAI)
- (b) (4) (Voluntary Action Indicated (VAI), FORM FDA 483 was issued with four observations)

DMPQ requested records for review of the (b) (4) manufacturing facility, according to FD&C 704(a)(4), in advance of a PLI. Items identified to be of concern during the manufacturing site's record review were followed up during the on-site PLI (see Compliance Management System (CMS) Work # 502500 and also in CBER Connect – uploaded March 29, 2023)

Additionally, an inspection of (b) (4) located at (b) (4) was waived on (b) (4).

Reviewer's comment: Based on the information provided and reviewed as documented in this memo, all manufacturing steps to produce VOWST appear to have been validated and the overall control strategy appears acceptable to assure consistent manufacture of the product. The manufacturing facilities supporting the manufacture of VOWST appear acceptable to manufacture the product safely and according to applicable standards.

B. RECOMMENDATION

I. APPROVAL

Based on information provided in this application, DMPQ recommends the approval of VOWST, which is manufactured at Seres Therapeutics, Inc. at 200 Sidney St., Cambridge, MA and (b) (4)

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Miriam Ngundi, CSO, DMPQ/MRB1	Concur	
Kathleen Jones, Biologist, DMPQ/MRB1	Concur	
Lori Peters, Branch Chief, DMPQ/MRB1	Concur	
Carolyn Renshaw, Director, DMPQ	Concur	

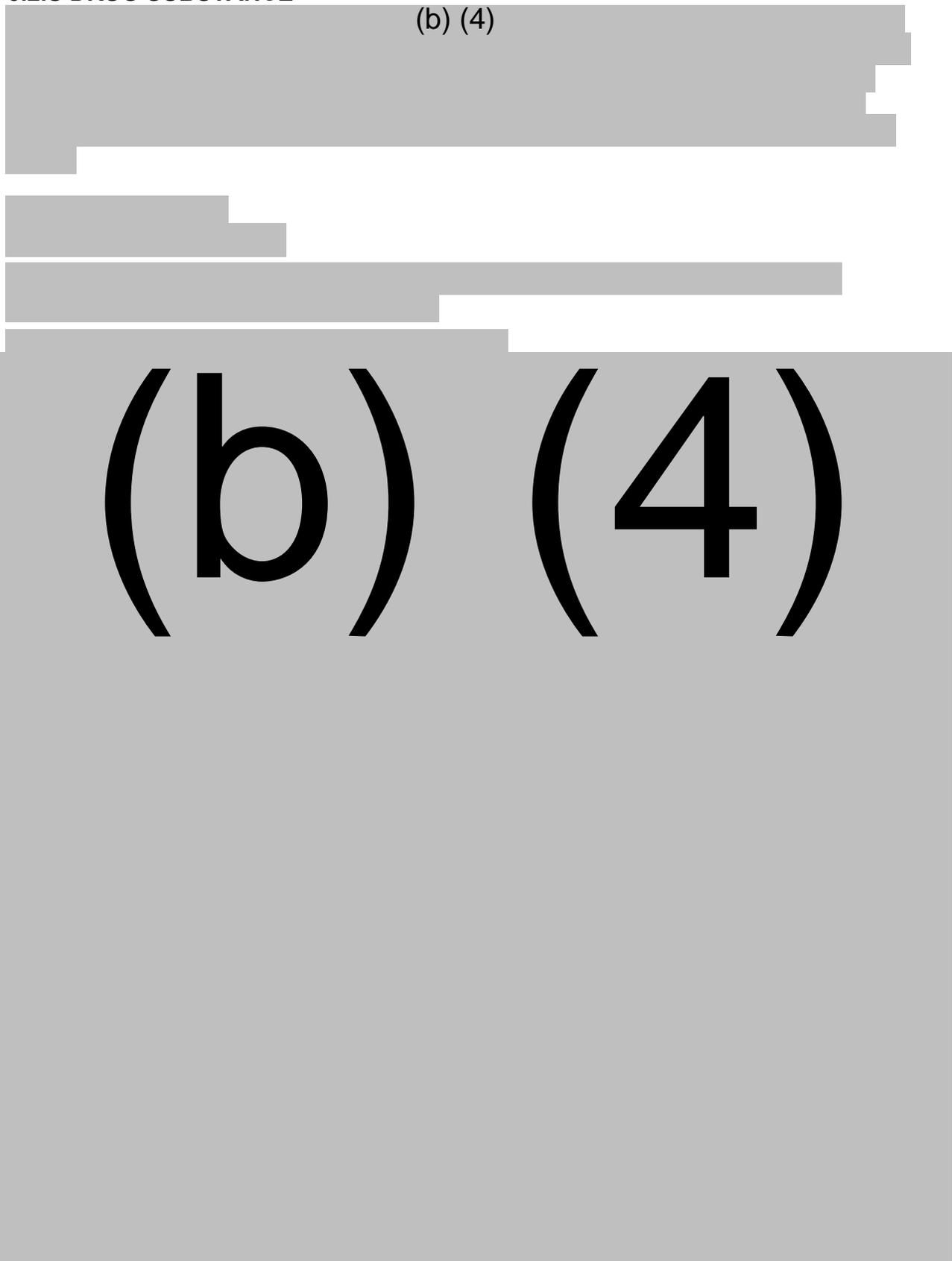
Table of Contents

3.2.S DRUG SUBSTANCE.....	8
3.2.S.2 Manufacture	8
3.2.S.2.1 Manufacturer(s).....	8
3.2.S.2.2 Description of Manufacturing Process	9
3.2.S.2.3 Control of Materials	12
3.2.S.2.4 Controls of Critical Steps and Intermediates.....	13
3.2.S.2.5 Process Validation and/or Evaluation.....	14
3.2.S.4 Control of Drug Substance.....	15
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s).....	15
3.2.S.4.4 Batch Analyses	16
3.2.S.6 Container Closure System	16
3.2.S.7 Stability.....	16
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data	16
3.2.P DRUG PRODUCT	17
3.2.P.1 Description and Composition of the Drug Product.....	17
3.2.P.2.5 Microbiological Attributes	17
3.2.P.3 Manufacture	17
3.2.P.3.1 Manufacturer(s).....	17
3.2.P.3.3 Description of Manufacturing Process	18
3.2.P.3.4 Controls of Critical Steps and Intermediates.....	19
3.2.P.3.5 Process Validation and/or Evaluation.....	20
3.2.P.5 Control of Drug Product.....	23
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).....	23
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.....	24
3.2.P.5.4 Batch Analyses	26
3.2.P.7 Container Closure System	27
3.2.P.8 Stability.....	28
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	28
3.2.A APPENDICES	29
Donor Collection Facilities (DCFs)	29
Equipment.....	30
Prevention of Cross-Contamination.....	30
Quality Oversight	31
3.2.A.1 Facilities and Equipment – Seres Cambridge, MA	31
Facility Design	31
Facility Cleaning and Disinfection	34
Critical Utilities.....	35
Equipment.....	39
Computer systems.....	40
3.2.A.1 Facilities and Equipment – (b) (4)	40
Facility Design	40
Facility Cleaning and Disinfection	42
Critical Utilities.....	43

Equipment.....	48
Computer systems.....	53

3.2.S DRUG SUBSTANCE

(b) (4)



(b) (4)

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

Reviewer’s comment: DMPQ defers the review of the DS stability information to OVRP.

3.2.P DRUG PRODUCT

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

VOWST DP consists of Firmicutes bacterial spores purified from human stool, formulated in 88% – 96% w/w glycerol in 0.9% saline, and encapsulated for oral administration. The non-sterile, non-lyophilized DP is a white opaque capsule printed with “SER109”. Each capsule contains 1x10⁶ to 3x10⁷ SCFU. The product is dosed orally at 4 capsules each day for 3 consecutive days, providing (b) (4) SCFU per daily dose. Twelve capsules are packaged in 40 cc high-density polyethylene bottle with an induction foil seal and a polypropylene cap. The proposed shelf-life for the DP is 36 months when stored at (b) (4).

3.2.P.2.5 Microbiological Attributes

VOWST DP is a non-sterile, orally administered product. The bioburden acceptance criteria of (b) (4) detected is aligned with (b) (4). The product has a requirement that (b) (4) organisms be detected. Seres described how the microbial enumeration method was developed to reduce background product organism growth while providing sensitivity to detect potential contaminant organisms.

Reviewer’s comment: Because of the nature of the product, bioburden is an inherent component of the DP. DMPQ defers the review of the microbiological attributes and the corresponding analytical procedures used to determine microbial quality of the DP to OVRP.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The manufacturing facilities that support the production of VOWST DP and the associated responsibilities are as follows:

Manufacturing / Testing activities	Responsibilities
(b) (4)	<ul style="list-style-type: none"> • DP manufacture • DP primary packaging • DP storage
Seres Therapeutics, Inc. 200 Sidney St. Cambridge MA 02139 FEI: 3012828816	DP release and stability testing
Seres Therapeutics, Inc. (b) (4)	DP release and stability testing
(b) (4)	Microbial identification (part of DP release test)
(b) (4)	Formulated bulk release testing

Manufacturing / Testing activities	Responsibilities
(b) (4)	
(b) (4)	Formulated bulk release testing
(b) (4)	DP secondary packaging, labeling, storage, and distribution
(b) (4)	DP storage
(b) (4)	Storage of DP stability samples

Reviewer's comment: Seres provided a final list of DP manufacturers in amendment STN 125757/0.35.

3.2.P.3.3 Description of Manufacturing Process

The DP process consists of the following (b) (4) unit operations, performed at (b) (4) temperature ((b) (4)) unless otherwise stated:

(b) (4)

Encapsulation: (b) (4)

Over-encapsulation: (b) (4)

(b) (4)



Seres stated that the (b) (4) glycerol concentration used throughout the VOWST DP process provides for (b) (4). The (b) (4) is below the limits for microbial outgrowth and, therefore, contributes to microbial control of the DP. Seres stated that the formulation met the criteria for (b) (4) demonstrating anti-microbial effectiveness against vegetative bacteria and fungi.

Reviewer's comment: Due to the nature of the product, there are no steps that are critical to microbial quality, e.g., bioburden and endotoxin reduction, or sterile filtration. There are no intermediates during the manufacture of VOWST DP. DMPQ defers to OVR to assess whether the control strategy is appropriate to assure product quality and process consistency.

3.2.P.3.5 Process Validation and/or Evaluation

Seres manufactured three consecutive DP lots (#s (b) (4)) at commercial scale to demonstrate process consistency. The DP lots were manufactured from the (b) (4) DS PPQ lots (Section 3.2.S.2.5, above). Therefore, each DP lot was manufactured using SRM from a single donor, (b) (4). Seres stated that reprocessing (defined above in section 3.2.P.3.3) was not included in the PPQ protocol, because reprocessing steps, limited to primary packaging, are completed according to written procedures and within the original allowed processing time for the individual operations or total process.

The defined process parameters and critical IPCs (section 3.2.P.3.4, above) were evaluated during the process validation study. The results for all three PPQ runs met the defined acceptance ranges. The executed PPQ lots met both predefined and refined (after PPQ) acceptance criterion for target spore content.

To assess the process step yields after encapsulation, over-encapsulation, and primary packaging, Seres performed visual inspections, which are considered critical IPCs. The acceptance criteria and rejects for each lot for these tests are:

(b) (4)



Additionally, all PPQ lot met the following percentage process step yields, where yields are calculated based on capsule counts and the theoretical maximum is (b) (4):

(b) (4)

Microbial Contamination Control and Process Holds

Seres stated that the (b) (4) glycerol concentration used throughout the VOWST DP process provides for (b) (4). Therefore, the (b) (4), which is below the limits required for microbial outgrowth, controls bioburden. All three PPQ lots met the following acceptance criteria for bioburden and (b) (4):

- Bioburden: (b) (4)
- (b) (4)

Seres stated that the (b) (4) reduces the risk of microbiological outgrowth (based on (b) (4)) and allows for extended process hold times. The hold times and conditions used for the PPQ study were evaluated in characterization studies (module 3.2.P.2.3.1), and therefore, intermediate microbial hold studies were not performed for DP PPQ.

Deviations

Seres reported two deviations that occurred during the PPQ study. In DEV-21-200, the container closure integrity test (CCIT) results for (b) (4) lots did not meet the acceptance criterion ((b) (4)) because the samples were not (b) (4) prior to execution of test per the test method. The corrective and preventive action (CAPA) included a revision to the test method for (b) (4) period at (b) (4) for CCIT samples. The samples were retested and passed using the revised (b) (4) period.

In DEV-22-009, there was misalignment in the procedure for the DP storage temperature at (b) (4) and the storage and shipment temperature for release, retain, and stability samples. There was insufficient documented justification for the samples being stored and shipped at (b) (4) while the product was stored at (b) (4) even though the stability data shows product is stable at both temperature conditions.

Reviewer's comment: VOWST is not a sterile product. Due to the nature of this product where bioburden is an inherent component, DMPQ defers to OVRP the assessment of the bioburden levels in the product as well as the critical IPCs tested during the PPQ study.

All the process parameters for assessing primary packaging met the predefined acceptance criteria with the sampling procedure based on (b) (4). The information provided appears acceptable.

The results for the percentages of the process step yield for the visual inspections appear to indicate that the equipment used for encapsulation, over-encapsulation, and

induction seal performed as expected. DMPQ defers the assessment of the number of capsules rejected to OVR.

The deviation associated with the CCIT appeared to be resolved and did not appear to have an impact on the validation or the product. DMPQ defers to OVR for the assessment of the deviation due to product and sample storage temperatures. The information provided for the process validation under DMPQ purview appears acceptable to support consistent manufacture of VOWST DP.

Shipping Qualification

(b) (4)

[Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

- [Redacted]
- [Redacted]

(b) (4)

[Redacted]

[Redacted]

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)

The release specification for formulated bulk:

(b) (4)

The release specifications for the DP are based on the following tests:

- Identity (b) (4) : (b) (4) detected
- Potency (spore forming unit assay for viable spore count):
 - (b) (4) (lower specification limit (LSL))
 - (b) (4) (upper specification limit (USL))
 - 1×10^6 SCFU/capsule (LSL)
 - 3×10^7 SCFU/capsule (USL)
- Bioburden (microbial enumeration by (b) (4))

(b) (4)

(b) (4)
(b) (4)

- Appearance and physical characteristics (visual inspection): White, opaque capsules consistent with size 00 standard. Possible (b) (4). Printed with “SER109” in blue ink on capsule body.
- Container closure integrity ((b) (4) method): No seal failure following application of (b) (4).
- (b) (4) : Acceptance value calculated per (b) (4)

Container closure integrity testing (CCIT) is performed on the primary packaging (bottles) to ensure low levels of (b) (4) (low risk of microbial proliferation/contamination) and prevent potential microbial contamination of the product ((b) (4)). The criteria for the specification of CCIT are informed by the FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics and the (b) (4) —Test Method Selection and Validation.

Reviewer’s comment: The CCIT method specifications appears acceptable to provide assurance of package integrity, thus minimizing DP contamination. DMPQ defers the assessment of the other specifications to OVR.

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

Container Closure Integrity

Seres uses test method TM-0007 to perform the CCIT, which is a (b) (4) test method utilizing a (b) (4) to enable a visual evaluation of the integrity of the aluminum induction seal of the VOWST DP container closure system (CCS). Seres stated that TM-0007 was developed in accordance with FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics and the (b) (4) — Test Method Selection and Validation.

(b) (4)

(b) (4)

Seres validated the test method for the specificity, accuracy, precision, limit of detection (LOD), and robustness, as well as establishing a positive control. The validation study (protocol PROT-0171) was executed by (b) (4) operators over (b) (4) days using VOWST DP CCS in the Quality Control Laboratories at Seres, 200 Sidney St. Cambridge, MA and documented in report RPT-00177. The following parameters were assessed, and results met the predefined acceptance criteria, as indicated:

- LOD
(b) (4)
- Specificity
(b) (4)
- Accuracy
(b) (4)
- Precision (repeatability, (b) (4))
(b) (4)
- Precision (intermediate precision, (b) (4))
(b) (4)
- Robustness
(b) (4)
- System suitability
(b) (4)

There were two discrepancies reported and investigated during the execution of the method validation protocol PROT-0171:

(b) (4)

(b) (4)

In amendment STN 125757/0.30, Seres provided an addendum report (RPT-00360) to the method validation executed per addendum protocol PROT-0240 to assess the robustness of the samples' (b) (4) conditions (various sample (b) (4)) for the CCIT. The results met the acceptance criteria when the samples were at (b) (4) and (b) (4). Based on this study, Seres did not make any recommendations or modifications to TM-0007 for the sample (b) (4) steps.

In amendment STN 125757/0.30, Seres clarified that sampling for CCIT is per batch production record MPF-149 Section PF-149D where a total of (b) (4) bottles are sampled per batch: (b) (4)

Reviewer's comment: Based on the results of the CCIT validation studies, test method TM-0007 appears acceptable for the intended use. The information provided appears acceptable.

3.2.P.5.4 Batch Analyses

Seres included Phase II (b) (4) lots) and Phase III (b) (4) lots) clinical studies as well as the PPQ lots for the batch analyses. The lots were manufactured between December 3, 2014 and November 17, 2021. The applicant stated that the results of analytical release testing were generated according to analytical procedures and specifications in place at the time of product release. All the results for CCIT passed the specifications (no seal failure following application of (b) (4)).

(b) (4)

(b) (4)

Reviewer's comment: Seres' assessment of the impact of using non-validated CCIT methods on clinical lots appears acceptable. The information provided on batch analyses, under DMPQ purview, appears acceptable.

3.2.P.7 Container Closure System

VOWST DP capsules are contained in a 40 cc opaque white high-density polyethylene (HDPE) wide-mouth pharmaceutical bottle capped with a child-resistant cap. Seres stated that the cap is made from polypropylene with 21 CFR 177.1210-compliant foil liner. The inner liner consists of a laminate structure of (b) (4) (bottle-facing), polyethylene terephthalate film, foil, and pulp.

The bottle and cap are manufactured by (b) (4) (reference DMF (b) (4) and DMF (b) (4), respectively), while the foil-liner is manufactured by (b) (4). The applicant provided bottle, cap, and foil-liner certificates of compliance as well as drawings. The bottle's component materials are (b) (4) polyethylene (reference DMF (b) (4)) and White (b) (4) colorant (b) (4) (reference DMF (b) (4)). The bottles' release specifications and acceptance criteria are:

- Visual inspection: (b) (4)
- Identification (by (b) (4)): Conforms with the reference (b) (4).

The component materials for the child-resistant cap are (b) (4) polypropylene homopolymer (reference DMF (b) (4)) and White (b) (4) colorant (b) (4) (reference DMF (b) (4)) and for foil liner is (b) (4) (reference DMF (b) (4)). The release specifications and acceptance criteria are:

- Visual inspection: (b) (4)
- Identification of the lining material (by (b) (4)): Conforms with the reference (b) (4).

Reviewer's comment: Seres performed CCIT as part of batch analyses and DP stability studies (section 3.2.P.8, below) and the results appear to support the use of the CCS. The information provided under DMPQ's purview appears acceptable. DMPQ defer the evaluation of compatibility of the CCS (extractable and leachable) to OVR.

3.2.P.8 Stability

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

The proposed commercial shelf life for VOWST DP is 36 months when stored under the long-term storage condition of (b) (4) °C. The following tests are assessed for stability:

- Identity (b) (4)
- Potency (SCFU)
- (b) (4)
- (b) (4)
- Appearance and physical characteristics
- Container closure integrity with acceptance criterion: no seal failure following (b) (4).

Seres assessed the stability of (b) (4) Phase III clinical lots (SERES-012/013) stored at (b) (4) 5 °C, and 25 °C for 0, 1, 3, 6, 9, 12, 18, 24, and 36 months using the above test parameters. Additionally, (b) (4) lots stored at (b) (4) and 5 °C were tested after (b) (4) months to extend lot expiry for clinical use. (b) (4) stored at 25 °C was tested for SCFU after (b) (4) months to support long-term trending analysis of potency.

All the results for CCIT met the acceptance criterion based on the version of the test method in use at the time. There was a deviation at the 6-month time point for samples stored at (b) (4) due to missing data; however, the data collected after 6 months met the acceptance criterion. The applicant stated that an investigation was completed and determined the root cause (not provided in submission) and that the missing data did not impact the assessment of DP stability.

To assess the impact of short-term temperature excursions, (b) (4) subject to (b) (4) under the following conditions:

(b) (4)
The samples were then tested after the completion of (b) (4) cycles at each condition, and all results met the CCIT acceptance criterion.

Seres is currently executing stability studies for the (b) (4) PPQ lots stored at 5 °C, 25 °C, (b) (4) and tested at various time points ranging between 0 and 36 months. CCIT is assessed at following time points:

- 0, 12, 24 and 36 months for PPQ lots stored at 5 °C and 25 °C
- 0 and 12 months for samples stored at (b) (4)
- 0 and 6 months for samples stored at (b) (4)

The applicant has reported results up to the 6-month time point, and all the results for

CCIT met the acceptance criterion.

Seres will monitor the stability of commercial VOWST DP stored at 25°C (b) (4) at time points 0, 6, 12, 24, 36 and (b) (4) months. CCIT will not be assessed at the 6-month time point. A minimum of (b) (4) commercial DP (b) (4) per year will be included in the stability program.

Reviewer's comment: All the CCIT results met the acceptance criterion. Even though the CCIT for Phase III lots was performed using a non-validated method that may not have been able to detect (b) (4)-defects, the test method appears acceptable given the applicant's assessment per 3.2.P.5.4, above. The 6 month data was missing for (b) (4) temperatures; however, data was collected for time points after 6 months for the same conditions and met the criterion. The CCIT results appear to demonstrate that the primary packaging remains intact, thus providing assurance against contamination or cross-contamination. Based on the available CCIT results, it appears there is support for the proposed shelf life of 36 months for DP when stored at 25 °C.

3.2.A APPENDICES

The following facilities are associated with the manufacture of VOWST:

1) Donor collection facilities (see facility table in Section 3.2.S.2.1)

2) Seres Therapeutics, Inc.
200 Sidney St. Cambridge, MA 02139
FEI: 3012828816

This facility is referred to as Seres Cambridge and is responsible for the manufacture of (b) (4).

3) (b) (4)

This facility is referred to as (b) (4) and is responsible for the manufacture of the VOWST DS and DP.

Donor Collection Facilities (DCF)

Reviewer's comment: Below, I have provided a summary review of the information Seres provided to document the type of equipment utilized at the DCFs, procedures followed to prevent cross-contamination of the DSM, and quality oversight of the DCFs. The information appears acceptable.

(b) (4)

One page determined to be not releasable: (b)(4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Quality Oversight

Seres stated that a quality management system model based on blood and plasma regulations (21 CFR 606, § 610 and § 630) has been implemented. The donation operations program quality management system consists of following primary process systems based on the *FDA Compliance Program Guidance Manual for Blood Banks, Brokers, Reference Laboratories and Contractors (CPGM 7342.001)*: QA system; donor eligibility system; DSM inspection; DSM collection, handling, and labeling system; and storage, quarantine, and disposition system. The system has a dedicated donation operations QA unit within Seres Corporate Quality responsible for managing quality within the donor program. This QA is responsible for the processes and procedures performed within the donor program.

3.2.A.1 Facilities and Equipment – Seres Cambridge, MA

Facility Design

Seres Cambridge at 200 Sidney St. Cambridge, MA 02139, which manufactures (b) (4), an intermediate for VOWST, is a commercial and clinical, multiproduct, microbiome manufacturing site. Seres stated that these products include natural and fermented product lines of oral dosage forms with live bacterial active ingredients in non-aqueous (b) (4) form. Additionally, the facility houses donor derived products, (b) (4) DS, and (b) (4) DP. In amendment STN 125757/0.30, Seres provided a

list of donor-derived ((b) (4)) and cultivated ((b) (4)) products manufactured at the facility and included the corresponding IND numbers for each product.

The facility consists of the following areas/classification and the corresponding role in manufacture of VOWST (provided in Table 1, module 3.2.A.1):

- Manufacturing corridor (Controlled, not classified – CNC)
- Locker rooms (CNC)
 - Entry and primary gowning
- Gowning and airlock (ISO (b) (4))
 - Secondary gowning
- Supply side support area and associated airlocks (Grade (b) (4))
 - (b) (4) staging of process materials
 - (b) (4) area for SRM and (b) (4) storage
 - Temperature-controlled (b) (4) of SRM in (b) (4)
 - Autoclave and preparation area for single-use materials
- Productions suites with airlocks to both supply and return corridors (Grade (b) (4))
 - Suite (b) (4) – not used for VOWST
 - Suite (b) (4) – not used for VOWST
 - Suite (b) (4) – equipment and material staging
 - Suite (b) (4) – (b) (4) manufacturing operations
- Return side support and associated airlocks (CNC)
 - Decontamination of waste
 - Disposal of suitable liquid wastes
 - Sample passthrough to QC laboratory
- Manufacturing corridor and airlock (CNC)
 - Personnel access
 - Automated systems displays
 - Non-process working area
- Warehouse/storage (unclassified)
 - Materials storage
 - Temperature-controlled storage of SRM and (b) (4)

Seres stated that the manufacturing suites are not product-dedicated; however, (b) (4) processing is limited to (b) (4) and product is manufactured on a campaign basis. The manufacturing areas and any adjacent suites are separated with airlocks at the entry and exit of the manufacturing suites. Movement of personnel directly between the suites is only allowed when the suites are both active for the same manufacturing process.

In amendment STN 125757/0.30, Seres clarified that under (b) (4) active status (per SOP-0224), unidirectional personnel, material, and equipment flows are required from Suite (b) (4) to Suite (b) (4) via a pass-through airlock between the suites. Entry to manufacturing Suite (b) (4) as well as the Staging room (separate room between Suites (b) (4)) is via the supply corridor. (b) (4)

rooms. Equipment remains in Suite (b) (4) until changeover equipment cleaning is performed. The clean equipment is then transferred to (b) (4).
Waste generated in Suite (b) (4) to the decontamination and waste area. No other activities may occur in Suites (b) (4) during the (b) (4) active status.

In amendment STN 125757/0.30, Seres provided the description of gowning levels required in the manufacturing areas. Personnel don (b) (4), which is the minimum gowning level required to enter (b) (4) active production suites and the return side support areas. In the amendment STN 125757/0.30, Seres clarified that there is an active cascade with differential pressure of (b) (4) in Suites (b) (4), with the airlocks serving as sinks.

Seres provided descriptions as well as matching diagrams showing the manufacturing areas: flow of materials, equipment, and personnel; direction of room differential pressure; and gowning levels.

In amendment STN 125757/0.30, Seres clarified that manufacturing processes performed (b) (4)

Prevention of Contamination and Cross-contamination

The risk for cross-product contaminants is mitigated through room segregation, ongoing environmental controls and monitoring, manufacturing (b) (4) using (b) (4) processing or (b) (4) for (b) (4) operations, unidirectional flow of personnel and materials, gowning/de-gowning as well as cleaning and sanitization procedures. (b) (4)

Campaign changeover and room clearance are performed according to established procedures and occur between lots of (b) (4) from different donor-sourced SRM. Changeover activities include room clearance, suite cleaning and disinfection,

equipment cleaning and disinfection, and QA verification of suite status. Seres provided the activities included in room clearance in module 3.2.A.1, Table 4.

Reviewer's comment: The flow diagrams as provided appear acceptable to support segregation controls during the manufacture of VOWST. Procedural and process design controls appear acceptable to prevent cross-contamination and product mix-ups in the manufacturing facility. The information provided on facility design appears acceptable.

Facility Cleaning and Disinfection

Information on facility cleaning was provided in amendment STN 125757/0.12. Cleaning in the manufacturing suites and support areas occurs (b) (4) (level 1 cleaning) or (b) (4) (level 2 cleaning) per SOP 0113. (b) (4) cleaning using sporicidal agent (b) (4) is performed on all (b) (4)

The manufacturing processes at Seres Cambridge are not aseptic; however, Seres stated that the efficacy of cleaning and disinfection is critical as part of a quality contamination control strategy. Disinfectant efficacy testing was performed by third-party laboratory, (b) (4), and covered both the facilities at Seres Cambridge and (b) (4) and was reported in RPT-00342. The study used the following surfaces/coupon:

(b) (4)

The following disinfectants were tested using the indicated exposure time.

(b) (4)

The testing included the following organisms:

(b) (4)



The results (compared to positive controls) for all the tests met acceptance criteria of (b) (4), except for (b) (4) against (b) (4). Based on the study, Seres decided to exclude the use of (b) (4) as a disinfectant for surfaces at Seres Cambridge.

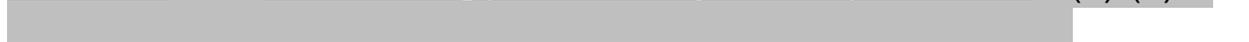
Reviewer's comment: The results of the disinfectant effectiveness study met all acceptance criteria except for (b) (4), which did not meet the acceptance criteria for cleaning (b) (4) and is not used at Seres Cambridge. The facility cleaning SOP-0113 indicates that (b) (4) are the sporicidal agents used. The information provided appears acceptable.

Critical Utilities

Most of the utilities information was provided in amendment STN 125757/0.12. Purified water system and heating, ventilation, and air conditioning (HVAC) are the only utilities used at Seres Cambridge.

Water system

Seres uses a qualified purified water generation and distribution system to produce the water used for facility cleaning and autoclaves. The applicant stated that autoclaves are used for sanitization of non-product contact material loads only. The water is not directly used in the (b) (4) manufacturing process. The system components are: (b) (4)



The purified water testing acceptance criteria are:

(b) (4)



Seres provided the verification report for the installation and operational verification of the purified water system (17-V021). The results for (b) (4) verification tests executed during the IQ/OQ met the acceptance criteria with all 14 discrepancies having been resolved.

The performance qualification (PQ) of the water system was (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

HVAC system

The primary air handling unit (AHU) PAHU-(b) (4) serves all (b) (4) manufacturing and manufacturing support areas. Air supply to manufacturing suites is controlled by dedicated secondary AHUs to each suite, SAHU-(b) (4) (Suite (b) (4)) and SAHU-(b) (4) (Suite (b) (4)), respectively. Air change rate/hour of (b) (4) and a differential pressure of (b) (4) are applied in the manufacturing suites, while at CNC areas the air exchange rate/hour is (b) (4) manufacturing areas are maintained at (b) (4) and a relative humidity of (b) (4) .

The final IOQ report, 17-V045, indicates that after verifications of all installation requirements for the HVAC system, the following critical aspects were completed and met the established criteria:

(b) (4)



Routine monitoring of the HVAC system is performed (b) (4), with (b) (4) monitoring for differential pressure, and the following acceptance criteria are applied:

(b) (4)



Seres stated that recertification of the HVAC system with an updated testing, adjusting, and balance report occurs following any facility maintenance that affects the certification state or as necessary based on (b) (4) monitoring of the system to ensure it remains within specification and within control.

Reviewer's comment: The information provided appears acceptable. The results for the qualification of the critical utilities (purified water and HVAC) met the acceptance criteria and, therefore, appear to operate at acceptable conditions to support the manufacture of (b) (4). The autoclaves are used for sanitization of non-product contact materials and appear acceptable.

Environmental monitoring

The EMPQ was executed per protocol 16-V129 and documented in report 17-V051. Sampling was performed at static (at rest) conditions for (b) (4) followed by (b) (4) days at dynamic (in operation). The results of the EMPQ met the following acceptance criteria (based on (b) (4)) with all discrepancies having been resolved:

(b) (4)



(b) (4)

Additionally, the acceptance criteria for (b) (4) were met.

Routine EM for non-viable and viable (b) (4) in the (b) (4), Grade (b) (4) and Grade (b) (4) areas is performed (b) (4), respectively, using (b) (4). All areas are also monitored (b) (4) using (b) (4). The alert / action levels are as follows:

(b) (4)

The alert / action limits ((b) (4)) applied during EM for non-viable are:

(b) (4)

In amendment STN 125757/0.30, Seres provided the number (Table 14) and locations (Figures 5 & 6) inside Suite (b) (4) and (b) (4) that were sampled during the EMPQ. Seres does not consider maximum room occupancy during (b) (4) manufacturing a necessary control given the nature of the product; therefore, the EMPQ study was not designed to establish a specific maximum occupancy requirement.

In amendment STN 125757/0.30, Seres removed the reference to ISO classification for the alert/action limits to have the correct correlation between the limits and classification system. The applicant stated that historical data suggests that Grade (b) (4) conditions can be consistently achieved in the manufacturing areas.

Reviewer's comment: The results of EMPQ met the acceptance criteria and appear acceptable to demonstrate that the environment in the manufacturing areas is under control. The sampling locations appear to be adequately distributed in the individual space and include the pass-throughs. The routine EM limits appear acceptable based on the (b) (4) and considering the nature of the product. The information provided appears acceptable.

Equipment

Seres uses only single-use disposable product-contact equipment in the manufacture of (b) (4) at Seres Cambridge, and provided a list in amendment STN 125757/0.12, Attachment 1. Seres provided a list of product non-contact equipment in amendment 125757/0.12, Table 11, which include:

- (b) (4)
Seres provided the verification report for the functionality of the (b) (4), which indicate that all excepted results, including calibration were achieved.

- (b) (4)
Seres performed OQ/PQ of the (b) (4) with an operating range of (b) (4) to verify that the equipment could maintain a temperature of (b) (4) and that the MFMS data is consistent with mapping sensors, with unloaded and loaded chambers. The results for IQ, OQ, and PQ for the two (b) (4) met the acceptance criteria, with the equipment maintaining the operating temperature range.

In amendment STN 125757/0.30, Seres provided the qualification protocols and reports for the (b) (4) used in the manufacture of (b) (4). The following qualification tests met the acceptance criteria (based on manufacturers specifications and (b) (4) standard):

(b) (4)

The (b) (4) are recertification every (b) (4).

Equipment Cleaning

In amendment STN 125757/0.12, Seres stated that single-use disposable product contact equipment is used in the manufacture of (b) (4). The non-product contact equipment is cleaned per procedure. There are no sterilization steps in the process; therefore, no sterilization validation is required.

Reviewer's comment: The only major equipment used in the manufacture of (b) (4) are (b) (4). The qualification of the (b) (4) met the acceptance criteria and appear to operate at acceptable conditions. The information provided appears acceptable.

Computer systems

Most of the information on computer systems was provided in amendment STN 125757/0.12. The computer systems supporting manufacturing are:

- (b) (4), which is a computerized maintenance management system. The system was qualified per protocol and documented in 16-V173 (summary) and RPT-00298. The qualification verified the requirements for installation and testing of the Computerized Maintenance Management System (CMMS), used at Seres manufacturing sites. The CMMS was identified as a direct impact system based on the generation of electronic records supporting manufacturing equipment and systems operations.

All requirements were met with all deviations having been resolved.

- Manufacturing Facility Monitoring System (MFMS) is used to monitor all manufacturing activities in the facility. The qualification process per protocol verified the following critical aspects: alarms, data storage (Part 11 Requirements) and regulatory compliance (21 CFR 11 and (b) (4)) as documented in 17-V067.

All verification results met the acceptance criteria with no discrepancy occurring during the qualification.

- Building Management System (BMS) is an industrial control system intended to control and monitor the manufacturing facility's HVAC and utility systems. The verification results, which are documented in qualification report 17-V026, met all the acceptance criteria and discrepancies were resolved.

Reviewer's comment: The computer systems were qualified and met the acceptable criteria. The information provided appears acceptable.

3.2.A.1 Facilities and Equipment – (b) (4)

Facility Design

The (b) (4) facility used to manufacture VOWST DS and DP consists of approx. (b) (4) production area located on the (b) (4) floor of the building. The warehouses used to support the manufacture of VOWST are located on the (b) (4). Seres stated that the applicant has a quality agreement in place with (b) (4) to ensure compliance of the manufacturing facility.

The multiproduct facility consists of (b) (4) independent production rooms across (b) (4) production units. Manufacture of VOWST DS and DP occurs in Unit (b) (4) which includes rooms (b) (4). Room (b) (4) is dedicated to the manufacture of VOWST DS and may be used to prepare solutions used in the manufacture of VOWST.

Seres provided diagrams with narratives for the flow of personnel, materials, product, and waste (Attachments 1 and 2), which appear to indicate a (b) (4) flow with separate entry and exit airlocks. Additionally, the air flow in the manufacturing areas was provided in Attachment 3, which indicate a pressure cascade to maintain a differential pressure of (b) (4). The diagram indicates air flows into the VOWST manufacturing suites from the adjacent airlocks. In amendment STN 125757/0.34, Seres provided the gowning requirements for each room/area. Regardless of the room within Unit (b) (4), personnel wear (b) (4) (if appropriate). To enter the manufacturing suites (b) (4) are donned.

Prevention of Contamination and Cross-contamination

VOWST is manufactured in dedicated rooms (b) (4) with dedicated AHUs. Other engineering and procedural controls to mitigate risk of contamination and cross-contamination include room pressure cascade designs, EM as well as established room changeover procedures for activities including decontamination, removal of materials, cleaning and disinfection, and (b) (4) of production rooms. Manufacturing process changeover is conducted following the manufacture of each product lot. The room changeover and cleaning are verified before the start of any new manufacturing processes. In amendment STN 125757/0.34, Table 3, Seres provided the SOPs for the cross-contamination controls.

Reviewer's comment: The flow diagrams as provided in the submission appear acceptable to support segregation controls during the manufacture of VOWST. Open processes are performed (b) (4) which mitigates the risk of contamination. The control of intrinsic bioburden spores within the manufacturing rooms (b) (4)

The controls to mitigate contamination and cross-contamination appear acceptable. The information provided appears acceptable.

Facility Cleaning and Disinfection

Seres provided the cleaning and disinfection of the (b) (4) facility in SOP BF.003 in amendment STN 125757/0.12. The following cleaning agents and disinfectants, with the indicated contact time, are used in the (b) (4) facility:

(b) (4)

(b) (4) is used to remove any disinfectant residue.

As described in the Facility Cleaning and Disinfection section for Seres Cambridge, disinfectant efficacy testing was performed by third-party laboratory, (b) (4), and covered both the facilities at Seres Cambridge and (b) (4) and was documented in RPT-00342 (please see details above under Seres Cambridge). Facility disinfectants (b) (4) solution are rotated (b) (4).

In amendment STN 125757/0.34, Seres clarified that (b) (4) is used for periodic (b) (4) of rooms (b) (4) and provided the effectiveness assessment reports (VR-210 and VR-223). The (b) (4) agent comprises of (b) (4) utilized in a system including (b) (4) equipment for production of (b) (4). The validation for both rooms utilized (b) (4) biological indicators of (b) (4). Re-validation of the (b) (4) occurs (b) (4).

In amendment STN 125757/0.34, Seres clarified that (b) (4) is not used for routine disinfection of facility surfaces (walls, floors, ceilings, countertops, and equipment), but is used to disinfect materials (b) (4) is used in Units (b) (4), where (b) (4) is handled for non-Seres processes.

The following areas in the QC lab, weighing room, warehouses, and common areas are cleaned (b) (4), benches, floor, general surfaces, and equipment. Incubators in the QC lab and curtains in the weighing room are cleaned (b) (4). Manufacturing units, airlocks, and corridors are cleaned (b) (4) if one production room is in use. Manufacturing rooms are cleaned (b) (4) or at the (b) (4) of a batch production. Manufacturing units are also cleaned if the EM performed in one unit shows a high microbial load or the presence of difficult microorganisms to eliminate (e.g., spore forming microorganisms). (b) (4) of (b) (4), and QC lab is performed if the EM reveals the presence of difficult removal microorganisms (e.g., spore forming microorganisms like (b) (4)).

Reviewer's comment: The disinfectant and (b) (4) effectiveness studies met all acceptance criteria. The information provided appears acceptable.

Critical Utilities

Most of the information on utilities was provided in amendment STN 125757/0.12. Compressed air, WFI, and HVAC are the only utilities used at the (b) (4) manufacturing facility.

Compressed air

Seres states that compressed air complying with (b) (4) is supplied to the (b) (4). Seres provided the IQ/OQ/PQ of the compressed air system in amendment STN 125757/0.12. The qualification met the following requirements:

- IQ requirements per SOPs

(b) (4) [Redacted]

- OQ requirements

(b) (4) [Redacted]

All the requirements were met. The compressed air is monitored (b) (4) using the above quality specifications.

WFI system

WFI produced at the (b) (4) facility is used for the preparation of process solutions, cleaning of reusable parts and the facility, and generation of pure steam for the autoclave, which is used for sanitization loads only. The major WFI system components include a (b) (4)

Seres provided the for the IQ/OQ/PQ of the WFI system in amendment STN 125757/0.12. The qualification was performed per (b) (4). The results of the qualification studies met all acceptance with all deviations having been resolved and corrective actions implemented. Based on the qualification, Seres established the following specifications (also compliant with (b) (4)) for routine monitoring:

(b) (4) [Redacted]

Seres provided the sampling frequency and points in amendment STN 125757/0.12, Table 6 and include:

(b) (4) [Redacted]

(b) (4)

Seres states that the sanitization and maintenance practices for the WFI system is per established procedures. The sanitization is performed routinely, whenever an out-of-specification test result is confirmed, or when planned or unplanned maintenance or interventions are performed that have the potential to introduce microbial contamination.

HVAC system

(b) (4) facility has (b) (4) HVAC systems dedicated to the production areas with (b) (4) of systems supporting the manufacture of VOWST. AHU (b) (4) services Rooms (b) (4), and supporting airlocks. AHU (b) (4) are dedicated to manufacturing rooms (b) (4), including the associated airlocks, respectively. The specification of the AHUs are: (b) (4)

(b) (4). Seres provided the IQ/OQ/PQ of the HVAC system in amendment STN 125757/0.12.

In amendment STN 125757/0.34, Seres stated that the qualification reports provided were for the initial qualification performed in 2009. In 2015, (b) (4) altered the layout of Unit (b) (4) and installed (b) (4) (b) (4) uses (b) (4) air and (b) (4) air, while (b) (4) use (b) (4) air (b) (4). The applicant provided the HVAC requalification reports in amendment STN 125757/0.34. The results of the performance requalification show that the following tests met the acceptance criteria:

(b) (4)

There were no discrepancies during the requalification. The HVAC system is requalified (b) (4) where the routine EM viable and non-viable limits are applied.

Reviewer's comment: The results of the qualification for the utilities (compressed air, WFI, and HVAC systems) met the defined acceptance criteria and deviations were resolved, where applicable. The information provided appears acceptable.

Environmental monitoring

Seres provided the EMPQ for the (b) (4) facility in amendment STN 125757/0.34. EMPQ was performed per protocol VP-342-01 with the associated SOP (b) (4).005 and results are documented in VR-166. Seres stated that a risk assessment on the EM program was performed to evaluate the viable EM sampling locations (RAR-054) based on the room area, smoke studies, manufacturing activities, and historical data since 2017. The minimum number sampling locations/volumes was determined per (b) (4)

(b) (4) and are described in the protocol and SOP. Seres stated that equipment such as (b) (4) were not in the scope of the protocol; however, SOP (b) (4).005 includes the sampling points for all (b) (4).

The qualification was executed in (b) (4) for static and (b) (4) runs ((b) (4) different days) for dynamic conditions. During EMPQ under dynamic conditions, all equipment including (b) (4) were (b) (4) and the maximum number of personnel (b) (4) inside rooms (b) (4) were applied. All the EMPQ results for (b) (4) were below the following levels:

(b) (4)

(b) (4)

(b) (4)

The following limits were applied during the EMPQ both at rest and in operation:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

EM results are trended following the SOP.QC.016 with periodic reports issued. EM requalification is performed (b) (4).

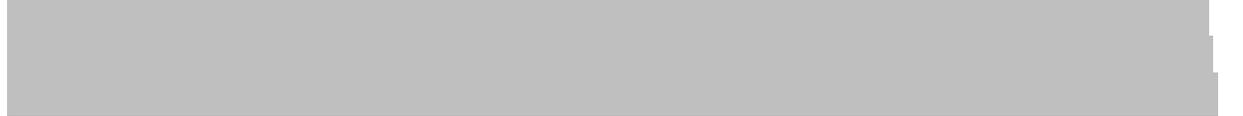
Reviewer's comment: The EMPQ results appear acceptable to demonstrate that the environment in the manufacturing areas is under control. While some sampling locations exceeded the limits, these sites are not inside the manufacturing suite and the results appear not to have affected the EM in the manufacturing rooms. Additionally, the applicant reinforced the sampling at these locations. The sampling locations appear to

be distributed in the individual space and include the airlocks. The routine EM limits appear acceptable based on the (b) (4) and considering the nature of the product. The information provided appears acceptable.

Equipment

(b) (4) uses single-use or cleaned and sanitized equipment for the manufacture of VOWST. Product-contact, reusable equipment are decontaminated by (b) (4) prior to cleaning per validated processes. The applicant states that all product-contact, reusable equipment used to manufacture VOWST is dedicated. Seres provided a list single-use, product-contact materials in amendment STN 125757/0.12, Attachment 2 and reusable equipment in Table 12. The applicant provided the qualification reports for the reusable equipment and below is a brief summary of the qualification of critical product-contact equipment.

(b) (4)



One page determined to be not releasabe: (b)(4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Reviewer's comment: The critical equipment identified for use in the manufacture of VOWST were qualified and met the acceptance criteria. The information provided appears acceptable.

Equipment Cleaning

The product-contact, reusable equipment ((b) (4) machines) is cleaned (b) (4), per SOP.PRD.016. In amendment STN 125757/0.12, Seres provided an interim report (VR-203 rev00) for the cleaning validation for the pieces from the three equipment and other equipment pieces (e.g., (b) (4), etc.). Seres stated that the parts sampled/tested during the cleaning validation were identified as worse-case ((b) (4)) per document RAR-070 (Risk Assessment Manufacturing, Equipment Cleaning Sample Site Assessment). A list and description of the equipment parts covered and tested during the validation were provided in Annexes 1 and 2 of the VR-203. A brief description of the same equipment cleaning validation was provided in 3.2.P.3.5 of the submission.

The validation was performed using (b) (4)

[Redacted]

In amendment STN 125757/0.36, Seres provided SOP.PRD.016, which describes the procedure for washing re-usable equipment parts, RAR-070 and the final cleaning validation report VR-203 rev01.

(b) (4)

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Reviewer's comment: The cleaning validation did not evaluate (b) (4) the cleaned equipment; therefore, the validation appears not to be acceptable. At the conclusion of the (b) (4) PLI, a Form FDA 483 was issued with an observation regarding the cleaning validation of product-contact equipment used to manufacture VOWST. In response to the FDA 483 item, Seres committed to perform cleaning verification testing for (b) (4) on the (b) (4) samples until a new cleaning validation protocol is executed. The cleaning validation will include (b) (4)

(b) (4)

(b) (5), (b) (7)(E)

Computer systems

Most of the information on computer systems was provided in amendment STN 125757/0.12. The computer systems supporting manufacturing are:

- (b) (4) is used for document and equipment management. The system is validated per report AQ-011 and AQ012-00. The report indicated that IQ, OQ, and PQ of the system were executed and OQ/PQ met the acceptance criteria for user requirements (editor/reader user creation and access privileges) with all deviations having been resolved.

In amendment STN 125757/0.12, Seres stated that validation was in progress for a new system, (b) (4), to be used for management and asset calibration, maintenance, and validation activities with a completion date 30 Nov 2022. (b) (4) will replace the (b) (4) system. In amendment STN 125757/0.34, Seres provided the summary of the completed qualification (report VR-205), which indicates that the system passed all test after all deviations (except for one) were resolved. Seres determined that the un-resolved, and still open, deviation (DEV-1271; System security – unable to test the system ability to enforce the user to change the password when the maximum password age is achieved) was minor and released (b) (4) for use.

- (b) (4) is the operating program used with the automatic filling and sealing machine (b) (4). The (b) (4) system is controlled using an HMI screen and is validated per report VR-183 and VR-105 (initial validation). The validation covered IQ, OQ, and PQ including results met acceptance criteria with all deviations having been resolved.
- Building Management System (BMS) validation included IQ/OQ and is documented in validation report VR-108 and addendum VR-108. The room assessed during the validation included manufacturing Room (b) (4) and all acceptance criteria were met.
- (b) (4) monitors the temperature and humidity of the facility and is validated per report VR-190. All the tests for the IQ/OQ/PQ met the specifications with (b) (4) data loggers with (b) (4) probes each distributed throughout the facility during the OQ phase. All deviations were resolved.

Reviewer's comment: The computer systems were qualified and met the acceptance criteria. The information provided appears acceptable.