

CBER CMC BLA Review Memorandum

BLA STN 125757

Fecal Microbiota Spores, Live-brpk; VOWST

Siobhan Cowley, PhD, Research Biologist, CBER/OVRR/DBPAP/LMPCI
Steven Derrick, PhD, Microbiologist, CBER/OVRR/DBPAP/LMPCI
Amy Yang, MS, Research Biologist, CBER/OVRR/DBPAP/LMPCI

1. **BLA#:** STN 125757

2. **APPLICANT NAME AND LICENSE NUMBER**

Seres Therapeutics, Inc; License #2262

3. **PRODUCT NAME/PRODUCT TYPE**

VOWST; Fecal Microbiota Spores, Live – brpk

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

1. Dosage form: Capsules
2. Strength/Potency: (b) (4) Spore Colony-forming Units (SCFU)^{(b) (4)}
3. Route of administration: Oral
4. Indication(s): For the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI.

5. **MAJOR MILESTONES**

Filing Meeting – 06 October 2022
Mid-Cycle Meeting – 19 December 2022
Late-Cycle Meeting – 22 February 2023
PDUFA action date – 26 April 2023

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Siobhan Cowley (SC), OVRP/DBPAP/LMPCI	DS manufacture, sections 3.2.S.1, 3.2.S.2.1 through 3.2.S.2.3; sections 3.2.S.3, 3.2.S.4, and 3.2.S.5; section 3.2.S.7 DP manufacture, sections 3.2.P.2.6, 3.2.P.5, 3.2.P.6, 3.2.P.8 Section 3.2.A.2, Adventitious Agents safety evaluation Module 5, clinical assay validation studies and exploratory endpoint studies

Steven Derrick (SD), OVRP/DBPAP/LMPCI	DS manufacture, section 3.2.S.6 DP manufacture, section 3.2.P.2.4 and 3.2.P.7
Amy Yang (AY), OVRP/DBPAP/LMPCI	DS manufacture, sections 3.2.S.2.4 and 3.2.S.2.6 DP manufacture, sections 3.2.P.1, 3.2.P.2, 3.2.P.3 and 3.2.P.4

7. INTER-CENTER CONSULTS REQUESTED

Not applicable.

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
08/26/2022	STN 125757/0	Complete submission
9/26/2022	STN 125757 /0.6	Updated stability results
10/19/2022	STN 125757 /0.10 (response to IR #6)	Assay SOPs and validation protocols
11/02/2022	STN 125757 /0.13 (response to IR #9)	PPQ protocols and reports; CCNA assay
11/16/2022	STN 125757 /0.15 (response to IR #9)	E&L information
12/05/2022	STN 125757 /0.19 (response to request during 11/28/2022 telecon)	Raw potency assay data
12/12/2022	STN 125757 /0.22 (response to IR #12)	Potency assay validation protocol
12/13/2022	STN 125757 /0.23 (response to IR #17)	Removal of (b) (4) susceptibility testing of bioburden results at (b) (4)
12/16/2022	STN 125757 /0.24 (response to IR #17)	Details on (b) (4) assay, Identity assay, (b) (4) assay validation report, (b) (4) verification report
12/28/2022	STN 125757 /0.27	Non-proprietary name justification
12/30/2022	STN 125757 /0.28 (response to IR #21)	Stability and storage times (SRM, (b) (4), DS); Shipper qualification studies (samples for donor screening, stability, and lot release testing)

1/03/2023	STN 125757 /0.29 (response to IR #20)	Potency and (b) (4) validation protocol
1/25/2023	STN 125757 /0.33 (response to IR #25)	(b) (4) assay qualification; (b) (4) assay responses
1/27/2023	STN 125757 /0.34 (response to IR #27)	The number of lots/year they intend to manufacture
1/30/2023	STN 125757 /0.35	Removal of (b) (4) warehouse location from the file (for storage)
2/10/2023	STN 125757 /0.39 (response to IR #23)	Potency assay validation report and (b) (4) acceptance criteria
2/14/2023	STN 125757 /0.40 (response to IR #30)	PPQ studies, E&L studies and container closure information
2/15/2023	STN 125757 /0.41 (response to IR #25)	Updated (b) (4) assay SOP
2/17/2023	STN 125757 /0.42 (response to IR #31 and #33)	Updated operating ranges; E&L studies information; updated stability information
2/23/2023	STN 125757 /0.45 (response to IR #33)	Potency assay control information
3/02/2023	STN 125757 /0.47 (response to IR #33)	Updated precision calculations in the potency assay validation report
3/14/2023	STN 125757 /0.51 (response to IR #37)	Stability (DP post-approval plan); E&L and (b) (4) responses
3/15/2023	STN 125757 /0.53 (response to IR #40)	Final potency assay validation report; adjusted DS release specification
3/24/2023	STN 125757/0.56 (response to IR#44)	Adjusted DS and DP release specifications
3/31/2023	STN 125757/0.59 (response to IR#51)	Revisions to the Lot Release Protocol
3/31/2023	STN 125757/0.60 (response to IR#48 and IR#52)	Updated dossier and stability (shelf life extension) reporting agreement
4/3/2023	STN 125757/0.61 (response to IR#53)	Agreement to submit changes to release specifications as a PAS
4/7/2023	STN 125757/0.64 (response to IR#56)	Applicant proposal to exclude bioburden testing from DP stability protocol
4/10/2023	STN 125757/0.65 (response to IR#57)	Dossier updates
4/11/2023	STN 125757/0.66 (response to IR#58)	Revisions to the Lot Release Protocol
4/12/2023	STN 125757/0.69 (response to IR#61)	Addition of (b) (4) bioburden testing to DP stability protocol

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)	(b) (4) White PE MB	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
DMF (b) (4)	(b) (4)	Plastics closures	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
DMF (b) (4)	(b) (4)	(b) (4)	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
DMF (b) (4)	(b) (4)	(b) (4) White PP MB	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
DMF (b) (4)	(b) (4)	(b) (4)	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
DMF (b) (4)	(b) (4)	Plastic Bottles	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4

DMF (b) (4)	(b) (4)	(b) (4)	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
DMF (b) (4)	(b) (4)	Empty Hard Capsules from Hypromellose	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
DMF (b) (4)	(b) (4)	(b) (4) Empty Hypromellose	yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
DMF (b) (4)	(b) (4)	Empty Hard Capsules from Hypromellose		Information pertinent to container closure was reviewed, assessed and documented in the memo by Steven Derrick in Section 3.2.P.2.4
MF (b) (4)	(b) (4)	(b) (4) Assay	yes	Information pertinent to this assay was reviewed, assessed and documented in the memo by Siobhan Cowley in Section 3.2.S.2.3

10. REVIEWER SUMMARY AND RECOMMENDATION (SC)
A. EXECUTIVE SUMMARY

Seres submitted a Biologics License Application (BLA; STN 125757/0) for licensure of Fecal Microbiota Spores, Live – brpk (VOWST) on 26 August 2022. VOWST is a fecal microbiota spore suspension encapsulated for oral delivery and indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI.

The source material for VOWST is donor human stool. Seres qualifies donors through screening via questionnaire, physical examination, and blood and stool testing for pathogens of concern. Seres administers the donor questionnaire, performs physical examinations, and collects donor stools at one of their Donor Collection Facilities (located in (b) (4), and Cambridge, MA). Seres ships donor blood and stool samples for testing to CLIA/CAP-accredited laboratories belonging to (b) (4). Seres ships

the stool donations at (b) (4) to their Cambridge, MA site, where they are stored at (b) (4). Seres only releases donor stool from quarantine for manufacture after review of acceptable donor screening results.

Seres initiates the manufacturing process at their Cambridge, MA site. (b) (4)

(b) (4)

(b) (4)

Seres formulates the DS to the desired spore concentration in $92\% \pm 4\%$ w/w glycerol in 0.9% saline, followed by capsule filling and over-encapsulation to create the Drug Product (DP). Seres fills the DP into 40 cc HDPE bottles, which are stored and shipped at (b) (4) prior to secondary packaging at (b) (4). Seres requested a 36-month shelf life for VOWST stored at (b) (4). The dating period for the final drug product begins on the Date of Manufacture, which Seres defines as the date of the first day of capsule filling of the formulated bulk. Seres submitted results from stability studies to support their shelf life. Data from these studies demonstrate product stability for 36 months when stored at (b) (4) 2-8°C, and 25°C. The VOWST label instructs patients to store VOWST at 2-25°C.

We identified deficiencies in Seres' potency assay validation studies, (b) (4) assay, and donor screening assays:

1. We requested that Seres submit additional information on the verification and validation/qualification of some of their stool donor screening methods. Seres provided the requested information, which included verification data demonstrating that an FDA-cleared assay performed according to the manufacturer's standards, and validation/qualification data for two laboratory-developed stool assays.
2. In their initial submission, Seres did not adequately validate their potency assay. We requested Seres repeat their validation study to address the deficiencies we identified. Seres repeated their validation study and submitted the data for review.
3. We determined that Seres' method to assess (b) (4) was not adequate and we requested they use their potency assay to measure (b) (4)

Seres addressed the above deficiencies and all other deficiencies we identified during our review. The CMC product information and data in this BLA support manufacturing consistency and product quality. We recommend approval of this BLA.

B. RECOMMENDATION

I. APPROVAL

Based on the CMC information and data provided in this application, we recommend approval of this BLA. Lot release will be performed via protocol review only. Please refer to the DBSQC reviewer’s memo for additional information on the Lot Release Protocol.

Manufacturing facilities:

1. Seres Therapeutics, Inc.
200 Sidney St.
Cambridge, MA 02139
FEI number: 3012828816
DUNS number: 070561786

2. (b) (4)
FEI number: (b) (4)
DUNS number: (b) (4)

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Siobhan C. Cowley, PhD, Research Biologist, DBPAP/LMPCI	Concur	
Steven Derrick, PhD, Microbiologist, DBPAP/LMPCI	Concur	
Amy Yang, MS, Biologist, DBPAP/LMPCI	Concur	
Earle S. Stibitz, PhD, Chief, DBPAP/LMPCI	Concur	

Jay E. Slater, MD, Director, DBPAP	Concur	
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Review of CTD
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Module 3

3.2.S DRUG SUBSTANCE¹

(b) (4)

(b) (4)

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

(b) (4)

3.2.P DRUG PRODUCT²

3.2.P.1 Description and Composition of the Drug Product (AY)

VOWST consists of Firmicutes bacterial spores derived from stool collected from qualified healthy human donors. The spores are formulated in 88% to 96% w/w glycerol in 0.9% saline, filled into inner capsules (white, size 0 hypromellose (hydroxypropyl methylcellulose) [HPMC]), and over-encapsulated (white, size 00 HPMC with gellan gum capsules). “SER109” is printed on the outer capsule in blue ink. VOWST is packaged in a single high-density polyethylene (HDPE) 40 cc. bottle, each containing 12 capsules, sealed by (b) (4) sealing with a child-resistant cap. VOWST is for oral administration.

3.2.P.2 Pharmaceutical Development (AY)

The pharmaceutical development of VOWST includes sections outlining the components, formulation, encapsulation, and critical quality attributes of the DP. Additionally, Seres provided information on the development of the DP manufacturing process and assessment of suitability of materials for the container closure system.

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance (AY)

The DS consists of Firmicutes bacterial spores derived from the stool of qualified healthy human donors. The fecal spores are the active ingredient in the DP. The DS bacterial spore suspension is formulated in (b) (4) w/w glycerol (b) (4) with 0.9% w/w saline.

3.2.P.2.1.2 Excipients (AY)

The compendial and non-compendial excipients and their respective functions in the VOWST DP are listed below:

(b) (4) Excipients:

- (b) (4) – To optimize the formulation for (b) (4) and stabilize the spore active ingredient. It is compatible with the HPMC capsule.
- Sodium chloride – To prepare 0.9% saline solution
- (b) (4) – To prepare 0.9% saline solution and (b) (4) solution (for (b) (4) purposes).

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development (AY)

Seres states that the DP formulation was designed to achieve DP stability and delivery to the appropriate anatomical location. Seres states that phase 2/3 formulation development was the result of several formulation and process improvements compared to their phase 1 product, which included the following:

(b) (4)



Seres states that other than the inner capsule sealing step, the Phase 3 and commercial DP formulations remain unchanged from the Phase 2 formulation.

3.2.P.2.2.2 Overages

Not applicable.

3.2.P.2.2.3 Physicochemical and Biological Properties (AY)

The DS contains a bacterial spore suspension formulated in (b) (4) w/w glycerol (b) (4) with 0.9% w/w saline. To make the final DP, Seres performs the following steps:

- (b) (4)
- Seres fills the FB into HPMC inner capsules and over-encapsulates with the HPMC/gellan gum outer capsules. The final filled DP has a target dosage

strength of 1×10^6 - 3×10^7 SCFU per capsule. Each DP lot is derived from a single donor.

Seres states that the DP excipients must be acceptable for oral administration and must be obtained from qualified sources. Seres states that the pharmacokinetic characteristics of VOWST must meet the requirements of the capsule (b) (4) test, and that the microbiological impurities of VOWST must not exceed those specified in (b) (4) for non-sterile, aqueous preparation, oral dosage forms. Seres indicates that once the capsule shells are dissolved, the bacterial spores are expected to disperse well in an aqueous environment. Since the over-encapsulated formulation behaves like immediate release capsules, Seres uses a (b) (4) per (b) (4) for release of DP.

3.2.P.2.3 Manufacturing Process Development (AY)

Seres made several changes from DP Process Version B (phase 2) to E (phase 3). These changes include:

(b) (4)



Seres made four additional changes from Version E to the PPQ batches which include:

(b) (4)



Seres states that the product formulation did not change between the clinical and commercial lots. A summary comparison of the batch size, equipment, and materials used between the Phase 3, PPQ, and commercial DP lots is provided in Table 5 in Section 3.2.P.2.3.2.2 of the submission.

3.2.P.2.4 Container Closure System (SD)

The container closure system for VOWST DP capsules is a 40 cc, opaque, white, high-density polyethylene (HDPE), wide-mouth pharmaceutical bottle with an induction foil seal and a polypropylene child-resistant cap. Seres provided a description in Table 1 of the Container Closure System document under Section 3.2.P.2, Container Closure System. During product development, The applicant tested bottles that contained either

(b) (4) 12 capsules. For commercial distribution, Seres will use bottles that contain 12 capsules (the full 3-day dosing regimen).

Seres lists the following critical quality attributes that they considered in their evaluation for the container:

(b) (4)

Capsules

Seres provided LoAs for CMC information for the HPMC (hydroxypropyl methylcellulose; Hypromellose) inner capsule ((b) (4) ; size 0) and HPMC/gellan gum ((b) (4) ; size 00) outer capsule. Both the outer and inner capsules are composed of HPMC and the opacifier is (b) (4) . Tables 3 and 4 of Section 3.2.P.4.1, Specifications, list the composition of the inner and outer capsules respectively. HPMC is a (b) (4)-based substance derived from cellulose and is considered by the FDA to be safe for human consumption (21 CFR 172.874); thus, E&L assessments are not required for the capsule. Seres also provided quality control specifications with acceptance criteria for the inner and outer capsules, which are summarized in Tables 6 and 7 of this section, and include Identity – (b) (4)

(b) (4) Seres provided sample CoAs for the capsules and I find them acceptable.

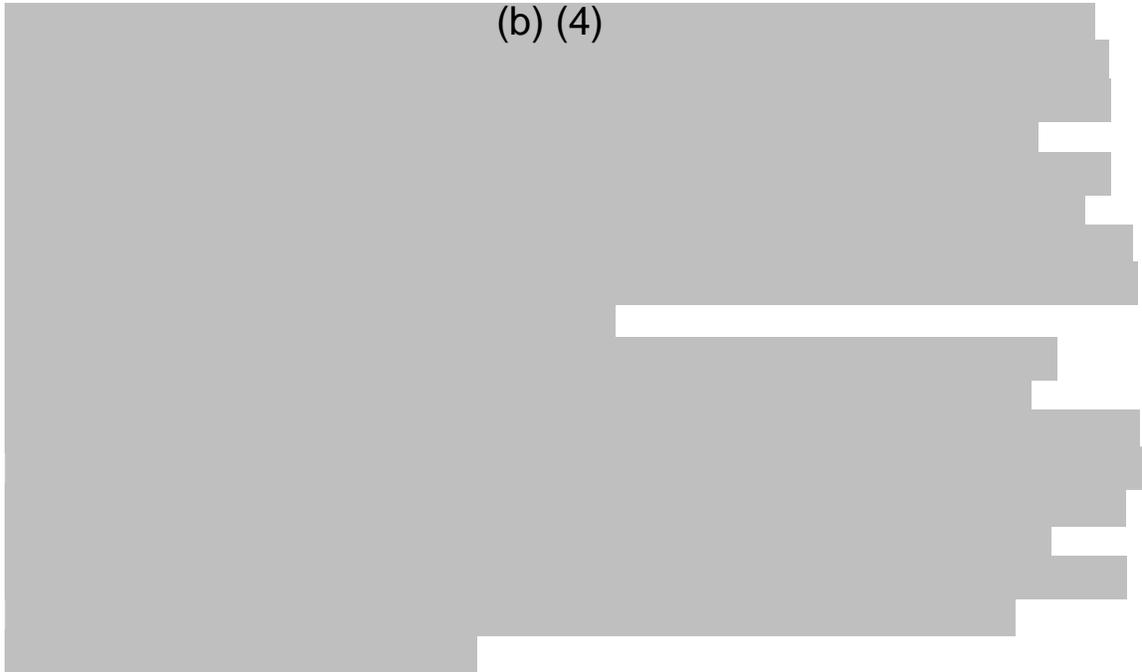
HDPE Bottle

The FDA considers HDPE (code 2 plastic) to be a food grade plastic per 21 CFR 177; thus, E&L assessments are not necessary for the capsule container. These plastic containers comply with (b) (4) for polyethylene containers for non-volatile residues, heavy metals and buffering capacity. Also, the HDPE material matches reference (b) (4) and (b) (4) for a (b) (4) HDPE reference standard. Seres provided certificates of compliance for the bottle, cap and foil liner under Section 3.2.P.7, Container Closure System. The foil liner seal consists of an aluminum foil layer, polyethylene terephthalate layer and a (b) (4) seal layer consisting of medium density polyethylene.

Seres tested the container closure for the following:

(b) (4)

(b) (4)



Caps

Seres provided test results from the manufacturer of the container caps ((b) (4) 33 mm (b) (4) Caps), which showed that the caps used for the VOWST DP are child-resistant. Testing was done according to U.S. Consumer Product Safety Commission guidelines (16 CFR part 1700.15 and 1700.20) using 100 children aged 42 – 51 months and results confirmed that the closures meet the requirements for poison prevention and child resistance.

3.2.P.2.5 Microbiological Attributes (SC)

VOWST consists of live Firmicutes bacterial spores derived from qualified healthy human donor stool and is a non-sterile product. The applicant screens stool donors for infectious diseases, which I review in detail in Section 3.2.S.2.3.

The applicant tests the DP for bioburden as part of lot release. Please see the DBSQC reviewer’s memo for details on the bioburden assay. The bioburden acceptance criteria are:

(b) (4)



In addition to the aforementioned controls, the applicant's manufacturing process includes:

- An ethanol treatment step that can reduce the presence of pathogens in the product (reviewed in Section 3.2.A.2).
- Formulation of the DP to provide a final concentration of $92 \pm 4\%$ w/w glycerol, which ensures the DP maintains a (b) (4) that inhibits microbial proliferation.

I find the analytical procedures and acceptance criteria for the product's microbiological attributes acceptable.

3.2.P.2.6 Compatibility (SC)

Not applicable.

Overall Reviewer's Assessment of Section 3.2.P.2 (SD):

In IR#30 (06 February 2023) I requested additional information regarding the applicant's assessments of (b) (4), the method for monitoring (b) (4) from the ink used to label the outer capsules, and an explanation of the difference in their proposed (b) (4) acceptance criteria for DP release and stability. In STN 125757/0.40 (14 February 2023), Seres submitted the relevant technical reports to address the gaps I identified regarding their assessment of (b) (4):

- Technical Report: "Projected (b) (4) of VOWST DP (b) (4) 12 capsules/bottle over Time" (FM-21-00009), which provides details for how (b) (4) values are predicted over several months.
- Determination of (b) (4) for High Density Polyethylene Screw-cap Bottles authored by PQRI Container Closure Working Group, which describes the study to find ways to improve (b) (4).

In response to my request about monitoring (b) (4) from the ink, Seres also submitted:

- Documentation from the capsule supplier ((b) (4)) that explained the method for monitoring (b) (4)
- Ink Quantitative Information Sheet ((b) (4))
- Technical Reference File 221A, (b) (4)
- Work Instruction for (b) (4) Analysis documents ((b) (4))

I reviewed these documents and find the responses acceptable.

Regarding the differences in acceptance criteria for (b) (4), Seres clarified that for lots manufactured prior to 2021, they used an acceptance criterion of (b) (4) for their stability studies as they gained more experience with the container closure system at various storage temperatures. For lots manufactured starting in 2021, they adjusted the acceptance criterion to (b) (4). Seres further stated that their proposed stability

criterion for DP release testing is set lower than the acceptance criterion for stability ^{(b) (4)} for DP release versus (b) (4) for stability) to allow for (b) (4) over time while still remaining below levels that would support microbial growth ((b) (4)). I find the applicant’s responses acceptable, especially since (b) (4) testing is integrated into the VOWST stability program and will be measured routinely over time.

I have reviewed all the information in this section and find it acceptable.

3.2.P.3 Manufacture

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

Table 9: VOWST Drug Product Manufacturers

Manufacturer	Responsibility
Seres Therapeutics, Inc. 200 Sidney St. Cambridge, MA 02139 FEI number: 3012828816 DUNS number: 070561786	<ul style="list-style-type: none"> DP release and stability testing: identity, bioburden, (b) (4), appearance, container closure integrity test
Seres Therapeutics, Inc. (b) (4) MA (b) (4) FEI number: (b) (4) DUNS number: (b) (4)	<ul style="list-style-type: none"> DP release and stability testing: identity, potency, bioburden, (b) (4)
(b) (4)	<ul style="list-style-type: none"> DP manufacture DP primary packaging DP storage
(b) (4)	<ul style="list-style-type: none"> Formulated bulk release testing: (b) (4)
(b) (4)	<ul style="list-style-type: none"> Formulated bulk release testing: (b) (4)
(b) (4)	<ul style="list-style-type: none"> DP secondary packaging, labeling, storage, and distribution

(b) (4)	<ul style="list-style-type: none"> Storage of DSM, SRM, and DS stability samples
(b) (4)	<ul style="list-style-type: none"> Storage of DSM, SRM, and DS stability samples
(b) (4)	<ul style="list-style-type: none"> Microbial identification

3.2.P.3.2 Batch Formula (AY)

Seres provided a list of the components used and the amounts required to produce one DP lot in the table below:

Table 9: Proposed DP Batch Formula

Component	Grade	Function	Minimum batch (b) (4) Formulated Bulk)	Maximum batch (b) (4) Formulated Bulk)
VOWST DS	NA	Active Ingredient	(b)	(4)
Glycerol	(b) (4)	Excipient	(b)	(4)
Sodium Chloride		Excipient		
(b) (4)		Excipient		
Inner Capsule		Primary capsule, sealed		
Outer Capsule		Appearance		
(b) (4) solution		(b) (4)		

Overall Reviewer’s Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2 (AY):

Seres states that their maximum batch size can produce up to (b) (4) capsules based on a maximum manufacturing limit of (b) (4) of FB. I did not agree with their proposed maximum batch size because the applicant did not provide data to support the manufacture of (b) (4) capsules in their PPQ studies. The applicant’s PPQ lots produced the following:

- (b) (4) capsules (PPQ lot (b) (4))
- (b) (4) capsules (PPQ lot (b) (4))
- (b) (4) capsules (PPQ lot (b) (4))

In IR #30 (06 February 2023), I requested that Seres revise their maximum batch size based on available data. In STN 125757/0.40 (14 February, 2023), Seres provided the FB (b) (4) and numbers of capsules produced from (b) (4) PPQ and (b) (4) engineering lots. The largest batch sizes were the following:

- Engineering lot (b) (4) (FB (b) (4) of (b) (4) produced (b) (4) capsules,
- Engineering lot (b) (4) (FB (b) (4)) produced (b) (4) capsules,
- PPQ lot (b) (4) (FB (b) (4) of (b) (4) produced (b) (4) capsules.

Based on the data from these lots, Seres agreed to specify a maximum batch size of (b) (4) capsules.

Sered states that the quantity of FB is dependent on the (b) (4) and quantities of DS available from a single donor. They noted that it is generally not possible to successfully target an exact batch size. Seres agreed that they will submit a post-approval supplement should they decide to modify their maximum batch size as they obtain more manufacturing data.

The information submitted in this section is acceptable.

3.2.P.3.3 Description of Manufacturing Process (AY)

Seres states that the DP manufacturing process is divided into (b) (4) major operations which are (b) (4) and Primary Packaging. Operations in the DP manufacturing area are conducted at controlled (b) (4) temperature ((b) (4)) and humidity ((b) (4)). Seres states that the entire process must be (b) (4) .

(b) (4)

(b) (4)

(b) (4) Primary Packing: Seres packs 12 capsules into each 40 cc white HDPE bottle with a foil induction seal and child-resistant closure, performs a (b) (4) to confirm the number of capsules, and bulk-packages the DP bottles into transport boxes for storage and shipment to the secondary packaging facility for labeling.

The critical process parameters for (b) (4) steps are summarized in the next section (3.2.P.3.4, Controls of Critical Steps and Intermediates).

Overall Reviewer’s Assessment of Section 3.2.P.3.3 (AY):

The information submitted in this section is acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates (AY)

Seres established a list of critical process parameters (CPPs) and critical in-process controls (IPCs) to ensure the quality of each step in the DP manufacturing process. The critical process parameters for (b) (4) steps are summarized in the table below:

(b) (4)

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

(b) (4)

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

(b) (4)

Seres provided only one-sided limits for most of the acceptable/operating ranges for their DP process parameters. Therefore, I sent IR#30 (06 February 2023) requesting that Seres define both upper and lower limits for these parameters. In STN 125757/0.42 (17 February 2023), Seres updated their operating ranges to include upper and lower limits based on their PPQ runs. All process parameter results for the PPQ lots were within the newly proposed operating ranges. Seres' response is acceptable.

Overall, I find the information submitted in this section to be acceptable.

3.2.P.3.5 Process Validation and/or Evaluation (AY)

For their process validation study, Seres manufactured three DP PPQ lots ((b) (4)) at commercial scale to demonstrate that the manufacturing process is repeatable and consistently produces lots that meet their pre-determined quality attributes. Process parameter results of all PPQ lots were within the operating ranges and all lots met the DP release specifications.

A list of the critical process parameters (CPPs), their associated acceptable ranges, the operation ranges for each of the DP manufacturing unit operations are summarized in Section 3.2.P.3.4 (Controls of Critical Steps and Intermediates) of this memo.

Overall Reviewer’s Assessment of Section 3.2.P.3.5 (AY):

Seres did not provide the statistical analysis report comparing their DP PPQ runs with their historical clinical manufacturing data. For this reason, I sent IR#30 (6 February 2023) to request this report. In STN 125757/0.40 (14 February 2023), Seres compared the process performance indicators and release testing data sets for three PPQ and (b) (4) clinical DP lots. Seres used (b) (4) to assess variability, identify outliers, and test for equivalency. The (b) (4) results for all (b) (4) of the process performance indicators showed comparability between the PPQ and clinical lots. For DP release testing, Seres’ potency test results were comparable between the PPQ and clinical lots, while their (b) (4) results did not show comparability when analyzed using (b) (4). However, their (b) (4) analyses showed comparable (b) (4) with overlapping values between (b) (4). Seres stated that they did not evaluate the remaining release test results ((b) (4), identity, bioburden, (b) (4), appearance and physical characteristics, container closure integrity, and (b) (4)) because they are non-numeric qualitative tests and cannot be statistically analyzed. Seres explained that the (b) (4) analysis is limited because their data sets are small and non-normal (with only (b) (4) PPQ lots). Seres will continue to collect and evaluate DP process and release data as part of their continued process verification, per SOP-0477. Overall, the statistical analysis results indicate that the processes for Seres’ PPQ and clinical DP lots are comparable.

The information submitted in this section is acceptable.

3.2.P.4 Control of Excipients (AY)

3.2.P.4.1 Specifications

Seres submitted the Certificates of Analyses (COAs) for Glycerol and Sodium Chloride.

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

Seres states that the analytical procedures for (b) (4) excipients including Glycerol, Sodium Chloride, and (b) (4) are tested in accordance with (b) (4).

3.2.P.4.4 Justification of Specifications

Seres states that the specifications for (b) (4) excipients are aligned with their respective (b) (4). All analytical procedures are (b) (4) and there are no acceptance criteria or tests beyond those included in the (b) (4). In addition, method verifications were completed as required per (b) (4). The internal testing for (b) (4) materials is based on the manufacturer’s certificate of analysis and

		(b) (4)	
(b) (4)			See DBSQC reviewer's memo
(b) (4)			See DBSQC reviewer's memo
Appearance and physical characteristics	Visual inspection (TM-0009)	(b) (4)	See DBSQC reviewer's memo
Container closure and integrity (CCIT)	(b) (4)	(b) (4)	See DMPQ reviewer's memo
(b) (4)	(b) (4)	(b) (4)	(b) (4)

The sponsor describes the methods listed in Table 5 in detail in Section 3.2.P.5.2 of the submission.

In a meeting with DBSQC on 05 October 2022, we agreed that DBSQC would be responsible for review of the Identity, Bioburden, (b) (4), and Appearance methods, DMPQ would be responsible for review of the CCIT method, and DBPAP would be responsible for review of the Potency assay and (b) (4) methods. Please refer to the DBSQC and DMPQ reviewer's memos for review of the methods not described below.

- Potency:** The applicant's potency assay acceptance criterion during their phase 2/3 clinical studies was (b) (4). The applicant updated their potency assay acceptance criteria for licensure by calculating a tolerance interval (TI) on

release data from (b) (4) DP lots manufactured for their SERES-012/013 phase 3 clinical studies and their (b) (4) PPQ lots. Given the limited number of lots available for their analysis, Seres chose a TI which brackets (b) (4) population coverage (approximately (b) (4) standard deviations) and (b) (4) confidence. Seres calculated their acceptance limits to be (b) (4) or (b) (4) SCFU/capsule (note: one capsule contains (b) (4)). Please see below for further discussion on my communications with the applicant regarding their potency acceptance limits.

2. (b) (4): Seres used their (b) (4) assay and a modified (b) (4) analysis to assess (b) (4) during their phase 2/3 clinical studies and submitted this approach for licensure. However, with the statistical review team, we determined that (b) (4) content is not highly correlated with potency and varies significantly from batch to batch; therefore, (b) (4) content is not an appropriate method to measure (b) (4) for DP release. We sent IRs to Seres regarding our concerns, which are outlined in detail at the end of this section. After these discussions, Seres changed their (b) (4) method to calculate a (b) (4)-coverage/(b) (4)-confidence tolerance interval (TI) using the potency measurements (TM-0006) of (b) (4) capsules; the resulting TI must fall within (b) (4) for the batch to pass lot release.

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

1. **Potency:** The applicant's proposed acceptance criteria range are acceptable. However, because Seres based their specifications on a limited number of lots, in IR#40 (10 March 2023) we asked them to re-evaluate their acceptance criteria range and TI parameters when (b) (4) and (b) (4) DP lots have been produced. In STN 125757/0.53 (15 March 2023), Seres committed to re-evaluate and potentially revise their acceptance criteria when (b) (4) and (b) (4) lots have been produced. However, Seres stated that they will provide the information in an Annual Report, which is not acceptable. Therefore, in IR#53 (30 March 2023), I informed Seres that they must submit any changes to any lot release specifications in a PAS. In STN 125757/0.61 (3 April 2023), Seres agreed to submit this information in a PAS.

In IR#44 (20 March 2023), together with the statistical reviewers, we asked the applicant to recalculate their DP potency acceptance criterion using (b) (4) data rather than (b) (4) because their data are normally distributed on the (b) (4) scale. In addition, we asked the applicant to provide both normal scale (b) (4) and (b) (4) units in their specifications and Lot Release Protocol (LRP), and to include a conversion of the (b) (4) results into SCFU/capsule to align with the dose information on the label, which is provided as SCFU/capsule for patient clarity. In STN 125757/0.56 (24 March 2023), STN 125757/0.65 (10 April 2023), and STN 125757/0.66 (11 April 2023), Seres updated their potency specifications as requested. Therefore, the applicant's final DP potency acceptance criteria are:

- Normal scale: (b) (4)
- (b) (4) scale: (b) (4)

2. (b) (4) : As noted above, I found the applicant's (b) (4) method (b) (4) assay and (b) (4) unacceptable. On 12 December 2022, we sent Seres IR#20 detailing our concerns. After further discussions, Seres chose to validate their potency assay (TM-0006) to assess (b) (4). Their new method uses the potency of (b) (4) capsules to generate a (b) (4)-coverage (b) (4)-confidence TI, and the TI is compared to a pre-specified range. Our communications with Seres on this subject are summarized in Sections 3.2.P.5.2 and 3.2.P.5.3.

In STN 125757/0.39 (10 February 2023), Seres established their (b) (4) acceptance criterion by analyzing data from (b) (4) DP lots (report CNSLT-SERS-2023-001). Seres' (b) (4) acceptance criterion requires that their TI fall within (b) (4).

Seres' (b) (4) limits are narrower than their potency assay acceptance limits ((b) (4) (b) (4)), and therefore may result in rejection of good batches. Therefore, in IR#35, we informed the applicant that they may want to revisit their (b) (4) acceptance criterion after licensure. In STN 125757/0.47 (02 March 2023), Seres agreed to revise their criterion, if necessary, and submit it as a PAS. I found this information to be acceptable.

Seres has addressed all CMC concerns related to their DP release specifications.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures (SC)

Analytical methods for the DP release tests are listed in Table 5 above (3.2.P.5.1 and 3.2.P.5.6). Please refer to the DBSQC and DMPQ reviewer's memos for methods not reviewed here.

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.5.4 Batch Analyses (SC)

Seres provided a summary list and the certificates of analysis for all product batches (a total of (b) (4)) manufactured for use in their phase 2/3 clinical studies and PPQ studies. Seres included the batch number, manufacture date, (b) (4) FB processed, the number of capsules manufactured, and release specification results. All batches met their acceptance criteria and passed release testing.

3.2.P.5.5 Characterization of Impurities (SC)

Please refer to Section 3.2.S.3.2 for review of impurities and their control during (b) (4) manufacturing.

Because Seres performs an (b) (4) step during (b) (4) manufacturing, they measure (b) (4) in their (b) (4) via (b) (4). The release specification for (b) (4) is (b) (4). Please see the DBSQC reviewer’s memo for review of the (b) (4) assay.

In addition, to control for microbial contamination, the applicant performs bioburden testing as part of DP lot release (please see Section 3.2.P.5.1). Please see the DBSQC reviewer’s memo for review of the bioburden assay.

Overall Reviewer’s Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5 (SC):

The information Seres submitted in these sections is acceptable.

3.2.P.6 Reference Standards or Materials (SC)

Please refer to Section 3.2.S.5 for information on the potency assay (TM-0006) assay control material.

3.2.P.7 Container Closure System (SD)

Please also see my review of the capsules, bottle and cap in Section 3.2.P.2.4.

Seres also provides information on the VOWST DP container closure system in Section 3.2.P.7 (Table 1) of the submission. This table also contains links to Letters of Authorization (LoA) from manufacturers of different components of the container closure for Seres to cross-reference Drug Master Files in their submission ((b) (4)). Tables 2 and 3 from this section contain release specifications for the opaque, white, HDPE, wide-mouth pharmaceutical bottle and child-resistant cap, respectively. Seres states that packaging materials must be supplied with a Certificate of Analysis and must pass visual inspection criteria upon receipt. The applicant provided drawings for the DP bottle, cap and foil seal from the manufacturers as well as all relevant Declaration or Certificate of Compliance documents in this section.

Using methodology outlined in m3.2.S.2.6.1 of Section 3.2.S.6, “Manufacturing Process Development – Process Control Strategy and Characterization” of the submission, Seres performed a risk assessment of extractables and leachables for container closure product contact components using industry guidance for extractables testing of polymeric single-use components. Based on the route of administration (oral) and the likelihood of interaction between capsules and components, the assessment ranked the material safety concern as low risk and, thus, Seres deemed it acceptable for use. Results from (b) (4) studies for the container closure are discussed above under Section 3.2.P.2.4, Container Closure System. Seres states that the HPMC capsules are compatible with glycerol in Table 1 of Section 3.2.P.4.1 of the submission.

Overall Reviewer’s Assessment of Section 3.2.P.7 (SD):

As noted in previous sections of this memo (3.2.P.2.4), the capsules and bottle are considered food grade and safe for human consumption; therefore, E&L assessments are not necessary. Section 3.2.P.2.4 of the memo also covers the applicant’s evaluation of the suitability of the container with respect to protection from (b) (4) . The applicant did not evaluate prevention of microbial ingress since there is no claim for sterility for VOWST DP; however, Seres performs Container Closure Integrity, Bioburden and (b) (4) testing for DP release. In addition, Container Closure Integrity and (b) (4) testing are components of the DP stability program. The information provided by Seres as well as stability data indicate that the DP and container closures are suitable and compatible.

I defer to the DMPQ reviewer as to the appropriateness and validity of the applicant's shipping validation studies.

3.2.P.8 Stability (SC)

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

Proposed product storage and shipping:

- Phase 3 clinical studies: Seres stored the DP at (b) (4) prior to distribution, at (b) (4) in the clinic, and participants stored the DP at 2 - 8°C.
- Commercial DP lots: Seres stores the DP (b) (4) at (b) (4) prior to shipment (b) (4) to either (b) (4) (for storage) or (b) (4) (for secondary packaging). Once the DP arrives at either location, it is stored at (b) (4) and all additional shipping is at (b) (4). Of note, the applicant does not state whether their stability samples underwent the same (b) (4) as the commercial DP prior to long-term storage.
- Seres proposes a DP shelf life of 36 months at (b) (4), with temperature excursions permitted (b) (4).

Stability studies:

Seres is performing stability studies on (b) (4) clinical and (b) (4) PPQ lots:

- Phase 3 clinical study (SERES-012/013) lots:

Seres provided 36 months of stability results for (b) (4) clinical lots (Lot numbers (b) (4) (b) (4)). Seres tested identity (b) (4), potency (SCFU), (b) (4), appearance, and container closure integrity (CCIT) at all time points (0, 1, 3, 6, 9, 12, 18, 24, and 36 months). All (b) (4) lots were stored under the following conditions:

(b) (4)

2-8°C

- 25°C/ (b) (4)

- PPQ lots:

Seres provided 6 months of stability results for (b) (4) PPQ lots (Lot numbers (b) (4) (b) (4)). All (b) (4) PPQ lots are stored under the following conditions and the studies are ongoing:

- 2-8°C for up to 36 months: Seres is testing potency, (b) (4), and appearance at 0, 3, 6, 9, 12, 18, 24, and 36 months. In addition, Seres is testing identity (0 and 36 months), (b) (4) (0, 12, 24, and 36 months) and CCIT (0, 12, 24, and 36 months).
- 25°C/ (b) (4) for up to 36 months: Seres is testing potency (SCFU), (b) (4), and appearance at 0, 3, 6, 9, 12, 18, 24, and 36 months. In addition, Seres is testing identity (0 and 36 months), (b) (4) and CCIT (0, 12, 24, 30, and 36 months).

(b) (4)

(b) (4)

- (b) (4)

The applicant stored their clinical stability samples in the same containers as those used for the commercial process (induction-sealed 40 cc white wide-mouth round HDPE bottles with white 33 mm ribbed side text tops). The clinical lot stability samples were stored as (b) (4) capsules/bottle whereas the commercial DP and PPQ stability samples are stored as 12 capsules/bottle. I do not consider this a concern as the stability samples had a higher air-to-surface ratio than the commercial DP and therefore represent a worse-case scenario.

Stability results for all the lots and temperature conditions met the commercial lot release acceptance criteria. Of note, the SCFU results for clinical lot samples stored at 25°C/(b) (4) indicate a downward trend at later time points (which included a (b) (4) month SCFU time point for one lot) but remain above the lower specification limit for potency. In addition, long-term storage at (b) (4) indicates (b) (4) SCFU trends at later time points (however, they remain (b) (4) the lower potency specification limit). Therefore the DP appears to be sufficiently stable to support 36 months of storage at (b) (4). However, to avoid confusion, the applicant must set a temperature storage range with upper and lower limits for the label. Our communications with the applicant on issues related to product stability are outlined in more detail below.

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

The applicant proposes to monitor a minimum of (b) (4) per year for stability at 25°C/(b) (4). Seres will monitor potency, (b) (4), and appearance (at 0, 6, 12, 24, 36, and (b) (4) months), and identity, (b) (4), and CCIT (at 0, 12, 24, 36, and (b) (4) months). The acceptance criteria are the same as for lot release, except for (b) (4), which has a higher specification of (b) (4) (please see Section 3.2.P.2 for communications with the applicant on this subject).

Seres states that they will investigate and report all out of specification results in their Annual Reports. Seres also states they will provide any extensions to the DP expiry period (based on real-time data) in an Annual Report. However, I do not consider an Annual Report an appropriate method to report changes to the DP expiry period.

Since the product will be stored at 2-25°C, and their ongoing PPQ lot stability samples do not monitor stability at 2-8°C, the applicant should also monitor the stability of commercial batches stored at 2-8°C after licensure. In addition, since the product is not sterile and the applicant has increased the DP long-term storage temperatures from (b) (4) and (b) (4) during their phase 3 clinical studies to 2-25°C for their commercial lots, the applicant should include bioburden testing in their stability protocol. Our communications with the applicant on these matters are outlined in more detail below.

Overall Reviewer’s Assessment of Section 3.2.P.8 (SC):

In IR#21 (16 December 2022), I asked the applicant to define their date of manufacture and to specify when they remove samples for DP lot release and stability testing. In STN 125757/0.28 (30 December 2022), the applicant stated that their date of manufacture is the first day of capsule filling of FB into size 0 capsules. This date applies to both their commercial manufacturing lots and stability samples. Seres removes samples for lot release and stability testing after primary packaging into 40 cc bottles. I find this information acceptable.

To determine whether the applicant’s stability samples underwent the same (b) (4) as the commercial lots, in IR#31 (09 February 2023) I asked the applicant to clarify whether their stability samples were stored and shipped at (b) (4) prior to long-term storage. I also asked the applicant to clarify how long they stored their stability samples at (b) (4) prior to initiation of their stability protocol, and the amount of time they will store commercial DP at (b) (4) prior to shipment to (b) (4) or (b) (4). In STN 125757/0.42 (17 February 2023), Seres responded that their stability samples were stored/shipped at (b) (4) for an average of (b) (4) days prior to transition to the temperature conditions in their stability protocols. Seres states that storage of their commercial DP at (b) (4) will not have a time restriction. Since the DP is stable at both (b) (4) and (b) (4) for up to (b) (4) months, I find this plan acceptable.

To ensure the product is stored correctly by patients, in IR#37 (07 March 2023) I asked the applicant to set a specific storage temperature range and remove references to temperature excursions on the label. In STN 125757/0.51 (14 March 2023), the applicant agreed to set storage at 2-25°C for 36 months and to remove references to temperature excursions from the label. These changes are acceptable.

To evaluate the adequacy of the applicant’s post-licensure stability program, I asked Seres to clarify the number of lots per year they anticipate manufacturing post-licensure (IR#27; 25 January 2023). In STN 125757/0.34 (27 January 2023), the applicant stated that they plan to manufacture (b) (4) lots per year at launch and will ramp up to (b) (4) lots per year over the following (b) (4) years. To ensure the applicant captures sufficient data to ensure stability at 2-25°C, I asked them to monitor a minimum of (b) (4) batches per year and to include samples stored at 2-8°C in their stability program (IR#37; 07 March 2023). In STN 125757/0.51 (14 March 2023), the applicant submitted an updated post-

approval stability protocol to monitor a minimum of (b) (4) batches per year stored at both 2-8°C and 25°C/(b) (4).

To ensure that product bioburden remains at acceptable levels during storage at 2-25°C, I asked the applicant to perform annual bioburden testing as part of their post-licensure stability program (IR#56; 4 April 2023). In STN 125757/0.64 (7 April 2023), the applicant proposed to exclude bioburden testing from their DP stability program because the (b) (4) of their product is expected to inhibit microbial growth and that this may be used as a rationale to reduce the frequency of bioburden testing of non-sterile products (per (b) (4)). In support of their proposal, Seres cites:

- the (b) (4) of their DP,
- their inclusion of (b) (4) and CCIT testing in their DP stability protocol to ensure that (b) (4) remains (b) (4) over time, and
- the results of (b) (4) testing that demonstrate their (b) (4) has antimicrobial activity.

In response (IR#61; 10 April 2023), I informed the applicant that we do not have sufficient history with their product and manufacturing site to draw conclusions about microbial contamination. In addition, I stated that (b) (4) testing should be performed on the DP and not just the (b) (4), as the components of the DP could impact the results of the test. I again requested that they perform (b) (4) bioburden testing on DP lots stored at (b) (4)°C and 2-8°C. I informed them that they may request a modification to their bioburden testing schedule in a PAS once they have accrued sufficient stability data from commercial lots to demonstrate low bioburden in their DP. In STN 125757/0.69 (12 April 2023), the applicant agreed to my request and adjusted their post-approval stability program to perform (b) (4) bioburden testing on one DP lot per year stored at 2-8°C and 25°C/(b) (4).

In IR#52 (28 March 2023), I asked the applicant to submit all post-licensure shelf-life extension requests based on their approved stability protocols in a CBE 30 and to submit any changes to their approved stability protocols in a PAS. In IR#53 (30 March 2023), I asked the applicant to submit out-of-specification and atypical stability results and investigations as a product correspondence. In STN 125757/0.60 (31 March 2023) and STN 125757/0.61 (3 April 2023), the applicant agreed to these requests. These changes are acceptable.

The applicant has addressed all CMC concerns regarding their stability data and plans.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

I defer review of this section to the DMPQ reviewer.

3.2.A.2 Adventitious Agents Safety Evaluation (SC)

Seres performed bench-scale studies to evaluate the ability of various steps in their manufacturing process to remove bacterial, fungal, parasitic, and viral organisms.

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

(b) (4)

(b) (4)

Overall Reviewer’s Assessment of Section 3.2.A.2 (SC):

During manufacturing, Seres performs (b) (4) ethanol treatment steps to kill fecal organisms that are not spores. However, these and other steps in the manufacturing process may also kill and/or remove pathogens. For this reason, Seres performed studies to examine the ability of these manufacturing steps to reduce the levels of model infectious agents. The applicant’s adventitious agent inactivation studies support their conclusion that steps in their manufacturing process (e.g., ethanol treatment, (b) (4) can reduce the presence of a variety of pathogens. I have reviewed the information in this section and find it acceptable.

3.2.A.3 Novel Excipients

Not applicable.

3.2.R Regional Information (USA)

❑ Executed Batch Records (SC)

Seres provided a blank master batch record document for the DS and DP and an executed batch record for DS PPQ lot #(b) (4) and DP PPQ lot #(b) (4). Because Seres’ blank master batch record did not include changes made to their maximum capsule batch size and operating ranges over the course of the review cycle, I requested they submit an updated master batch record in IR#48 (22 March 2023). In STN 125757/0.60 (31 March 2023), Seres submitted a new master batch record containing the requested updates.

The information provided is acceptable.

❑ Method Validation Package

Please see section 3.2.P.5.3 for discussion of the method validation packages.

❑ **Combination Products (SC)**

Not applicable.

Overall Reviewer’s Assessment of Combination Products Section:

Not applicable.

❑ **Comparability Protocols**

Not applicable.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion (SC)

In section 1.12.14, Seres claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR part 25.31 (c). I agree with this assessment.

B. Reference Product Designation Request (SC)

Seres requested reference product exclusivity for VOWST on 26 August 2022. They assert that no other licensed biological products are structurally related to VOWST. I agree that this product should receive exclusivity as requested and have completed the T846.02: Reference Product Exclusivity Period Determination Review.

C. Labeling Review (SC)

Full Prescribing Information (PI):

Carton and Container Label:

I identified the following deficiencies in the draft Prescribing Information (PI) (submitted in STN 125757/0.02 on 26 August 2022):

- Seres refers to their product as a “purified microbiome therapeutic”. For clarity regarding the source material and nature of the final product, we asked Seres to change this to “fecal microbiota spores, live” throughout the document.
- Dosage Forms and Strengths (3): Seres included information regarding the appearance, route of administration, and SCFU content of the product. We edited this section to only state the dosage form (capsules) and strength (4 capsules).

- Description (11): Seres included promotional information in this section that includes:
 - “The manufacturing and purification process ensures selection of the target bacterial spores and separates the resulting spore population from the starting raw materials”.
 - “It is a microbiome therapeutic that contains a consortium of purified Firmicutes bacteria in spore form which reside in the healthy human gastrointestinal microbiome”.

We updated this section to remove the promotional information, describe the manufacturing process, and include the following information (per CFR 210.57): nonproprietary name, ingredient information, and source material.

- Mechanism of Action (12.1): Seres included conclusions from their clinical studies that were derived from unvalidated assays (further details are provided in the Module 5 section below). We edited this section to state that the mechanism of action has not been established.
- How Supplied/Storage and Handling (16): Seres stated that VOWST is stored ^{(b) (4)} °C with temperature excursions permitted (b) (4) . We informed the applicant that the storage temperature must have upper and lower limits and they should not mention temperature excursions. We edited this section to state “Store VOWST in the original packaging at 2° to 25°C (36° to 77°F). Do not freeze.”

Carton and Container Label:

I reviewed the product information in the current versions of the Carton and Container labels and found it to be incorrect. I identified similar issues to those indicated in my review of the prescribing information above. I requested that Seres update the non-proprietary name and the storage and handling instructions.

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints (SC)

A. Clinical Primary/Secondary Endpoint Assays:

Seres used *Clostridioides difficile* diagnostic tools to identify subjects for enrollment and also to identify study failures (i.e. recurrence of *C. difficile* infection). Seres used a two-step diagnostic algorithm to reduce false positive test results. The applicant’s algorithm consisted of an Enzyme Immunoassay (EIA) targeting a *C. difficile* specific antigen (GDH) and the *C. difficile* toxin. Seres considered any individual testing positive for both antigens a positive infection, and those with negative results for both antigens negative for *C. difficile* infection. Seres tested individuals exhibiting discordant results (i.e. GDH⁺, toxin⁻, or GDH⁻, toxin⁺) for toxin by a Cell Cytotoxicity Neutralization Assay (CCNA).

Seres designated samples that were CCNA positive for toxin following discordant EIA results as positive for *C. difficile* infection/recurrence. This diagnostic algorithm is consistent with current clinical recommendations for *C. difficile* clinical diagnostics.

Verification/validation of clinical assays:

(1) GDH and Toxin EIA tests:

Seres used commercially available FDA-cleared diagnostic EIA tests performed at accredited clinical microbiology laboratories. Therefore I did not require verification/validation of these methods.

(2) CCNA

Seres performed the CCNA assay at (b) (4) using a commercially available kit (called “(b) (4)”, manufactured by (b) (4) intended use of this assay is for *in vitro* diagnostic qualitative detection of *C. difficile* in stool samples.

Assay procedure:

(b) (4)

(b) (4)

I find the information submitted by Seres sufficient to support the use of this assay in their clinical studies.

B. Clinical Exploratory Analyses:

Seres performed studies to evaluate the effects of VOWST on the microbiome and metabolites (fatty acids and bile acids) in stool samples from phase 3 clinical study participants (SERES-012). The applicant states that there were not enough *C. difficile* recurrences in the VOWST arm to draw conclusions about changes in any of these stool components and treatment outcomes.

- Study SER-DSC-0090: The applicant assessed engraftment of VOWST (i.e., newly appearing spore-forming species) via whole metagenomic sequencing (WMS) of stool. Seres' results showed that engraftment was significantly higher in the treatment arm as compared to placebo (weeks 1 through 24).
- Study SER-DSC-0091: The applicant evaluated changes in microbial beta-diversity in stool via WMS. Seres found that beta-diversity was significantly higher in the treatment arm as compared to placebo (weeks 1 through 24).
- Study SER-DSC-0092: The applicant evaluated changes in bile acid (BA) concentrations in stool. Seres observed significantly lower primary BA concentrations in the VOWST arm relative to placebo one week after dosing, and significantly higher secondary BA concentrations in the VOWST arm relative to placebo 1 – 8 weeks after dosing.
- Study SER-DSC-0098: The applicant evaluated changes in the concentrations of short, medium, and branched chain fatty acids (FA) in stool. Seres observed significant increases in the short chain FA butyrate and the medium chain FAs valerate and hexanoate in the VOWST arm relative to placebo 1-8 weeks after dosing. The concentrations of branched chain fatty acids were not significantly different between arms.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5 (SC):

Seres' conducted exploratory studies to evaluate changes to the stool microbiome and metabolites using unvalidated assays. In addition, as noted above, the applicant was unable to draw conclusions about the role of their observed changes on treatment outcomes. Therefore, I do not consider the results of these studies sufficient to support statements on the label.

Overall, I find the information submitted in these sections acceptable.

