

CBER BLA Device Review Memorandum – Prefilled Syringe (PFS)

BLA STN 125814

CAPVAXIVE [Pneumococcal 21-valent Conjugate Vaccine]

**Andrea Gray, PhD
Device Reviewer
CBER/ORO/DROP/RPB**

1. BLA#: STN 125814

2. APPLICANT NAME

- Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

3. PRODUCT NAME/PRODUCT TYPE

- Non-Proprietary/Proper/USAN: Pneumococcal 21-valent Conjugate Vaccine
- Proprietary Name: CAPVAXIVE

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- General Description: Solution for injection
- Route of administration: Intramuscular
- Indication(s): Prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older

5. COMBINATION PRODUCT INFORMATION

- Type: Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)
 - Biologic Constituent(s): Vaccine
 - Drug Constituent(s): n/a
 - Device Constituent(s): Prefilled syringe

6. MAJOR MILESTONES

- Filing Meeting: November 30, 2024
- Midcycle Internal Meeting: January 18, 2024
- Late Cycle Internal Meeting: March 12, 2024
- PDUFA Action Date: June 17, 2024

7. QUALITY REVIEW TEAM

Reviewer/Affiliation	PFS-Relevant Subject Matter
Shonoi Ming, CBER/OVRR/DBPAP/LBP	CMC (Extractables and Leachable, Toxicological Risk Assessment, Biologic Compatibility)
Hector Carrero, CBER/OCBQ/DMPQ/MRB2	Container Closure Integrity, Shipping Validation

8. INTRA- & INTER-CENTER CONSULTS

n/a

9. SUBMISSION(S) REVIEWED

Date Received	eCTD Sequence	STN 2 nd Level	Comments
October 18, 2023	0001	0	Original submission
November 30, 2023	0005	4	Updated drug product stability data
December 19, 2023	0008	7	Response to Information Request (IR)#5 (device IR)
March 28, 2024	0019	18	Response to IR#14 (device IR)
May 13, 2024	0050	32	Response to IR#27 Comment 1

10. RELEVANT REFERENCED REGULATORY SUBMISSIONS

Submission Type & STN (Center)	Holder	Referenced Information	Letter of Authorization	Comments/Status
DMF (b) (4) (CDER)	(b) (4)	Sterilization validation (b) (4)) Biocompatibility ((b) (4)) Sterilization validation (b) (4))	Yes	Review of sterilization validation information deferred to DMPQ. Review of biocompatibility information leveraged from review for BLA 125769
DMF (b) (4) (CDER)	(b) (4)	Sterilization validation, Biocompatibility, (b) (4)	Yes	Review of sterilization validation information deferred to DMPQ. Review of biocompatibility information and (b) (4) compliance information documented in a separate memo in the DMF record.
MF (b) (4) (CBER)	(b) (4)	Piston (Plunger): (b) (4) Gray, (b) (4) (b) (4) coating), (b) (4)	Yes	No review needed. Necessary information provided in the BLA and other DMFs.

DMF (b) (4) (CDER)	(b) (4)	Compound (b) (4) washing process / Depyrogenation Process	Yes	Review of washing/ depyrogenation information deferred to DMPQ. Other necessary information provided in the BLA and other DMFs. No review needed for the scope of this memo.
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11. RELEVANT PRIOR INTERACTIONS

12. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Merck submitted BLA 125814 for licensure of their 21-valent Pneumococcal Conjugate Vaccine (CAPVAXIVE), which consists of a non-graduated 1 mL glass Luer-lock pre-filled syringe (PFS) containing a single-dose suspension of the drug product. The scope of this review memo includes: PFS description, PFS design verification (including device essential performance, e.g., deliverable volume, [REDACTED]), verification of device essential performance over the proposed shelf life and after shipping, control strategy to ensure the final combination product meets essential performance requirements, PFS biocompatibility, and compliance with applicable device quality system regulations (design controls regulations (21 CFR 820.30), purchasing control regulations (21 CFR 820.50)). Review of information cross referenced to master files are documented in separate memos available in the master file's record, including those leveraged from recent reviews in support of similar previous submissions. Based on the information provided in the application and cross-referenced master files, as well as additional information submitted interactively, I recommend that the BLA can be approved from a device/combination product perspective.

B. RECOMMENDATION: Approval

I. APPROVAL

- Comparability protocol in Module 3.2.R related to drug product shelf-life extension is acceptable from a device perspective.

II. SIGNATURE BLOCK

Reviewer, Title, Affiliation	Signature and Date
Andrea Gray, PhD Device Consult Reviewer CBER/ORO/DROP/RPB	

CBER BLA PFS Device Review Memo | BLA 125814 | Pneumococcal 21-valent
Conjugate Vaccine

<p>Cherie Ward-Peralta, MS Branch Chief CBER/ORO/DROP/RPB</p>	
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I. Product Description

A. Combination Product

The combination product consists of the drug product silted into a glass syringe barrel assembly, stoppered with a plunger stopper, and assembled with a plunger rod.

B. Drug/Biologic

Module 2.3 Introduction states “The 21-valent Pneumococcal Conjugate Vaccine (V116)... is composed of a sterile solution of the capsular polysaccharide antigens of *S. pneumoniae*, serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B, and deOAc15B, individually conjugated to carrier protein CRM197 that is purified from *P. fluorescens*.... V116 DP is formulated in PS-20, and buffer containing 150 mM NaCl and 20 mM LHistidine ((b) (4)).”

C. Syringe

From Module 3.2.P.7:



Information in the table below was compiled from

- Table 1 in Module 3.2.P.2.3.3 Manufacturing Process Development – (b) (4) Comparability
- Table 3 in Module 3.2.P.2.4 Drug Product Container Closure Development
- Table 1 in Module 3.2.P.7

Component	(b) (4) Syringe	(b) (4) Syringe
Syringe Barrel	(b) (4) 1.5 mL glass barrel with LLA. Barrel lubricated with (b) (4). Polypropylene rigid tip cap with (b) (4) (styrene-butadiene blend) elastomeric product contact component.	(b) (4) 1.5 mL glass barrel with LLA. Barrel lubricated with (b) (4). Polypropylene rigid tip cap with (b) (4) (synthetic isoprene-bromobutyl blend) elastomeric product contact component.
Plunger Rod	Light blue plunger rod, buttress thread	Light blue plunger rod, buttress thread
Plunger Stopper	(b) (4) bromobutyl plunger stopper with a fluopolymer lamination	(b) (4) bromobutyl plunger stopper with a fluopolymer lamination

Components and Suppliers	See table above
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Connection Type	Luer
Intended Connector(s)	Needle hub
Materials of Construction	See table above
Dimensions	See Appendix 1 of this memo
Syringe Volume	1.5 mL
Fill Volume	(b) (4)
Sterilization Method	Syringe barrel assemblies: (b) (4) Plunger stoppers: (b) (4)
Injection Site	For vaccines, injection site necessary for intramuscular routes of administration of vaccines is common knowledge in healthcare community and described by ACIP guidelines
Injection Tissue and Depth	For vaccines, injection site necessary for intramuscular routes of administration of vaccines is common knowledge in the healthcare community and described by ACIP guidelines
Type of Use	Single Use
Storage Conditions and Proposed Expiry	2°C to 8°C, 18 months
Intended User(s)	Healthcare professional
Intended Use Environment	Clinic
Needle Length, Gauge, Tip Style	For vaccines, needle specifications necessary for intramuscular routes of administration of vaccines is common knowledge in the healthcare community and described by ACIP guidelines .
Markings	None
Reuse Durability	n/a
Safety Features	n/a
Automated Functions	n/a

There are differences between the syringes used in the clinical studies, process performance qualification studies, and the commercial presentation, as summarized in Table 2 of Module 3.2.R.7 Development of the Combination Product. The information is extracted into the table below.

Combination Product Components	Component Description for Clinical (Ph1/2/3) Use	Component Description for Commercial Use	Differences
Syringe barrel assembly	<p>(b) (4) 1.5 mL Luer Lock Barrel Syringe with round flange and (b) (4)</p>	<p>(b) (4) 1.5 mL Luer Lock Barrel Syringe with round flange and (b) (4)</p> <p>(b) (4) 1.5 mL Luer lock barrel syringe with round flange and (b) (4)</p>	<p>(b) (4) (Clinical) and (b) (4) (Commercial) syringe barrel assemblies are identical. The (b) (4) specifications for the (b) (4) syringes were tightened for visual inspection and attribute testing only. The syringe barrel and components (i.e., tip cap and Luer Lock Adaptor), dimensions, site of sterilization and final packaging configuration remain the same as the (b) (4) syringe. Additional source for syringe barrel assembly is being included.</p>
Plunger stopper	<p>(b) (4) (regular Silicone) bromobutyl plunger stopper with a fluoropolymer lamination</p>	<p>(b) (4) (regular Silicone) bromobutyl plunger stopper with a fluoropolymer lamination</p> <p>(b) (4) (reduced Silicone) bromobutyl plunger stopper with a fluoropolymer lamination</p>	<p>The change of the supplier's in-process silicone nominal specification is to allow for manufacturing flexibility. Reduced silicone stoppers dimensions, site of sterilization and final packaging will remain the same as regular silicone stoppers. Regular and/or reduced silicone stoppers can be utilized.</p>
Plunger Rod	<p>(b) (4) Acme Thread - clear</p>	<p>(b) (4) Buttress Thread - Light Blue</p>	<p>Updated thread design - No impact to functionality</p>

Reviewer Comment: As listed in Section 10 Relevant Referenced Regulatory Submissions in this memo, Merck references several master files regarding the container closure components (DMF (b) (4), DMF (b) (4), DMF (b) (4) and DMF

(b) (4). Merck should clarify what specific information they are relying on in these master files. See **IR#14.5**.

Information Request (IR)#14.5 Date Sent: March 22, 2024 Date/Sequence Received: March 28, 2024 / 0019											
IR Comment: Module 1.4.2 contains Letters of Authorization (LOAs) permitting reference to DMF (b) (4), DMF (b) (4), DMF (b) (4), MF (b) (4), and DMF (b) (4) for the syringe components and materials. However, it is not clear whether you are referencing the master files for any specific type of information. For each referenced master file, please indicate what, if any, specific information you are relying on the master file for (e.g., verification of certain design aspects per (b) (4), biocompatibility). Please note you may need to communicate with the master file holder to confirm that the type of information that you are relying on is actually included in the master file.											
Applicant Response: Letters of Authorization for the Drug Master Files (DMF) are provided to enable the Agency to review proprietary information associated with the manufacturing and processing of CRM197 (DMF (b) (4)) and container closure components (DMF (b) (4), DMF (b) (4), DMF (b) (4) and DMF (b) (4)). As an example, DMF (b) (4) for (b) (4) provides a list of products manufactured in the multi-product facility used to manufacture CRM197, as well as manufacturing area drawings. The key information relied on in the component DMFs is summarized in Table 1.											
Table 1 Packaging Component DMF Information											
<table border="1"> <thead> <tr> <th>Component</th> <th>DMF</th> <th>Information Referenced</th> </tr> </thead> <tbody> <tr> <td>(b) (4) barrel assembly, tip cap elastomer</td> <td>(b) (4)</td> <td>Sterilization validation ((b) (4)) Biocompatibility ((b) (4)) (b) (4) Compliance Elastomeric parts for parenterals and for devices for pharmaceutical use ((b) (4)) (Letter of Authorization for (b) (4) DMF)</td> </tr> <tr> <td>(b) (4) – Syringe Barrel Assembly, Plunger Stopper</td> <td>(b) (4)</td> <td>Sterilization validation ((b) (4)) Biocompatibility ((b) (4)) Sterilization validation ((b) (4))</td> </tr> </tbody> </table>	Component	DMF	Information Referenced	(b) (4) barrel assembly, tip cap elastomer	(b) (4)	Sterilization validation ((b) (4)) Biocompatibility ((b) (4)) (b) (4) Compliance Elastomeric parts for parenterals and for devices for pharmaceutical use ((b) (4)) (Letter of Authorization for (b) (4) DMF)	(b) (4) – Syringe Barrel Assembly, Plunger Stopper	(b) (4)	Sterilization validation ((b) (4)) Biocompatibility ((b) (4)) Sterilization validation ((b) (4))		
Component	DMF	Information Referenced									
(b) (4) barrel assembly, tip cap elastomer	(b) (4)	Sterilization validation ((b) (4)) Biocompatibility ((b) (4)) (b) (4) Compliance Elastomeric parts for parenterals and for devices for pharmaceutical use ((b) (4)) (Letter of Authorization for (b) (4) DMF)									
(b) (4) – Syringe Barrel Assembly, Plunger Stopper	(b) (4)	Sterilization validation ((b) (4)) Biocompatibility ((b) (4)) Sterilization validation ((b) (4))									
Reviewer Comments: Response is acceptable. Review of sterilization validation information referenced in these master files is deferred to DMPQ. The referenced (b) (4) compliance and biocompatibility information is reviewed in separate memos for these master files.											

Reviewer’s Overall Assessment and Recommendations: The product description is adequate from a device perspective.

II. Manufacturing

A. Manufacturers

Facility	Responsibility
MSD (b) (4)	<ul style="list-style-type: none"> • Drug Product Release and Stability Test Site (Physical-Chemical, Biological and Syringe Functionality)
MSD (b) (4)	<ul style="list-style-type: none"> • Drug Product Manufacturing and Primary Packaging • Drug Product Release and Stability Test Site (Physical-Chemical, Biological, Microbiological and Syringe Functionality)
(b) (4)	<ul style="list-style-type: none"> • Drug Product Stability Test Site (Syringe Functionality and Container Closure Integrity)
(b) (4)	<ul style="list-style-type: none"> • Drug Product Release and Stability Test Site (Conjugated Saccharide Content)
Merck Sharp & Dohme LLC (b) (4)	<ul style="list-style-type: none"> • Combination Product Assembly • Labeling and secondary packaging • Finished product release site
Merck Sharp & Dohme LLC (b) (4)	<ul style="list-style-type: none"> • Combination Product Assembly • Labeling and secondary packaging • Finished product release site

B. Manufacturing Process

The table below is based on the flow diagram in Figure 2 of Module 3.2.P.3.3 Description of Manufacturing Process and Controls – Formulation and Fill, starting at filling:

Manufacturing Process	Critical Process Parameter
Filling	(b) (4)
Plunger stopper placement	-
Visual inspection	-
2-8°C storage	-

Section 3.2 of Module 3.2.P.3.3 Description of Manufacturing Process and Controls – Formulation and Fill also describes the steps above:

Preparation of Primary Packaging Components: “In preparation for filling, the tubs of pre-sterilized glass syringes are decontaminated via (b) (4) upon entry into the isolator. Stoppers that have been pre-washed, siliconized, and sterilized are received on site and transferred into the isolator via the transfer port.”

Filling: “An automated filling machine, equipped with sterile components, aseptically fills the (b) (4) into syringes such that each syringe contains the minimum recoverable volume... The filled syringes are automatically stoppered. During filling, in-process (b) (4) checks are performed to ensure the allowable syringe dose (b) (4) range is achieved.”

Visual Inspection: “After each syringe is filled and stoppered, the syringe exits the isolator and is transferred to the Automated Inspection Machine for 100% visual inspection for defects. Manual inspection using qualified inspectors can also be utilized as a means of visually inspecting the final filled containers in place of automated inspection. Samples are removed for testing”.

Storage: “After inspection, the syringes are placed into nested tubs and stored at 2–8 °C in preparation for packaging and labeling.”

The table below is based on an additional flow diagram in Figure 1 of Module 3.2.P.3.3 Description of Manufacturing Process and Controls – Combination Product:

Combination Product Constituent Parts	Assembly and Packaging Process Step	In-process Controls/Sample Locations
Combination product assembly and packaging components	Component Verification	(b) (4)
Pre-filled syringe drug product, plunger rod, syringe label	Assembly of combination product, print and apply label	
Assembled combination product packaging components	Packaging labeling and final packaging	

Combination Product Constituent Parts	Assembly and Packaging Process Step	In-process Controls/Sample Locations
		<div style="font-size: 48px; font-weight: bold;">(b) (4)</div>
-	Cold Chain Storage (2-8 °C)	

Module 3.2.P.3.3 Description of Manufacturing Process and Controls – Formulation and Fill also describes the steps above:

Assembly: “The combination product assembly process is an automated process. The PFS is fed into the syringe assembly and labelling machine, where a plunger rod is threaded to the PFS stopper. The syringe and plunger rod are inspected for plunger rod presence and correct color. Inspection for the presence of the plastic tip cap is performed after assembly.”

Labeling: “A batch number and expiry date are printed on each label, and the label is applied to the unlabeled syringe assembly. The label is verified via a 100% in-process control (IPC) check.”

Packaging: “The finished assembled syringe (combination product) is placed into a packaging tray in the tray loading section. The tray contents are inspected for accuracy and completeness before placement into a carton with a package insert. The cartons are arranged into the shipper containers. The finished product is stored refrigerated at 2–8 °C and protected from light for subsequent release and distribution.”

Combination Product Batch Numbering System: “Each finished goods batch is assigned a unique 7-digit number with the (b) (4) [redacted]. The numbers are automatically generated at the creation of a batch. The inventory management system picks the next sequential number from a global pool of batch numbers when assigning a batch number to a product.”

i. In Process Controls

See Section II.B.i Manufacturing Process in this memo (above).

Additionally, regarding (b) (4), Section 2.5 of Module 3.2.P.3.5.2 Process Validation and/or Evaluation – Drug Product Process Validation states (b) (4)

[Redacted]

ii. Final Product Specifications and Test Methods

Device relevant specifications listed in Table 1 in Module 3.2.P.5.1 are excerpted in the table below:

Attribute	Release Acceptance Criteria	Stability Acceptance Criteria	Test Method	Method Reference
Recoverable Volume (mL)	0.50 (b) (4)	0.50 (b) (4)	(b) (4)	Recoverable Volume and Syringeability
Syringeability	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage.	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage.	NA	Recoverable Volume and Syringeability
Syringe Functionality- (b) (4)	NA	(b) (4)	(b) (4)	Syringe Functionality

Recoverable Volume and Syringeability:

- Analytical method (Module 3.2.P.5.3): “The recoverable volume method is a (b) (4) method and is performed according to (b) (4) and (b) (4). While syringeability is not a (b) (4) method, it is assessed as part of the recoverable volume method, by visually observing the passage of the product through the syringe needle during the execution of the (b) (4) method. The test is to ensure that the liquid is dispensed in an even stream and there is no evidence of needle blockage or other conditions which could interfere with the discharge of the vaccine.”
- Validation (Module 3.2.P.5.6): “The syringeability method has been verified for recoverable volume and syringeability testing of DP at (b) (4). (b) (4) **representative DP batches** were formulated and filled into (b) (4) syringe images for a total of (b) (4) **unique samples each tested singly** to support method

verification at (b) (4). (b) (4) DP batch was formulated and filled into (b) (4) syringe images for a total of (b) (4) unique samples each tested in (b) (4) to support method verification at (b) (4).” The data in Tables 1 and 2 show that all samples met the acceptance criteria for recoverable volume and syringeability at (b) (4).

Reviewer Comment: *It’s not clear how the description of the test materials in the text match up with how the data is organized in Tables 1 and 2. The leftmost column (“Sample (syringe)”) in both tables lists (b) (4) syringe samples and (b) (4) syringe samples. The next column moving right (“Syringe Number”) lists (b) (4) syringes (b) (4) for each of the samples in the first column. It’s not clear how the data from (b) (4) representative DP batches... filled into (b) (4) syringe images for a total of (b) (4) unique samples each tested singly” at (b) (4) and (b) (4) representative DP ... filled into (b) (4) syringe images for a total of (b) (4) unique samples each tested in (b) (4) ” at (b) (4) result in the identical data organization in the two tables. Merck should clarify the discrepancy between the sampling plan description in the text and the data presented in Tables 1 and 2. See IR#14.4.*

Information Request (IR)#14.4

Date Sent: March 22, 2024

Date/Sequence Received: March 28, 2024 / 0019

IR Comment:

You provided information regarding validation of the recoverable volume analytical method in Module 3.2.P.5.6. The main text of this document states that data was obtained from “(b) (4) representative DP batches... filled into (b) (4) syringe images for a total of (b) (4) unique samples each tested singly” at (b) (4) and “(b) (4) representative DP ... filled into (b) (4) syringe images for a total of (b) (4) unique samples each tested in (b) (4) ” at (b) (4). However, in both the (b) (4) and (b) (4) data tables (Tables 1 and 2), the leftmost column (“Sample (syringe)”) lists (b) (4) syringe samples and (b) (4) syringe samples, and the next column moving right (“Syringe Number”) lists (b) (4) syringes (b) (4) for each of the samples in the first column. To ensure our understanding of the data, please provide additional information on the sampling plan for the recoverable volume method validation performed at (b) (4), as well as how it relates to the data organization in Tables 1 and 2.

Applicant Response: The Recoverable Volume method is a (b) (4) method which was evaluated in verification studies at the commercial testing sites at (b) (4). The verification studies at (b) (4) used different approaches to generate study samples and similar verification study replication.

For the verification study performed at (b) (4):

- (b) (4) representative DP batches were formulated
- each DP formulation was filled into (b) (4) syringe images: (b) (4) syringe (b) (4) and a (b) (4) syringe (b) (4)
- each DP formulation + syringe combination was subsequently tested in the format (b) (4), according to the Recoverable Volume Method.

For the verification study performed at (b) (4):

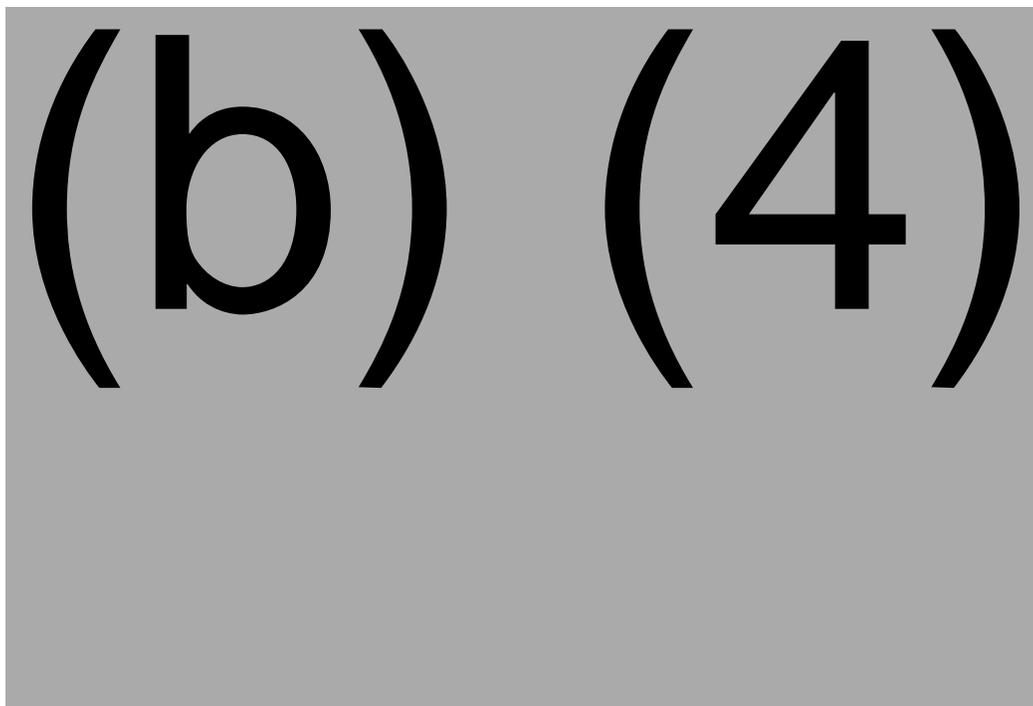
- (b) (4) representative DP batch was formulated
- the DP formulation was filled into (b) (4) syringe images: (b) (4) syringe (b) (4) and a (b) (4) syringe (b) (4)
- each DP formulation + syringe combination was subsequently tested in (b) (4), in the format (b) (4), according to the Recoverable Volume Method.

The data tables have been updated in module 3 to better represent the testing plans and to compliment the organization of the verification study results presented in 3.2.P.5.3.9 Validation of Analytical Procedures – Recoverable Volume and Syringeability. The revised summary tables, Table 1 and Table 2, are also provided in this response for ease of review.

Reviewer Comments: *Tables 1 and 2 are included in the response but are not recreated above, as the only difference is an additional first column that indicates the DP batch formulation ((b) (4) for (b) (4), and (b) (4) for (b) (4)). Upon further consideration, the source of confusion was the (b) (4) syringes associated with each (b) (4). The review failed to recall that for PFS containing less than (b) (4) mL, (b) (4) states (emphasis added by reviewer) (b) (4)*

Therefore, per (b) (4) each (b) (4) actually consists of (b) (4) individual syringes. Response is acceptable.

- Justification (Module 3.2.P.5.6): “Recoverable volume measurement is required as per (b) (4) and (b) (4) and (b) (4). While syringeability is not required per (b) (4), it is assessed as part of the recoverable volume method to confirm the qualitative functionality of the syringe... Release and stability results generated to date demonstrate the ability to meet the existing specification” (results graphed below; (b) (4) individual results are generated per batch).



Syringe Functionality (b) (4):

- Analytical method (Module 3.2.P.5.3): “Syringe functionality for the DP pre-filled syringe is determined by (b) (4) (b) (4) (b) (4) The method is based on the principles described in (b) (4) ”
 - Test Procedure: (b) (4) (b) (4) (b) (4) (b) (4)
 - Reportable results: “Acceptable syringe functionality is indicated by (b) (4) (b) (4) that meet pre-defined specifications measured in units of (b) (4) .”
- Validation (Module 3.2.P.5.6): “The syringe functionality method was **validated at (b) (4)** for the drug product pre-filled syringe by confirming **linearity, accuracy, precision, and (b) (4) repeatability and reproducibility**. Operational robustness was not evaluated during method validation, as instrument parameters are defined and followed per (b) (4) and are not modified during routine testing. The validation study included (b) (4) **syringes filled with (b) (4) V116 drug product batch and (b) (4) syringes filled with (b) (4) in lieu of product.** The (b) (4) syringe barrel is dimensionally equivalent to the (b) (4) syringe barrel.”

(b) (4)

(b) (4)

- Results are summarized in the table below recreated from Table 1 in this module.

Validation Parameter	Acceptance Criteria	Results
Linearity, Accuracy and Precision (through annual instrument calibration)	(b) (4)	Pass
Linearity, Accuracy and Precision (through annual instrument calibration)	(b) (4)	Pass
(b) (4) Repeatability and Reproducibility	(b) (4)	(b) (4)

- Justification (Module 3.2.P.5.6): “(b) (4) testing is performed to monitor syringe functionality. This attribute is performed on stability to meet (b) (4) requirements for pre-filled syringe combination products. Additionally, (b) (4) aspects of device functionality are demonstrated with each release and stability test for recoverable volume and syringeability. The requirement of (b) (4) is based on studies conducted to evaluate the maximum (b) (4) the syringe/plunger device. All stability results to date have met the stability specification.”

Reviewer Comment: Notably, Merck references (b) (4) regarding syringe functionality. This standard is not currently FDA-recognized. However, (b) (4) regarding (b) (4) refers to (b) (4) which is FDA-recognized. Therefore, the use of this non-recognized standards is acceptable.

iii. Batch Analyses

Release testing data is provided in Module 3.2.P.5.4 for the PFS batches tabulated below (excerpted from “Table 1 Batch Genealogy”; PSS is Primary Stability Study; PPQ

is Process Performance Qualification). All samples met acceptance criteria for recoverable volume and syringeability.

Batch Number	Site	Scale (b) (4)	Date of Manufacture	Purpose	Syringe Supplier (b) (4)	Data Location
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Phase 1/2 Clinical	(b) (4)	Table 3
				Phase 3 Clinical / PSS		Table 4
				Phase 3 Clinical / PSS		Table 4
				Phase 3 Clinical / PSS		Table 4
				PSS		Table 4
				PSS		Table 4
				PSS		Table 4
				PPQ		Table 5
				PPQ		Table 5
				PPQ		Table 5

Notably, the acceptance criteria recoverable volume for (b) (4) was 0.500(b) (4) mL; the acceptance criteria was subsequently changed to 0.500(b) (4) mL for Phase 3 and beyond. The (b) (4) recoverable volume data includes results for samples taken from the (b) (4) of filling (b) (4) results each); all samples met the acceptance criteria.

Additionally, there are differences between the PFS used in the PPQ studies and the commercial presentation, as summarized in Table 4 of Module 3.2.P.2.3.2 Manufacturing Process Development – Combination Product, recreated below (emphasis added by reviewer).

Component	PPQ	Commercial	Justification
Syringe Barrel	1.5mL LLA (b) (4)	1.5mL LLA (b) (4)	The (b) (4) specifications for the (b) (4) syringes were updated for visual inspection and attribute testing only . The syringe barrel and components (i.e., tip cap and Luer Lock Adapter), dimensions, site of sterilization and final packaging

Component	PPQ	Commercial	Justification
			configuration remain the same as the (b) (4) syringe used for PPQ. The (b) (4) specifications were tightened for release.
Plunger stopper	(b) (4)	(b) (4)	In addition to use of the (b) (4) plunger stoppers, a (b) (4) stopper will be used to allow for manufacturing flexibility. The supplier nominal target (b) (4) value for (b) (4) stopper is (b) (4) and for (b) (4) stoppers is (b) (4) . The stopper dimensions, site of sterilization and final packaging for the reduced silicone plunger stopper are the same as for the (b) (4) plunger stopper. (b) (4) stoppers can be utilized.

C. Process Validation

(b) (4)

[Redacted content]

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

(b) (4)

(b) (4)

III. Design Verification

A. Essential Performance Requirement Verification

Per Section 4 of Module 3.2.R.7 Development of the Combination Product.

Design Verification is discussed in Section 3 of Module 3.2.P.2.4 Drug Product Container Closure Development. Merck conducted testing for (b) (4), delivered dose (recoverable volume) and container closure integrity on the

combination product after manufacture as well as after labeling, assembly, packaging, and simulated shipping.

Reviewer Comment: Merck did not describe the simulated shipping protocol. Merck should provide additional information about how shipping was simulated, including any consensus standards used. See **IR#14.2**.

Information Request (IR)#14.2

Date Sent: March 22, 2024

Date/Sequence Received: March 28, 2024 / 0019

IR Comment:

In Section 3 of Module 3.2.P.2.4 Drug Product Container Closure Development, you presented the results of design verification of the combination product after labeling, assembly, packaging, and simulated shipping. However, you did not provide a description of the simulated shipping method(s). To fully interpret the data, please provide additional information about how shipping was simulated, including any consensus standards used.

Applicant Response: The simulated shipping methods used prior to design verification testing followed the (b) (4) test series. Pre-filled syringes (PFS) representing the (b) (4) of the assembly and packaging process were packed into shippers and (b) (4) at approximately (b) (4). Shippers of (b) (4) PFS (minimum and maximum load) and shippers of (b) (4) PFS (minimum and maximum load) were then subject to the (b) (4) test. Each shipper was (b) (4) as shown in Table 1. The (b) (4) was determined based on the (b) (4) of each shipper. The shipper orientation is shown in Figure 1.

(b) (4)

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

(b) (4)

B. Non-EPR Performance Requirements

Section 5.1 of Module 3.2.R.7 Development of the Combination Product states “Design verification testing to evaluate performance of the device components was performed by each supplier. These components are not modified by the Company after receipt from the supplier, and the assembly process for the combination product is not expected to adversely impact product quality.”

Syringe barrel assembly design verifications performed by the suppliers are summarized in Table 7 ((b) (4)) and Table 8 ((b) (4)) of this section. Plunger stopper design verification performed by the supplier is summarized in Table 9. Plunger rod design verification performed by the supplier is summarized in Table 10. These tables are recreated below.

(b) (4) Syringe Assembly:

Product Functions	Product Requirement	Test Method Description	Result
Protects drug from the environment	Container closure integrity	(b) (4) Acceptance criteria: (b) (4)	Conforms
		(b) (4) Acceptance criteria: (b) (4)	
Contains drug	(b) (4)	(b) (4)	Conforms
Allows end-user to remove the tip cap, (rigid cap RC + rigid tip cap RiTC)	Easy tip cap removal	(b) (4) Acceptance Criteria: (b) (4)	Conforms
LLA allows end user to obtain an	LLA (b) (4)	(b) (4) Acceptance Criteria: (b) (4)	Conforms

enhanced connection of connector on barrel tip by screwing			
LLA allows end user to obtain an enhanced connection of connector on barrel tip by screwing	LLA (b) (4)	LLA (b) (4) Acceptance Criteria: (b) (4)	Conforms

(b) (4) Syringe Assembly:

Product Functions	Product Requirement	Test Method Description	Result
Protects drug from the environment	Container closure integrity	(b) (4) Acceptance Criteria: (b) (4)	Conforms
Contains drug	(b) (4)	(b) (4) Acceptance Criteria: (b) (4)	Conforms
Allows end-user to remove the tip cap (RC + RiTC)	Easy tip cap removal	(b) (4) Acceptance Criteria: (b) (4) (b) (4) Acceptance Criteria: (b) (4)	Conforms
LLA allows end user to obtain an enhanced connection of connector on	LLA (b) (4)	(b) (4) Acceptance Criteria: (b) (4)	Conforms

barrel tip by screwing			
LLA allows end user to obtain an enhanced connection of connector on barrel tip by screwing	LLA (b) (4)	(b) (4) Acceptance Criteria: (b) (4)	Conforms

Additionally, Table 2 in Section 3 of Module 3.2.P.2.4 Drug Product Container Closure Development lists (b) (4) testing and applicable (b) (4) standards for the syringe components. The information is extracted into the table below.

Component(s)	Conformity	(b) (4) Tests and standards
Syringe Barrel and Tip Cap	Glass (Type (b) (4) glass)	(b) (4)
Syringe Barrel and Tip Cap	(b) (4)	
Syringe Barrel and Tip Cap	Sterility	
Syringe Barrel and Tip Cap	Endotoxin	
Syringe Barrel and Tip Cap	(b) (4) Elastomer Styrene-butadiene blend (b) (4) Synthetic Isoprene-Bromobutyl Blend (latex free) (tip cap, elastomer part)	
Syringe Barrel and Tip Cap	Polypropylene (tip cap, plastic part)	
Syringe Barrel and Tip Cap	Luer Connectivity	
Plunger Stopper	Bromobutyl elastomer	

Plunger Stopper	(b) (4)	(b) (4)
Plunger Stopper	Sterility	
Plunger Stopper	Endotoxins	
Plunger rod*	Polypropylene (plastic part)	

*The plunger rod does not have direct contact with the drug product solution and therefore is not considered a primary packaging component.

Reviewer Comment: Merck’s justification for the application of supplier component verification data to the finished PFS in their product is reasonable. Table 2 in Section 3 of Module 3.2.P.2.4 Drug Product Container Closure Development indicates that the syringe barrels conform to (b) (4). Tables 7 and 8 in Module 3.2.R.7 Development of the Combination Product summarize some evidence of verification per (b) (4).

No information is provided regarding verification of (b) (4). To confirm conformance with ISO 11040-4:2015, Merck should provide evidence of this verification. See **IR#14.1**.

Information Request (IR)#14.1
Date Sent: March 22, 2024
Date/Sequence Received: March 28, 2024 / 0019

IR Comment:
 Table 2 in Section 3 of Module 3.2.P.2.4 Drug Product Container Closure Development indicates that the syringe barrels conform to (b) (4). The standard requires verification of (b) (4). However, Tables 7 and 8 in Module 3.2.R.7 Development of the Combination Product which summarize supplier evidence of verification per (b) (4) does not include information regarding verification of (b) (4). Please provide evidence of confirmation that the supplier has verified (b) (4) of the syringes barrel assemblies.

Applicant Response: The syringe barrel assemblies, consisting of the syringe barrel and Plastic Tip Cap subassembly, are supplied by (b) (4).

respectively, have been verified by each component supplier, as described in their statements for (b) (4) provided with this response.

From the referenced (b) (4) statement dated March 26, 2024:

“This statement provides information on the level of compliance to the (b) (4) with the following sections:

(b) (4)

(b) (4)

From the referenced (b) (4) statement dated March 26, 2024:

“Glass barrel dimensional requirements are measured by (b) (4) for filling were tested during design verification incl. storage.

Flange and cone breakage resistance was checked according to chapters (b) (4). The stability of the syringes is guaranteed and allows the intended use without risk of failure (breakage).”

Reviewer Comments: Response is acceptable.

Reviewer’s Overall Assessment and Recommendations: Sufficient information regarding design verification was provided in the initial BLA and in response to IR#14.

IV. Design Validation

Information regarding design validation and human factors (HF) is included in Section 2.5 of Module 3.2.R.7 Development of the Combination Product, which states “A HF formative study was conducted for the comparator V114... The Threshold-Comparative Analysis results demonstrated there were only minor or negligible/no difference between V116 and the aforementioned comparator products and these differences do not introduce any significant use-related risks. The URRRA did not identify any new, differing, or unique risks for V116 as compared to the comparator products... Based on prior agency feedback, a HF validation study is not required for the V116 BLA... The HF program activities and results are detailed in Section 8 of the Human Factors Engineering Summary Report, located in Module 5.3.5.4.”

Reviewer Comment: Merck submitted their HF information including their justification for why no HF study is needed for V116 to IND 19316 under Amendment 24.

CDER/OSE/OMEPRM/DMEPA conducted a consult review (ICCR# 00082070; consult memo available in CBER Connect) of the information and concurred with Merck's decision that they do not need to submit results of a human factors (HF) validation study as part of the marketing application. The agreement was communicated to Merck via email on August 2, 2021 (teleconference record available in CBER Connect). Notably, however, the "Human Factors Engineering Summary Report located in Module 5.3.5.4" (referenced in the current BLA) was not found. For completeness, Merck should submit the referenced report to the BLA. See **IR#5** below.

Information Request (IR)#5 Date Sent: December 15, 2023 Date/Sequence Received: December 19, 2023 / 0008
IR Comment: In Section 2.5 (Design Validation and Human Factors) of Module 3.2.R.7 Development of the Combination Product, you indicate that the Human Factors (HF) program activities and results are detailed in Section 8 of the Human Factors Engineering Summary Report, located in Module 5.3.5.4. However, we could not locate Module 5.3.5.4 in your BLA. Please provide the missing HF information supporting your conclusion that a HF validation study is not required for the V116 BLA, including your URRA for V116 and the referenced Human Factors Engineering Summary Report.
Applicant Response: Module 5.3.5.4 has been created and the Human Factors (HF) Engineering Summary Report has been added [Ref. 5.3.5.4: 08GYBH]. The full Use Related Risk Analysis (URRA) is introduced in section 6.0 of the HF Engineering Summary Report, and the URRA table located in section 6.2.
Reviewer Comments: Response is acceptable.

Reviewer's Overall Assessment and Recommendations: HF information was reviewed via the supporting IND 19316 and consultation with CDER/.../DMEPA. No further HF review is required for the BLA.

V. Biocompatibility

Biocompatibility information is provided in multiple sections of the BLA. The most detailed information is provided in Section 3 of Module 3.2.R.7 Development of the Combination Product. Merck states the "formulation contacting components of the PFS ((b) (4) syringe barrel assemblies and the plunger stopper) were tested for and met the established (b) (4) criteria for the relevant biological safety endpoints supporting an **externally communicating medical device with tissue contact for limited duration** ((b) (4))". This information was summarized in Table 4, which is recreated below.

(b) (4) Biological Test	Standard	(b) (4) Syringe Barrel Assembly*	(b) (4) Syringe Barrel Assembly**	Plunger Stopper
(b) (4)		Passed, Considered (b) (4)	Passed, Considered (b) (4)	Passed, Considered (b) (4)
		Passed, Considered (b) (4)	Passed, Considered (b) (4)	Passed, Considered (b) (4)
		Passed, Considered (b) (4)	Passed, Considered (b) (4)	Passed, Considered (b) (4)
		Passed, Considered (b) (4)	Passed, Considered (b) (4)	Passed, Considered (b) (4)
		Passed, Considered (b) (4)	Passed, Considered (b) (4)	Passed, Considered (b) (4)
		Passed, Considered (b) (4)	Passed, Considered (b) (4)	Passed, Considered (b) (4)
		Passed, Considered (b) (4)	Passed, Considered (b) (4)	Passed, Considered (b) (4)

“The above studies were performed in compliance to Good Laboratory Practice Regulations (GLP) and the extractions used in the above studies were performed in accordance with (b) (4). (The (b) (4) testing is not needed for devices with tissue contact; however, the data was available and is included for completeness).

* (b) (4) Syringe Barrel Assembly tested consisted of glass syringe barrel with polycarbonate Luer Lock adaptor (LLA), (b) (4), elastomeric tip cap and polypropylene rigid cap.

** (b) (4) Syringe Barrel Assembly tested consisted of glass syringe barrel with polycarbonate LLA, (b) (4) and elastomeric tip cap.”

Additionally, “Based on the proposed use, contact to the Health Care Provider (user) is not anticipated as they follow Universal Precautions and would wear gloves when handling the pre-filled syringe. In the case a Health Care Provider does not wear gloves, the relevant biological safety endpoints outlined in (b) (4) for a surface medical device with limited intact skin contact (cytotoxicity, irritation and sensitization) were satisfied for the plunger rod”. This information was summarized in Table 5, which is recreated below.

(b) (4) Biological Test	Standard	Result
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(b) (4)	(b) (4)	Passed, Considered Non-cytotoxic
(b) (4)	(b) (4)	Passed, Considered Non-sensitizing
(b) (4)	(b) (4)	Passed, Considered Non-irritating

Reviewer Comment: Module 3.2.R.7 also refers to “V116 Biological Risk Assessment Report (Module 4, BRAR002-V116).” However, this report was not found in Module 4 of the BLA. Merck should provide the referenced report, as well as the reports for the biocompatibility testing. See **IR#14.3**.

<p>Information Request (IR)#14.3 Date Sent: March 22, 2024 Date/Sequence Received: March 28, 2024 / 0019</p>							
<p>IR Comment: In Section 3 of Module 3.2.R.7 Development of the Combination Product, you state the “formulation contacting components of the PFS ((b) (4) syringe barrel assemblies and the plunger stopper) were tested for and met the established (b) (4) criteria for the relevant biological safety endpoints supporting an externally communicating medical device with tissue contact for limited duration (b) (4))”. Ou also states that “In the case a Health Care Provider does not wear gloves, the relevant biological safety endpoints outlined in (b) (4) for a surface medical device with limited intact skin contact ((b) (4)) were satisfied for the plunger rod.” You summarize the test methods and results in Tables 4 and 5 of that section. However, we could not locate the corresponding test reports for these studies in your BLA. We note that you refer to “V116 Biological Risk Assessment Report (Module 4, BRAR002-V116),” but we also could not locate this report in Module 4. To complete review of your biocompatibility information, please provide test reports for the studies summarized in Table 4 and Table 5 of Section 3 of Module 3.2.R.7 Development of the Combination Product, as well as the V116 Biological Risk Assessment Report (BRAR002-V116).</p>							
<p>Applicant Response: An updated Biological Risk Assessment Report (BRAR003-V116) and all associated references are provided in Module 4 [Ref. 4.2.3.7.7: BRAR003V116]. The key difference between BRAR002-V116 referenced in 3.2.R.7 and BRAR003-V116 is the summary of the 9-month leachable data. The (b) (4) syringe barrel assembly, (b) (4) plunger stopper and (b) (4) plunger rod test reports for studies summarized in Table 4 and Table 5 of 3.2.R.7 Development of the Combination Product, were provided by (b) (4) in an update to their Drug Master File (DMF) (b) (4) submitted 27 March 2024. The (b) (4) syringe barrel assembly test reports for studies summarized in Table 4 of 3.2.R.7 Development of the Combination Product are included in the (b) (4) DMF (b) (4). The location of biological test information for each of the components is summarized in Table 1.</p>							
<p>Table 1 Component Biocompatibility Test Report Locations</p> <table border="1"> <thead> <tr> <th>Component</th> <th>Supplier</th> <th>Biological Test (Summarized in 3.2.R.7 Table 4 or Table 5)</th> <th>DMF Number</th> </tr> </thead> </table>				Component	Supplier	Biological Test (Summarized in 3.2.R.7 Table 4 or Table 5)	DMF Number
Component	Supplier	Biological Test (Summarized in 3.2.R.7 Table 4 or Table 5)	DMF Number				

Syringe barrel assembly and Plunger Stopper	
Syringe barrel assembly	
Plunger rod	

Reviewer Comments: The biocompatibility test reports referenced to (b) (4) DMF (b) (4) were previously reviewed in support of BLA 125769, for the same syringe configuration (see Section I.C of this memo and information excerpted from the referenced BRAR below). Therefore, a new memo will not be created for DMF (b) (4). Refer to separate memo for review of referenced biocompatibility information in DMF (b) (4).

BRAR003-V116 provided in the response to IR#14.3 describes “an evaluation of the manufacturing process, materials of construction, physical/chemical information and biological safety information. Based upon this evaluation, the materials of construction of the prefilled syringe meet the appropriate regulatory requirements and based upon the proposed use, the relevant biological safety endpoints outlined in (b) (4) have been satisfied. Collectively, these data support the biocompatibility and safe use of the V116 prefilled syringe in the proposed population (≥18 years of age and 2 to 18 years of age).”

The BRAR also provides additional information regarding material of construction, in Table 3, recreated below.

Table 3 Comparison of (b) (4) Syringe Barrel Assemblies

Parameter	(b) (4) Glass Syringe Barrel Assembly ((b) (4))	(b) (4) Glass Syringe Barrel Assembly ((b) (4))
Glass syringe barrel	(b) (4) 1.5 mL luer lock adaptor syringe barrel (Type (b) (4) glass) with round flange	(b) (4) 1.5 mL luer lock adaptor syringe barrel (Type (b) (4) glass) with round flange
Rigid cap	Rigid cap made of polypropylene with an elastomeric closure (drug contacting) made of (b) (4)	Rigid cap made of polypropylene with an elastomeric closure (drug contacting) made of (b) (4) rubber material

Sterilization of syringe barrel assembly	(b) (4) : All sterilization cycles are validated as per (b) (4) and meet the same acceptance criteria for SAL of (b) (4) and (b) (4)	(b) (4) sterilization: All sterilization cycles are validated as per (b) (4) and meet the same acceptance criteria for SAL of (b) (4) and (b) (4)
Syringe (b) (4)	(b) (4)	(b) (4)

Reviewer’s Overall Assessment and Recommendations: *Biocompatibility information is sufficient.*

VI. Sterilization

Module 3.2.P.2.4 Drug Product Container Closure Development states “Syringe barrels assembled with tip caps and sterilized by (b) (4) are received as ready-to-use from the vendor. Stoppers sterilized by (b) (4) and are received ready to use from the vendor.”

Table 2 in Section 1 of Module 3.2.P.7 Container Closure System summarizes sterilization method information. The information is extracted in the table below.

Component	Sterilization Process	Site of Sterilization
Syringe Barrel Assembly (A) (b) (4)	<div style="font-size: 4em; font-weight: bold;">(b) (4)</div>	
Syringe Barrel Assembly (B) (b) (4)		
Plunger Stopper		

		(b) (4)
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* Conformity of (b) (4) according to (b) (4)
– simulated use test according to (b) (4)

** (b) (4), meets sterility assurance level of (b) (4)

Section 1 of Module 3.2.R.7 Development of the Combination Product states (emphasis added by reviewer), “All sterilization cycles for the barrel assemblies are **validated as per (b) (4)** and **meet the same acceptance criteria for SAL of (b) (4) and (b) (4)**”

The Certificate of Conformance for the (b) (4) syringe assembly (b) (4) (b) (4) in Module 3.2.R includes the following information (emphasis added by reviewer):

- The sterility assurance level (SAL) is (b) (4) is reached based on:
(b) (4)
- Conformity of (b) (4) according to the (b) (4) (b) (4) ... are testing according to the (b) (4)
- **Bacterial endotoxins** are based on (b) (4) (b) (4) and the (b) (4) (b) (4), current editions. The limit is (b) (4).

The Certificate of Conformance for the (b) (4) syringe assembly (b) (4) (b) (4) in Module 3.2.R includes the following information (emphasis added by reviewer):

- “Sterility – The sterilization process is **validated according to (b) (4)** and executed by a contract sterilization company. The final sterility test, based on the current edition of **(b) (4)**, has been passed successfully.
- Endotoxin – Bacterial endotoxins are measured based on the current edition of **(b) (4)** and **(b) (4)**. The test has been passed successfully.
- **(b) (4)**

Reviewer’s Overall Assessment and Recommendations: Sterilization is sufficient. Review of drug product sterility and endotoxin levels is deferred to CMC and DMPQ review.

VII. Control Strategy

Essential Performance Requirement	Control Strategy Description (e.g., incoming acceptance, in-process control, release testing activities):
Recoverable volume	Design verification and PPQ studies, tested on release and primary stability studies (0.500 (b) (4) mL)
(b) (4)	Design verification and PPQ studies, tested on primary stability studies (b) (4) , recoverable volume and syringeability testing at release indicative of acceptable (b) (4) , supplier testing of (b) (4) quantity.

Reviewer’s Overall Assessment and Recommendations: EPR control strategy is adequate.

VIII. Packaging, Stability, Shipping

A. Packaging

Section 2 of Module 3.2.P.7 Container Closure System states “The syringes are packaged in a tray together with a package circular. The batch number and expiry date are applied to both the labels and cartons.”

B. Stability

Proposed Shelf Life and Storage Conditions: 2°C to 8°C, 18 months.

The table below is adapted from Table 1 DP Batches in Stability Studies in Module 3.2.P.8.3.1 (DOM = Date of Manufacture; TOS = Time Out of Storage). Information regarding photostability studies is not included as these studies did not evaluate device-relevant metrics.

Batch Number	DOM	Manufacturing Site / Syringe	Long-Term Studies 5 ± 3°C	TOS (b) (4)	TOS (b) (4)	TOS (b) (4)
(b) (4)	(4)		X	N/A	N/A	N/A
			X	N/A	N/A	N/A
			X	X	X	N/A
			X	X	N/A	N/A
			X	X	X	N/A
			X	X	N/A	N/A
			X	X	X	X
			X	X	N/A	X
			X	X	N/A	N/A
			X	X	N/A	N/A
			X	X	N/A	N/A
			X	X	N/A	N/A

*PPQ batches

**Pilot-scale batches.

Data for recoverable volume, syringeability, and syringe functions are available for T = 0, 3, 6, 9, 12, and 18 months, with planned timepoints for (b) (4) months, for all commercial scale batches in the long-term storage studies (5±3°C) except the PPQ batches, which have data up to 6 months. Additionally, the pilot-scale batches have data available through (b) (4) months.

Data for recoverable volume, syringeability, and syringe functions are available for T = 0, 2, 4, 8 and 14 weeks for all commercial scale batches included in the TOS (b) (4), except for the PPQ batches, that only have T = 0 data.

Data for recoverable volume, syringeability, and syringe functions are available for T = 0, 2, 4, 8 and 12 weeks for all commercial scale batches included in the TOS (b) (4).

Data for recoverable volume, syringeability, and syringe functions are available for T = 0 and 30 days for all commercial scale batches included in the TOS (b) (4).

All samples the acceptance criteria in Module 3.2.P.5.1 and reiterated in the table below.

Attribute	Stability Acceptance Criteria
Recoverable Volume (mL)	0.50 (b) (4)
Syringeability	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage.
Syringe Functionality (b) (4)	(b) (4)

Module 3.2.P.8.2 contains the post-approval stability protocol and stability commitment. “Stability studies on the PSS batches for the DP will be continued according to the schedule detailed in the data tables for these batches presented in Section 3.2.P.8.3.1 Stability Data. Annually, subject to DP manufacturing, a minimum of one DP batch will be enrolled in the commercial stability program at the long-term storage condition of 5 ± 3 °C. A summary of the routine annual stability protocol is provided in Table 1” (device-relevant metrics excerpted below).

Test Name	0 months	6 months	12 months	18 months	(b) (4)
Syringeability/ Recoverable Volume	X	X	X	X	(b) (4)
Syringe (b) (4)	X	X	X	X	

C. Shipping

Refer to Section III.A of this memo. Test samples used for design verification were preconditioned by simulated shipping per (b) (4).

Reviewer’s Overall Assessment and Recommendations: Sufficient information was provided regarding packaging, stability, and shipping in the initial BLA, from a device perspective.

IX. Comparability Protocols

Module 3.2.R contains several Post approval change management protocols (PACMP). Relevant to the device are 3.2.R.5.2 for drug product shelf-life extension and 3.2.R.20 for primary packaging components.

A. Drug Product Shelf-life Extension

Merck intends to (b) (4) the current shelf life from 18 months (b) (4) “based on an ongoing stability program with real time data from (b) (4) PSS batches. The ongoing studies will be completed to support the proposed shelf-life.” The specifications and acceptance criteria are as listed in Module 3.2.P.5.1. The sponsor proposes this as an annual reportable change (AR). Merck states “The affected manufacturing sites will not distribute product with (b) (4) shelf-life for either clinical or commercial use until the site’s quality control unit has confirmed that the criteria specified in this protocol have been met and have approved the implementation of the change. Any (b) (4) to the DP shelf-life will be implemented through the quality management system. This protocol will be considered effective upon Agency approval. The Company commits to update or withdraw this PACMP when it becomes obsolete or is no longer consistent with the approved BLA and current FDA policy.”

Reviewer Comments: Protocol for drug product shelf-life (b) (4) appears reasonable from a device perspective.

B. Primary Packaging Components

These protocols encompass changes two presentations: (b) (4)

Reviewer Comments: Review of the protocol for changes to (b) (4) is deferred to CMC.

Notably, the beginning of this document states “The applicant is submitting this post approval change management protocol (PACMP)/ comparability protocol (CP) (herein referred to as CP) as a trans-BLA (Biologics License Application) Prior Approval Supplement (PAS), to facilitate changes in primary packaging components/component suppliers for use in sterile vaccine products.”

Reviewer Comments: It appears Merck wants this CP to apply to their entire portfolio of sterile vaccine products. This not appropriate to do under this original BLA. CPs proposed in an original BLA should be limited to the product under that BLA. This was discussed with the CMC review team, who identified that this CP is recycled from a large trans-BLA PAS for several BLAs for vaccine products in Merck-s portfolio. Such a proposal should be submitted after approval as a PAS to the current BLA, to incorporate it into the CP approved under the referenced trans-BLA PAS. See IR#27. As this reviewer was not involved in the review of the referenced trans-BLA, the device-relevant aspects, for completeness.

Information Request (IR)#27.1

Date Sent: May 13, 2024

Date/Sequence Received: May 17, 2024 / 0050

IR Comment:

Please refer to your comparability protocol (CP) in Module 3.2.R.20 regarding primary packing components, where you state, “The applicant is submitting this post approval

change management protocol (PACMP)/ comparability protocol (CP) (herein referred to as CP) as a trans-BLA (Biologics License Application) Prior Approval Supplement (PAS), to facilitate changes in primary packaging components/component suppliers for use in sterile vaccine products.” While “a single CP can be used for one or more proposed CMC changes that apply to multiple products marketed by the same applicant”, as discussed in the FDA guidance Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA (<https://www.fda.gov/media/162263/download>), it is not appropriate to include such a proposal in an original BLA for a single product. Rather, such a proposal should be submitted as a post-approval submission (e.g., grouped supplements, trans-BLA prior approval supplement (PAS)) that clearly identifies the applicable approved products (i.e., BLA STNs) subject to the CP. CPs proposed in an original BLA for a single product should be limited to changes to the product that is the subject of the BLA. Therefore, please remove the CP proposal in Module 3.2.R.20 from your BLA. Should your BLA be approved, you may submit your multi-product CP as a trans-BLA PAS for the applicable products under approved BLAs. Alternatively, if this CP was previously approved for in a trans-BLA PAS approved BLAs, you may submit a PAS to this BLA, if and when it is approved to incorporate it into the previously approved CP.

Applicant Response:

With this response, the Company considers 3.2.R.20 Comparability Protocol – Alternative Components (DP) withdrawn from the V116 BLA.

Reviewer Comments: *Response acceptable.*

(b) (4)

The following tables from this document are excerpted in Appendix 2 of this memo:

- (b) (4)

Notable points include the following:

- After submission and approval for one product as described in this CP, subsequent, submissions for additional products using the same exact same components with the same extractable/leachable profile will be submitted as an AR category, providing acceptance criteria as described in section 4 [Supporting Information and Comparability Analysis] of this CP is met. For these scenarios the reporting category will revert to CBE-30, (i.e., reporting category for first product), in the event that the requirements described in section 4 are not met.

- Changes to (b) (4) components will be supported by:
 - Design control information
 - A summary of the risk analysis pertaining to the proposed change for each product will be provided
 - Design verification data relevant to the proposed change, including evaluation of (b) (4)
 - A summary of updates to the device risk management file
 - Product Release Results/Batch Analysis per final release specifications, which includes recoverable volume, and syringeability
 - Stability studies will be conducted, per criteria in 3.2.P.5.1, which includes (b) (4), recoverable volume, and syringeability
 - Distribution qualification will be performed as applicable per risk assessment

Reviewer’s Overall Assessment and Recommendations: *In general, the proposed reporting changes, reporting categories, and supporting data appear reasonable for the specific types of changes, as far as device-relevant information is concerned. Adequacy of the information provided would be a review issue at that time. Merck removed the proposed CP from this current BLA, as it is not appropriate as currently written (i.e., as a trans-BLA PAS within an original BLA).*

X. Quality System

Information on the Quality Management System (QMS) is provided in Module 3.2.R.4 Quality System for Combination Products. The QMS is drug-based and complies with the applicable 21 CFR 820 regulations called out in the streamlined approach described in 21 CFR 4.4(b)(1):

- 820.20 Management Responsibility
- 820.30 Design Controls
- 820.50 Purchasing Controls
- 820.100 Corrective and Preventative Actions (CAPA)

The quality system approach is summarized in Table 1 of this document, recreated below.

Role	Commercial Supply	cGMP/Quality System
Device Component Manufacturer/Supplier*	Glass syringe barrel assembly (including the plastic tip cap) Plunger Stopper Plunger Rod	820.20 Management Responsibility 820.30 Design Controls 820.50 Purchasing Controls 820.100 Corrective and Preventative Actions (CAPA) (b) (4)

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Role	Commercial Supply	cGMP/Quality System
Drug Product Manufacturer (Formulation and Filling)	Pre-filled syringes Device component intermediate manufacturing	Current good manufacturing practices under 21 CFR 210-211
Drug Product Manufacturer (Plunger rod assembly, labeling) Drug Packaging Site	Final vaccine pre-filled syringe * (Combination product manufacturing)	Current good manufacturing practices under 21 CFR 210-211, supplemented with: 820.20 Management Responsibility 820.30 Design Controls 820.50 Purchasing Controls 820.100 Corrective and Preventative Actions (CAPA)

Device GMP Requirement	Summary
21 CFR 820.20 Management Responsibility	Deferred to OCBQ/DMPQ review.
21 CFR 820.30 Design Controls	The summary in Module 3.2.R includes reference to design and development planning, design inputs, design outputs, design review, design verification, design validation, design transfer, design changes, and risk management. The design history file is referred to as the Global Design File. Design controls are further described in Module 3.2.R.7 Development of the Combination Product.
21 CFR 820.50 Purchasing Controls	The summary in Module 3.2.R supplier/manufacturer selection processes, Quality Agreements, audits, and incoming material specifications. Notably, “the quality agreement includes a change notification clause requiring all changes at the supplier or contract manufacturer to be notified to the Company for assessment through the Company’s change control evaluation process.”
21 CFR 820.100 Corrective and Preventive Actions	Deferred to OCBQ/DMPQ review.

Device GMP Requirement	Summary
21 CFR 820.170 Installation	N/A
21 CFR 820.200 Servicing	N/A

Reviewer’s Overall Assessment and Recommendations: Adequate information has been provided regarding design controls and purchasing controls. Review of management responsibility and corrective and preventative action (CAPA) is deferred to DMPQ.

XI. Appendices

A. Appendix 1 – Dimensions

From Module 3.2.P.7:

i. Syringe Barrel

Parameter	Dimension Acceptance Limits (mm) ^{(b) (4)}	Dimension Acceptance Limits (mm) ^{(b) (4)}
Flange Thickness	(b)	(4)
Overall Length		
Barrel Inner Diameter		
Barrel Outer Diameter		

ii. Plunger Stopper

Parameter	Dimension Acceptance Limits (mm)
Overall Height	(b) (4)
Outside Diameter (trim edge)	
Outside Diameter (ribs)	

iii. Plunger Rod

Parameter	Dimension Acceptance Limits (mm)
Overall Length	(b) (4)
Overall Diameter	

B. Appendix 2 – PFS Primary Packaging Components Comparability Protocol

From Module 3.2.R.20:

(b) (4)

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