

Application Type	Original BLA
STN	125757/0
CBER Received Date	08/26/2022
PDUFA Goal Date	04/26/2023
Division / Office	DBPAP/OVRR
Committee Chair	Christina Houck
CMC Reviewer	Siobhan Cowley
Project Manager	Qun Wang
Priority Review	Yes
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Review Completion Date / Stamped Date	
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Applicant	Seres Therapeutics, Inc.
Established Name	Purified Microbiome Therapeutic, (b) (4)
(Proposed) Trade Name	VOWST
Pharmacologic Class	Live Biotherapeutic

Formulation(s), including Adjuvants, etc	Each capsule contains 1×10^6 and 3×10^7 spore colony forming units in $92 \pm 4\%$ (w/w) glycerol in saline
Dosage Form and Route of Administration	Capsule, Oral
Dosing Regimen	4 capsules per day for 3 consecutive days
Indication and Intended Population	To prevent the recurrence of Clostridioides difficile infection (CDI) in adults with recurrent CDI

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GLOSSARY

%CV	percent coefficient of variation
AV	acceptance value
BLA	biologics licensing application
CBER	Center for Biologics Evaluation and Research
CDI	Clostridioides difficile infection
CI	confidence interval
CMC	chemistry and manufacturing controls
(b) (4)	
DP	drug product
(b) (4)	
DS	drug substance
IR	Information request
PPQ	process performance qualification
(b) (4)	
SCFU	spore colony forming unit
SE	standard error
TI	tolerance interval
(b) (4)	

1. EXECUTIVE SUMMARY

In this original BLA, Seres Therapeutics, Inc. seeks approval for SER-109 (Purified Microbiome Therapeutic, (b) (4)) to prevent the recurrence of Clostridioides difficile infection (CDI) in adults with recurrent CDI. This CMC statistical review focuses on the viable spore colony count assay (TM-0006) validation, the (b) (4) drug product (DP) potency specifications, the (b) (4) procedure, and shelf-life establishment for the (b) (4) DP.

CBER communicated with Seres several times during the BLA review about CMC statistics issues, including two major issues: Seres' original validation study for TM-0006 did not enable assessment of accuracy, precision, and linearity for (b) (4) DP, and Seres' original (b) (4) procedure did not ensure that lots that pass the procedure truly had acceptable (b) (4) .

Seres designed and conducted a new study to validate TM-0006 when assaying (b) (4) samples and (b) (4) DP capsules by evaluating accuracy, precision, and linearity. For (b) (4) DP, TM-0006 met the pre-specified acceptance criteria for accuracy and linearity in this new study. For (b) (4) DP, Seres' initial precision results used the wrong formula for the %CV. However, Seres provided revised precision results that met revised acceptance criteria based on the correct formula, and the revised results were consistent with the precision observed for similar types of assays.

Seres proposed acceptable (b) (4) potency specification lower limit and DP potency specification, based on their manufacturing capabilities.

In response to CBER's comments, Seres proposed a (b) (4) procedure based on a (b) (4) coverage/(b) (4)-confidence tolerance interval calculated from individual capsules' (b) (4) scale potencies, with an acceptance interval of (b) (4). Seres' (b) (4) proposal is acceptable, as acceptable lots have a high probability of passing and unacceptable lots have a low probability of passing. However, the (b) (4) acceptance criterion is much narrower than the DP potency specification ((b) (4)), which may result in a large proportion of lots not passing the (b) (4) proposal. Therefore, Seres may need to revise the (b) (4) specification in the future.

Seres proposed a shelf-life for (b) (4), of (b) (4) at (b) (4). However, the (b) (4) stability data did not support this conclusion, and my analyses suggested a shelf-life of (b) (4) at (b) (4) is appropriate. CBER communicated this to Seres, and they agreed to this revised shelf-life. Seres proposed a shelf-life for DP of 36 months at $\leq 25^{\circ}\text{C}$, based on stability data from (b) (4) lots stored at 25°C through (b) (4) months, although most lots were stored for a much shorter time (6 to 36 months). Seres justified their proposed shelf-life based on the expected average potency from stability data from lots with a narrow range of release potencies ((b) (4)). Because Seres' process may produce lots with a wider range of release potencies, I simulated the expected range of potencies from lots stored for 36 months at 25°C , based on Seres' stability data. My results suggest that most lots from Seres' process are unlikely to exceed the release specification after 36 months of storage at 25°C , although these results are based on relatively few lots and should be re-evaluated when Seres has more stability data.

Overall, the statistical issues with Seres' CMC studies and analyses were resolved satisfactorily during the BLA review. Seres has demonstrated that their spore colony counting assay (TM-0006) has adequate accuracy, precision, and linearity over acceptable ranges when assaying (b) (4) DP for use in their potency (b) (4) procedures. Seres has proposed acceptable DP potency and (b) (4) procedures and acceptable (b) (4) DP shelf-lives. Therefore, I recommend approval of this original BLA.

2. REGULATORY BACKGROUND

2.1 Pre- and Post-submission Regulatory Activity Related to the Review

CBER communicated with Seres several times during the BLA review about CMC statistics issues (Table 1). CBER identified several issues with Seres' viable spore count assay (TM-0006) and the corresponding validation report (RPT-00269), including that the original validation study design did not enable assessment of TM-0006's accuracy, precision, and linearity across a range of spore counts (in spore colony forming units per (b) (4)) for (b) (4) DP. CBER sent an IR on 18 November 2022 describing the

issues identified and providing guidance to Seres on the appropriate design, conduct, and analysis of a new validation study. CBER also met with Seres about these issues on 28 November 2022.

Seres submitted a new validation protocol for TM-0006 on 12 December 2022 (BLA 125757/0.22). CBER provided comments on this new protocol and Seres' proposed (b) (4) procedure in an IR sent on 16 December 2022. These comments included a recommendation that Seres measure (b) (4) via TM-0006 and revise their TM-0006 validation protocol accordingly. CBER met with Seres on 21 December 2022 to discuss these comments. In response, Seres provided a revised validation protocol for TM-0006 on 3 January 2023 (BLA 125757/0.29) that was intended to validate TM-0006 for use in both the potency (b) (4) procedures.

CBER sent Seres comments on the revised validation protocol on 6 January 2023. Seres provided the validation report and datasets from this validation study on 10 February 2023 (BLA 125757/0.39). CBER sent comments on Seres' validation analyses, including a request for revised precision results using the appropriate formula for (b) (4) -scale data on 24 February 2023, and Seres submitted revised results on 2 March 2023 (BLA 125757/0.47). CBER sent Seres comments about typos in the (b) (4) DP specifications and a request for revised validation report on 10 March 2023. In response, Seres corrected the typos and submitted the revised validation report on 15 March 2023 (BLA 125757/0.53).

The responses to all the IRs shown in Table 1 were acceptable.

Table 1. BLA 125757/0 CMC Statistical Information Requests (IR) and Responses

Submission	IR Sent	Response Received	Summary
BLA 125757/0.22	11/18/2022	12/12/2022	Revised spore count assay validation protocol
BLA 125757/0.29	12/16/2022	01/03/2023	Revised (b) (4) and spore count assay validation protocol
BLA 125757/0.31	01/04/2023	01/12/2023	Stability data
BLA 125757/0.39	01/06/2023	02/10/2023	Spore count assay validation results
BLA 125757/0.47	02/24/2023	03/02/2023	Spore count assay validation revised precision results
BLA 125757/0.53	03/10/2023	03/15/2023	Clarification of typos in drug product and drug substance specifications
BLA 125757/0.56	03/20/2023	03/24/2023	Drug product specification rounding

Source: Created from BLA 125757/0

3. SUBMISSION QUALITY

The submission was adequately organized for conducting a complete CMC statistical review without unreasonable difficulty.

4. SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please refer to product review for further details.

5. SOURCES OF INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on the viable spore colony count assay (TM-0006) validation, the ^{(b) (4)} DP potency specification, the ^{(b) (4)} procedure, and shelf-life establishment for the ^{(b) (4)} DP. At the product reviewer's request, I did not review the specificity assessment in the TM-0006 assay validation, nor did I review the DS stability results.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- BLA 125757/0.1 (seq. 0002)
 - Module 3.2.S.4.5: Justification of Specification (SER-109, all)
 - Module 3.2.P.5.6: Justification of Specification (SER-109, capsule)
 - Module 3.2.S.2.6: Manufacturing Process Development - Process Control Strategy and Characterization
 - Module 3.2.P.8.1: Stability Summary and Conclusion (SER-109, capsule)
 - Module 3.2.R: SCFU Validation Report (RPT-00269)
- BLA 125757/0.10 (seq. 0008)
 - Module 3.2.S.4.2: TM-0006 - Spore Colony Forming Unit Assay
 - Module 3.2.P.5.2: TM-0013 - Determination of ^{(b) (4)} of Dosage Units
- BLA 125757/0.22 (seq. 0020)
 - Module 3.2.S.4.2: TM-0006-v13 - Spore Colony Forming Unit Assay for Measuring Viable Spore Contents of Samples
 - Module 3.2.S.4.3: PROT-0258 - SCFU Method Validation Protocol
- BLA 125757/0.29 (seq. 0028)
 - Module 3.2.S.4.2: TM-0006 - Spore Colony Forming Unit Assay for Measuring Viable Spore Contents of Samples
 - Module 3.2.S.4.3: PROT-0258 - SCFU Method Validation Protocol
- BLA 125757/0.31 (seq. 0029)
 - Module 3.2.P.8.3: Stability Data (XLSX) (SER-109, capsule)
- BLA 125757/0.39 (seq. 0037)
 - Module 3.2.S.4.3: PROT-0258 - SCFU Method Validation Protocol
 - Module 3.2.S.4.3: RPT-00389 - Report Method Validation of SCFU Assay
 - Module 3.2.S.4.3: RPT-00389 Data Analysis (excel file)

- BLA 125757/0.47 (seq. 0044)
 - Module 1.11.1: Response to Quality RFI of 24 Feb 2023
 - Module 3.2.R: RPT-00389 Data Analysis 28Feb2023 (Excel File)
- BLA 125757/0.53 (seq. 0050)
 - Module 3.2.S.4.3: RPT-00389 - Report Method Validation of SCFU Assay

5.3 Literature Reviewed

This review references the following external guidance and literature:

(b) (4)

[Redacted]

6. DISCUSSION OF INDIVIDUAL STUDIES AND ANALYSES

6.1 Spore Count Assay (TM-0006) Validation Study

(b) (4)

[Redacted]

(b) (4)

(b) (4)

[Redacted]

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

(b) (4)

[Redacted]

[Redacted]

6.3 Justification of Specifications

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

6.4 (b) (4) Procedure

Seres originally proposed to assess (b) (4) using their (b) (4) assay, with a (b) (4) procedure based on (b) (4) :

(b) (4)

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

(b) (4)

6.5. Stability of (b) (4) Drug Product

(b) (4)

[Redacted content]

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

6.5.2 Drug Product

Seres has proposed a shelf-life for SER-109 DP of 36 months at $\leq 25^{\circ}\text{C}$. To justify this shelf-life, Seres analyzed stability data from (b) (4) Phase 3 clinical and (b) (4) PPQ lots. All SER-109 DP lots discussed in this section were manufactured at (b) (4). Table 9 shows the number of lots with data at each timepoint by storage condition and lot type. The PPQ lots only have data through 6 months at 5°C and 25°C .

Seres considered stability demonstrated if no significant trend was observed for any of the storage conditions and the 95% confidence interval for the potency loss per month at 25°C was within the DP specification through 36 months of storage. Seres modeled the potency loss using a linear model and tested for the poolability of the intercept and slopes (0.25 significance level), as per FDA guidance, “Q1E Evaluation of Stability Data” (June 2004 version).

Table 9. Drug Product Stability Study Design

Month	(b) (4) Clinical	(b) (4) Clinical	5°C Clinical	5°C PPQ	25°C Clinical	25°C PPQ
0	(b)	(4)	(b)	(4)	(b)	(4)
1						
2						
3						
6						
9						
12						
18						
24						
36						
(b) (4)						
(b) (4)						

Source: Created from the stability data in BLA 125757/0.31, Module 3.2.P.8.3 Stability Data

Reviewer’s Comment: Seres has only assessed the stability at 25°C . Given that the lower temperatures are expected to be more stable and do not exhibit changes over time in potency, this is acceptable.

Seres’ approach to assessing stability has several issues:

- Seres performed a test of the null hypothesis that the change in potency per month is (b) (4). The statistical significance of such a hypothesis test depends strongly on the sample size and variability of the underlying data. With a small sample size as is common for stability assessments, these tests are underpowered to detect meaningful changes per month, so that a non-significant result does not indicate a

- lack of meaningful changes per month. This effect is more pronounced when modeling stability over long time periods, as relatively small changes per month can result in substantial changes after a long storage period. Therefore, I do not discuss the results of these tests.*
- *Seres predicted the expected average potency during storage at 25°C with the corresponding (b) (4) confidence interval. This prediction reflects the expected potency after 36 months of storage for a lot that enters storage at the average potency and the expected range of potencies given the sampling error. This prediction does not account for manufacturing variability or assay error, nor does this reflect the worst-case scenario. To address this, I conducted additional analyses.*

Figure 4 shows the DP stability data for the clinical and PPQ lots by storage condition. There is little to no evidence of potency loss at (b) (4) and 5°C, but there is evidence of potency loss at 25°C. Using a model with a common slope and common intercept, Seres estimated that the lower bound of the (b) (4) CI would cross the lower specification bound at (b) (4) and no significant trend was observed for DP stored at (b) (4) 5°C.

(b) (4)

Reviewer's Comment: *Because Seres made very few changes to their manufacturing process when moving from clinical to commercial production, the product reviewer considers combining the clinical and PPQ lots appropriate. Furthermore, there is no evidence of significant differences between the clinical and PPQ lots, although this is based on limited data from the PPQ lots. Therefore, combining the data from these lots is reasonable.*

Seres did not report the estimated potency loss per month or confidence interval. Using the provided data and model, I find a potency loss per month (^{(b) (4)}-scale) of ^{(b) (4)} (^{(b) (4)} CI: ^{(b) (4)}). This model predicts that a lot with a release potency of ^{(b) (4)} will have an end-of-shelf-life potency of ^{(b) (4)} (^{(b) (4)} CI: ^{(b) (4)}).

Seres' analysis only models the end-of-shelf-life potency for a lot with a release potency of ^{(b) (4)}, even though their release specification spans a wider range (^{(b) (4)}), and their process is likely to produce lots with a range of potencies within this specification.

To address this limitation, I conducted a simulation study to estimate the end of shelf-life potency across the expected range of release potencies. I fit a linear mixed effects model to the 25°C stability data with a fixed effect for time and random effect (intercept) for lot:

$$y_{ij} = \mu + \alpha + \beta t_j + \varepsilon$$

where y_{ij} is the ^{(b) (4)}-scale potency for lot i at time j , μ is the overall mean potency at release, $\alpha \sim N(0, \sigma_\alpha)$ is the per-lot random intercept, β is the change per month, t_j is the number of months of storage at time j , and $\varepsilon \sim N(0, \sigma_\varepsilon)$ is the residual error term.

Then using the results of this model, I simulated the distribution of potencies after storage at 25°C for 36 months by simulating random lots:

- 1) I simulated the release potency for a random lot by drawing a random observation $p_0 \sim N(\mu, \sigma_\alpha)$.
- 2) I simulated the potency loss per month by drawing a random observation $l \sim N(\beta, SE(\beta))$, where $SE(\beta)$ is the standard error of the slope.
- 3) I simulated the assay error by drawing a random observation $e \sim N(0, \sigma_\varepsilon)$.
- 4) I predicted the ^{(b) (4)}-scale potency at 36 months as $p_0 + l \times 36 + e$.

I repeated this process 100,000 times and calculated the 2.5th and 97.5th quantiles to estimate the expected range of potencies at 36 months for lots from Seres' process. I find a range of ^{(b) (4)} SCFU^{(b) (4)}. These results suggest that a majority of lots will have potencies within the release specification after 36 months storage at 25°C.

This simulation relies on two important assumptions, and if these assumptions do not hold, the simulation results may not reflect the performance of Seres' manufacturing process:

- The simulations assume normally distributed data. As previously noted, there is evidence to suggest that this is a reasonable assumption.
- The simulations assume that the data provided is representative of Seres' manufacturing process. This assumption may not be reasonable, given the relatively limited range of release potencies (^{(b) (4)}) in the dataset compared to the release specifications and the small number of lots. This limitation is partially mitigated by assuming normally distributed release potencies where 99.7% of release titers fall between ^{(b) (4)}. That said, lots with potencies near the lower limit of the release specification may be at risk of

going out-of-specification if stored for long periods of time at 25°C. As Seres collects more stability data, they should reassess their release specification, accounting for any stability trends.

8. CONCLUSIONS

8.1 Statistical Issues and Collective Evidence

This submission included several CMC studies and analyses: spore colony counting assay (TM-0006) validation results, (b) (4) DP potency specification justifications, DP (b) (4) procedure, (b) (4) DP shelf-life justification. Seres validated their TM-0006 assay in an appropriately designed study for (b) (4) samples and (b) (4) DP capsules by evaluating accuracy, precision, and linearity. For (b) (4) DP, Seres' assay met the pre-specified acceptance criteria for accuracy and linearity. For (b) (4) DP, Seres' initial precision results used the wrong formula for the %CV. Seres provided revised precision results that met revised acceptance criteria based on the correct %CV formula and are consistent with the precision observed for similar assays. Therefore, Seres has demonstrated that their TM-0006 assay is acceptably accurate, linear and precise (b) (4) for DP capsules with potencies between (b) (4).

(b) (4)

Seres proposed a (b) (4) procedure that is based on a (b) (4)-coverage, (b) (4)-confidence tolerance interval calculated from (b) (4) capsules' potencies, with an acceptance interval of (b) (4). Seres' (b) (4) proposal is acceptable, as acceptable lots have a high probability of passing and unacceptable lots have a low probability of passing. However, the (b) (4) acceptance criterion is narrower than the proposed DP potency specification, which may result in a low probability of lots passing the (b) (4) proposal overall and this specification may need revision in the future.

(b) (4)

Seres has proposed a shelf-life for DP of 36 months at $\leq 25^{\circ}\text{C}$, based on the analysis of stability data from (b) (4) Phase 3 clinical and (b) (4) PPQ lots stored at 25°C through (b) (4)

months, although most clinical lots were stored for no more than 36 months and the PPQ lots were only stored through 6 months. Seres justified their proposed shelf-life based on the average expected potency of lots from their process after 36 months of storage. However, because many lots may fall below the average, I simulated storage of lots for 36 months at 25°C. My results demonstrate that lots from Seres' process are unlikely to exceed the release specification after 36 months of storage at 25°C. Therefore, Seres' proposed DP shelf-life is acceptable.

8.2 Conclusions and Recommendations

Overall, the statistical issues with Seres CMC studies and analyses were resolved satisfactorily during the BLA review. Seres has demonstrated that their spore colony counting assay (TM-0006) has adequate accuracy, precision, and linearity over acceptable ranges when assaying (b) (4) DP for use in their potency and (b) (4) procedures. Seres has proposed acceptable DP potency and (b) (4) procedures and acceptable (b) (4) DP shelf-lives. Therefore, I recommend approval of this original BLA.