CBER BLA Device Review Memorandum – Prefilled Syringe (PFS)

BLA STN 125817

NUVAXOVID [COVID-19 Vaccine, Adjuvanted]

(b) (6)

CBER/(b) (6)

1. **BLA STN**
   125817

2. **APPLICANT NAME**
   Novavax Inc.

3. **PRODUCT NAME/PRODUCT TYPE**
   - Non-Proprietary/Proper/USAN: COVID-19 Vaccine adjuvanted
   - Proprietary Name: NUVAXOVID

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**
   - General Description: NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is a colorless to slightly yellow, clear to mildly opalescent suspension for intramuscular injection that is practically free from visible particles. Each 0.5 mL dose of NUVAXOVID (2024 – 2025 Formula) contains 5 mcg of recombinant spike (rS) protein from the SARS-CoV-2 Omicron variant lineage JN.1 and 50 mcg Matrix-M adjuvant. It is supplied in single-dose pre-filled syringes.
   - Route of administration: Intramuscular injection
   - Indication(s): Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) in individuals 12 years of age and older

5. **COMBINATION PRODUCT INFORMATION**
   - Type: 3
   - Biologic Constituent(s): vaccine
   - Drug Constituent(s): n/a
   - Device Constituent(s): syringe

6. **MAJOR MILESTONES**
   - Filing Meeting: May 7, 2024
   - Midcycle Internal Meeting: September 15, 2024
   - Late Cycle Internal Meeting: November 22, 2024
   - PDUFA Action Date: April 1, 2025

7. **QUALITY REVIEW TEAM**

Reviewer/Affiliation	PFS-Relevant Subject Matter
(b) (6), CBER/OVRR/(b) (6)	Product compatibility, drug product quality attributes including sterility and endotoxin, container closure considerations (e.g., extractables/leachables and toxicological risk assessment, particulates, light protection)

Reviewer/Affiliation	PFS-Relevant Subject Matter
(b) (6), CBER(b) (6)	container closure integrity testing, aseptic processing, sterilization, dehydrogenation, shipping validation (CCIT, plunger stopper movement), quality system (management responsibility, CAPA)

8. INTRA- & INTER-CENTER CONSULTS

None

9. SUBMISSION(S) REVIEWED

Date Received	eCTD Sequence	Amd (STN 2nd Level)	Comments
31 Oct 2024	0044	42	CMC and nonclinical information for JN.1 strain in PFS
15 Nov 2024	0047	45	Updated stability data
12 Dec 2024	0053	51	PFS JN.1 Shipping Validation Final Report
25 Feb 2025	0078	76	Response to CMC IR dated 23 Feb 2025, regarding shipping validation
27 Feb 2025	0079	77	Response to device IR#52
04 Mar 2025	0087	85	Response to device IR#59

10. RELEVANT REFERENCED REGULATORY SUBMISSIONS

Submission Type & STN (Center)	Holder	Referenced Information	Letter of Authorization (Yes/No)	Comments/Status
DMF (b) (4)	(b) (4)	Syringe components	Yes	Separate review memo created, focusing on biocompatibility

11. RELEVANT PRIOR INTERACTIONS

- Novavax's COVID-19 vaccine, adjuvanted (Nuvaxovid) is currently under EUA (EUA 28237).
- FDA re-authorized Novavax's EUA for their covid-19 vaccine, 2024-2025 formula (JN.1), in PFS in individuals 12 years of age and older in August 2024. I was not involved in the device review for the EUA.
- The BLA was submitted on January 31, 2024, originally to support their XBB.1.5 strain in 5DV; however, since this strain is not actively circulating, FDA advised them to submit the supportive information for their 2024-2025 formulation (JN.1)

(currently submitted under EUA 28237) to the BLA so that FDA would be considering approval of a product that would be more appropriate and relevant.
- The proposal to change course regarding their formulation (and presentation), and to include all supporting information to the BLA, was agreed upon by CBER on October 18, 2024.
- Novavax confirmed via email (dated October 18, 2024), that they only plan to manufacture their JN.1 formulation in PFS and not multi-dose vials.
- A request to add a PFS device reviewer to the review team was received on November 4, 2024, after the mid-cycle meeting which was held on September 15, 2024.

12. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Novavax submitted a BLA for licensure of their COVID-19 vaccine (NUVAXOVID), which consists of a single-dose of drug product (DP) in a non-graduated 1 mL Type (b) (4) glass pre-filled syringe (PFS). The scope of this review memo includes device evaluation of the PFS. Specifically, the review memo include evaluation of PFS description, PFS design verification, including device essential performance (deliverable volume, (b) (4) , verification that device essential performance is maintained over the shelf life and after shipping, control strategy to ensure PFS meets device performance specifications, PFS device biocompatibility (excluding extractable/leachables and subsequent toxicological risk assessment, which is deferred to CMC), and compliance with design controls regulations (21 CFR 820.30) and purchasing control regulations (21 CFR 820.50). Information cross referenced to a master file is documented in a separate review memo. Based on the information provided in the application and in the cross-referenced master file, as well as additional information submitted interactively, I recommend that the BLA can be approved from a device/combination product perspective.

B. RECOMMENDATION

I. APPROVAL

- No PMCs or PMRs original from the device review.

II. SIGNATURE BLOCK

Reviewer, Title, Affiliation	Concurrence	Signature and Date
(b) (6) CBER/(b) (6)	-	
(b) (6) CBER(b) (6)	Concur March 17, 2025	

Table of Contents

I. Product Description 1
A. Combination Product 1
B. Drug/Biologic 1
C. Syringe 2
II. Manufacturing 3
A. Manufacturers 3
B. Manufacturing Process 4
i. In Process Controls 6
ii. Final Product Specifications and Test Methods 6
iii. Batch Analyses 8
C. Process Validation 9
III. Design Verification 11
IV. Design Validation 16
V. Biocompatibility 18
VI. Sterilization 22
VII. Control Strategy 26
VIII. Packaging, Stability, Shipping 27
A. Packaging 27
B. Stability 27
C. Shipping 30
IX. Comparability Protocols 38
X. Quality Management System 38

I. Product Description

A. Combination Product

The combination product consists of the drug product filled into a prefilled syringe (PFS) consisting of a Type (b) (4) glass syringe barrel with a luer lock adapter and rigid cap, plunger stopper, and plunger rod.

B. Drug/Biologic

Per Module 3.2.P.2 [JN.1], "SARS-CoV-2 rS Vaccine with Matrix-M1 Adjuvant is made by formulation of SARS-CoV-2 rS drug substance (DS) and the two components of Matrix-M1 Adjuvant, Matrix-A and Matrix-C, in a buffered solution of pH (b) (4) containing (b) (4) mg/mL of Disodium hydrogen phosphate heptahydrate, (b) (4) mg/mL of Sodium dihydrogen phosphate monohydrate, (b) (4) mg/mL Sodium chloride, and (b) (4) mg/mL Polysorbate 80." Refer to CMC memo for more information.

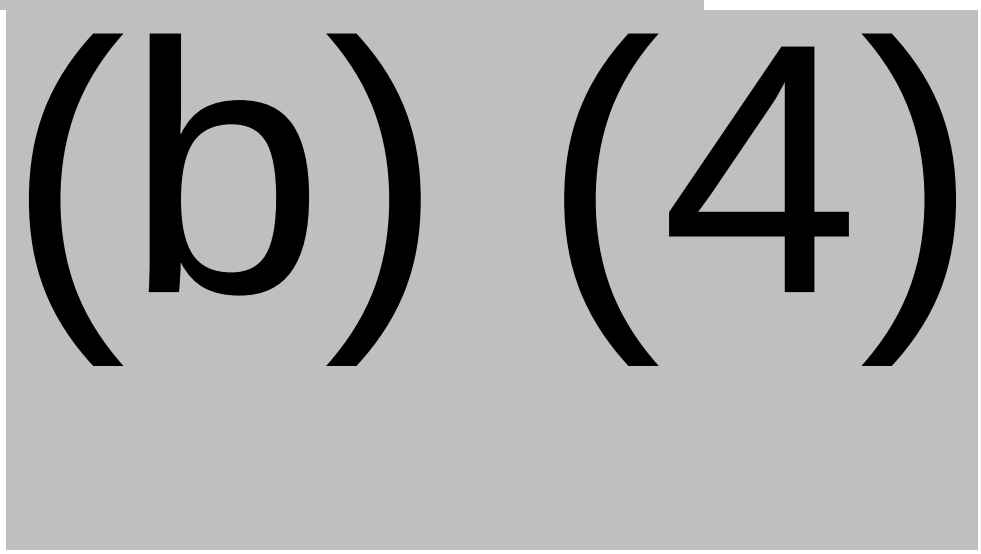
C. Syringe

Table 1: Packaging Components

Components	Description	Supplier	Drug Master File
Syringe Barrel	(b) (4) Sterile, Clean and ready to Fill 1 mL, Round Flange, Siliconized Type (b) (4) borosilicate glass syringe barrel with Luer lock and Plastic Rigid Tip Cap with (b) (4) Elastomer	(b) (4)	DMF (b) (4)
Syringe Plunger Stopper	(b) (4)		
Plunger Rod [1]	Polystyrene plunger rod		

From Module 3.2.P.7 Container Closure System

(b) (4)



Components and Suppliers	(b) (4) – syringe barrel assembly (barrel, luer lock adapter (LLA), rigid cap, tip cap), plunger stopper, plunger rod
Connection Type	Luer lock
Intended Connector(s)	Hypodermic needle
Materials of Construction	Syringe barrel: Type (b) (4) borosilicate glass LLA: polycarbonate Rigid cap: Tip cap: (b) (4) rubber Plunger stopper: (b) (4) rubber Lubricant: (b) (4) silicone (b) (4) Plunger rod: polystyrene
Dimensions	Engineering drawings are provided for the syringe barrel assembly (Module 3.2.P.7), plunger stopper (Module 3.2.P.7), and plunger rod (Module 3.2.R.1).
Syringe Volume	1 mL
Fill Volume	(b) (4) mL (Fill volume range (b) (4) mL to (b) (4) mL)
Sterilization Method	Syringe barrel assembly: (b) (4) sterilized by supplier Plunger stopper: (b) (4) by upplier

	Plunge rod: non-sterile
Route of Administration	Intramuscular injection
Administration Site	Injection site necessary for intramuscular injection of vaccines is common knowledge in the healthcare community per ACIP guidelines.
Target Tissue and Depth	Target tissue and depth necessary for intramuscular injection of vaccines is common knowledge in the healthcare community per ACIP guidelines.
Type of Use	Single
Storage Conditions and Proposed Expiry	3 months at 2-8°C
Intended User(s)	Healthcare professionals
Intended Use Environment	Clinic
Needle Length, Gauge, Tip Style	No needle supplied with vaccine. Needle specifications necessary for intramuscular injection of vaccines is common knowledge in the healthcare community, per ACIP guidelines.
Markings	n/a
Reuse Durability	n/a
Safety Features	n/a
Automated Functions	n/a

***Reviewer's Overall Assessment and Recommendations**:* Product description information provided in the BLA and referenced DMF is acceptable from a device perspective.

II. Manufacturing

A. Manufacturers

From Module 3.2.P.3.1:

Facility	Responsibility
Serum Institute of India Pvt. Ltd. (b) (4)	Drug Product Manufacture: • Formulation • Sterilization by (b) (4) • Aseptic filling • Primary Packaging Secondary Packaging: • Labelling • Packaging Quality Control Testing: • In-Process o (b) (4)

Facility	Responsibility
	(b) (4)
Novavax AB (b) (4) Uppsala, Sweden (b) (4)	Quality Control Testing: • Batch Release and Stability Testing o Matrix-A Content by (b) (4) o Matrix-C Content by (b) (4) o Particle Size by (b) (4)
(b) (4)	Quality Control Testing: • Batch Release and Stability o Identity by (b) (4)
(b) (4)	Quality Control Testing: • Batch Release o Expelled Volume • Stability o CCIT o(b) (4)

B. Manufacturing Process

The flow diagram below describes the device-relevant portions of the manufacturing process, beginning with introduction of the syringe components for filling.

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

(b) (4)

(b) (4)

ii. Final Product Specifications and Test Methods

Device-relevant final product specifications included in Module 3.2.P.5.1 are listed below:

Test Method	**Compendial Reference**	**Release Acceptance Criteria**	**Stability Acceptance Criteria**
Expelled volume	(b) (4)	The volume measured for each container is not less than the nominal volume.	NA

Test Method	Compendial Reference	Release Acceptance Criteria	Stability Acceptance Criteria
Container Closure Integrity Test (CCIT)	(b) (4)	NA	No failures allowed
(b) (4)	(b) (4)	NA	(b) (4)

***Reviewer Comment**: Although container closure integrity (CCI) review is deferred to* (b) (6)*, it is also noted throughout this review as CCI testing (CCIT) is often used in stability testing and shipping validation to demonstrate dose accuracy is maintained. The release acceptance criterion for expelled volume is inadequate. It vaguely refers to a "nominal value" rather than an explicit limit (e.g.,* (b) (4) *0.5 mL). Applicant should address this. See **IR#52.1**.*

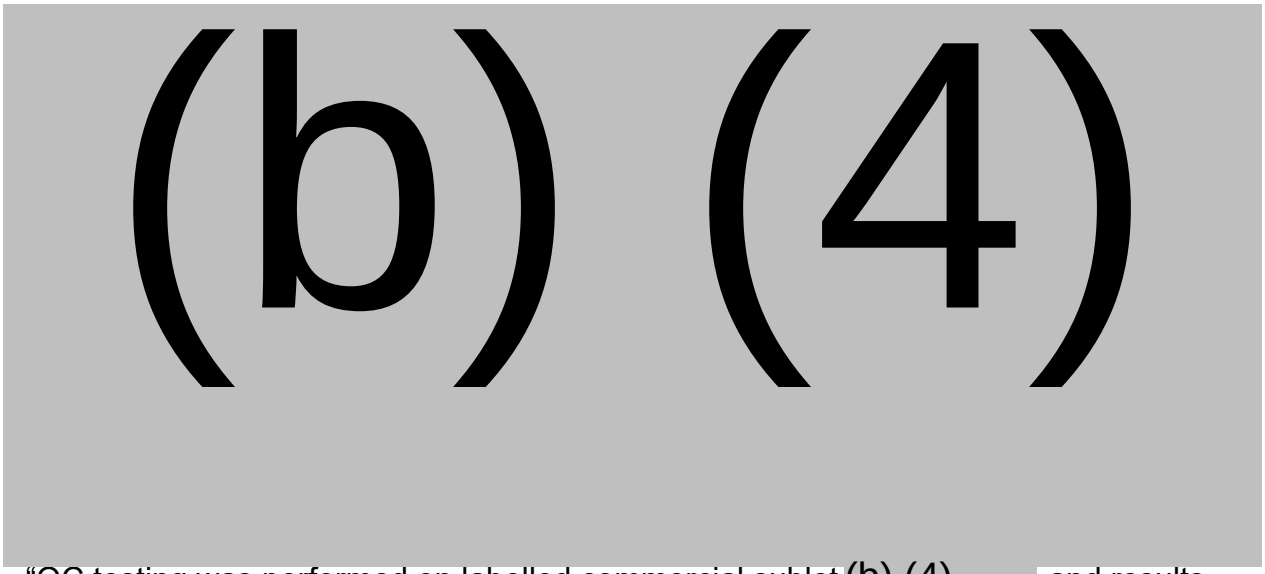
Information Request (IR)#52.1 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: The acceptance criterion for "expelled volume" in the release specifications listed in Module 3.2.P.5.1 is "The volume measured for each container is not less than the nominal volume." This acceptance criterion is not adequate, as it is not clear what the "nominal volume" refers to. To ensure the final product will deliver the intended dose (i.e., will meet its essential performance requirement for dose accuracy), please revise your release specification to explicitly state a quantitative limit or range for expelled volume (e.g., not less than 0.5 mL).
Applicant Response: Novavax acknowledges the Agency's request and has revised the acceptance criterion to reflect "The volume measured for each container is not less than the nominal volume, 0.5 mL". Sections 3.2.P.5.1 and 3.2.P.5.6 have been revised and provided in this response to reflect this updated criterion.
***Reviewer Comments**: Response is **acceptable**.*

Specification justifications are provided in Module 3.2.P.5.6. Notably, the justification for the (b) (4) acceptance criteria states that the values are based on a "peer reviewed and published research reference, "Injectability as a function of viscosity and dosing materials for subcutaneous administration" from The International Journal of Pharmaceuticals… The study results concluded that an (b) (4) (b) (4) was considered to be unacceptable for most participants, (b) (4) was considered the maximum acceptable (b) (4), and the preferred (b) (4) for injection was no more than (b) (4)."

***Reviewer Comment**: The full citation appears to be "Injectability as a function of viscosity and dosing materials for subcutaneous administration",* International Journal of Pharmaceutics*, Volume 554, 10 January 2019, Pages 376-386. The focus of this study appears to be patient comfort as opposed to administrator strength. Regarding the latter, Applicant states "HCP are experienced with the use of prefilled syringes and are considered healthy adults with the hand strength to deliver a dose of vaccine at a rate equal to 100 mm/min."*

iii. Batch Analyses

The only device-relevant specification included in the batch analyses in Module 3.2.P.5.4 is "dose delivery" per (b) (4), with an acceptance criterion of "The volume measured for each container is not less than the nominal volume." All samples for the (b) (4) batches tabulated below (adapted from Tables 1 through 4 in this module) met the acceptance criterion. These batches were all manufactured in the same facility (b) (4) Floor ((b) (4) premises SIIPL)).



"QC testing was performed on labelled commercial sublot (b) (4) and results are applicable to all clinical sublots."

[2] "QC testing was performed on labelled commercial sublot (b) (4) and results are applicable to all clinical sublots."

***Reviewer Comment**: Although the dose delivery relates to each container ("The volume measured for each container is not less than the nominal volume"), the data in Tables 1 through 4 in Module 3.2.P.5.4 only reports the average delivered dose from (b) (4) PFS. See **IR#52.2**.*

Information Request (IR)#52.2 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: In the Batch Analysis data included in Module 3.2.P.5.4, the specification of "dose delivery" was evaluated per (b) (4) with an acceptance criterion of "The volume measured for each container is not less than the nominal volume." Although the acceptance criterion relates to each container, the data in Tables 1 through 4 in Module 3.2.P.5.4 only reports the average delivered dose from (b) (4) PFS. To ensure the samples met the stated acceptance criterion, please provide the results for each PFS. Please also refer to Comment 1 above regarding the quality of the acceptance criterion.

Information Request (IR)#52.2
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

Applicant Response: The delivered dose results for each PFS tested for batches included in 3.2.P.5.4 in Table 1 are presented below. Each PFS tested met the acceptance criterion at the time of testing, "The volume measured for each container is not less than the nominal volume", with the nominal volume defined as 0.5 mL per the label claim.

(b) (4)

Reviewer Comments: *Response is **acceptable**. All PFS samples met the acceptance criterion.*

According to PPQ report QAG_28686 provided in Module 3.2.P.3.5, (b) (4) testing were also performed on a portion of these lots, as tabulated below.

(b) (4)

C. Process Validation

(b) (4)

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

(b) (4)

***Reviewer's Overall Assessment and Recommendations**:* Manufacturing information provided in the BLA and in response to IR#52 is acceptable from a device perspective.

III. Design Verification

Design verification information is provided in Module 3.2.R.1 Device Information, which states verification was performed using "a combination of testing, inspection, and review of design output documents… Novavax has leveraged (b) (4) design control and risk management processes to the extent they are applicable to our use of the PFS components… In addition to the component level design verification performed by (b) (4), Novavax also performed PFS system level design verification using PFS filled with Novavax's SARSCoV-2 rS Protein (COVID-19) Nanoparticle Vaccine."

***Reviewer Comment**: Sponsor should provide evidence of the leveraged component-level design verification information. See **IR#52.3b**.*

Information Request (IR)#52.3b **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: You provided design verification information in Module 3.2.R.1 Device Information. According to Table 2, you evaluated (b) (4) on baseline samples (time = (b) (4) and samples subjected to accelerated aging equivalent to over (b) (4) of aging at (b) (4)). You also state that you are leveraging component level design verification from the supplier (b) (4) Please address the following: a. … b. You mention component level design verification from the syringe components supplier (b) (4) However, you did not provide sufficient information regarding this leveraged data. Although you referenced the manufacturer's drug master file (DMF), reference to the DMF alone is not sufficient to demonstrate that you have objective evidence that the associated design inputs are met. Please provide supplier-provided documentation that describes component level verification (e.g., supplier's summary technical report demonstrating compliance with (b) (4)). This information should include but need not be limited to (b) (4) This is needed to demonstrate objective evidence of component design verification.

Information Request (IR)#52.3b
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

Applicant Response (emphasis added by reviewer):
S_EXT_04084 the (b) (4) specification for the syringe barrel assembly. Appendix 4 of this document provides (b) (4) **statement** of compliance and summary of related information and testing including how (b) (4) evaluates **syringe barrel flange** (b) (4) **and Luer cone** (b) (4) . Appendix 5 of this document provides (b) (4) **statement** of compliance and summary of related information and testing.

QAG_28156 Ver 1.0 is a (b) (4) report providing (b) (4) connectivity performance for (b) (4) PRTC (Plastic Rigid Tip Cap) syringes.

QAG_28152 Ver 1.0 is a (b) (4) report that provides syringe performance test data for **CCI,** (b) (4)

Reviewer Comments: *Response is **acceptable**. Referenced documents provide sufficient objective evidence of component-level design verification. Notably, according to PPQ reports QAG_28686 and QAG_29209 (in Module 3.2.P.3.5), preparation of the PFS syringe assemblies for filling includes '*(b) (4) *." The supplier document S_EXT_04084 provided in response to IR#52.3b states "As a result of* (b) (4) *Design Verification, when the* (b) (4) *process is used at customer site,* (b) (4) *guaranties conformity of product functionalities and on the level of compliance to standards referred in section 5.3 [e.g.,* (b) (4) *] after* (b) (4) *treatment."*

Applicant evaluated (b) (4) , expelled volume, (b) (4) on baseline samples (time = (b) (4) and samples subjected to accelerated aging equivalent to over (b) (4) of aging at (b) (4). Results from Table 2 in Module 3.2.R.1 Device Information are recreated below.

Parameter	Acceptance Criteria	Measured Value (T=0)	Result (T=0)	Measured Value (b) (4) years accelerated)	Result (b) (4) years accelerated)
(b) (4)		(b) (4)	Pass	(b) (4)	Pass
			Pass		Pass
expelled volume	(b) (4) 0.5 mL		Pass		Pass
(b) (4)			Pass		Pass
			Pass		Pass

***Reviewer Comment**: Additional information is needed regarding the verification study described above: sample size, batch(es) identification, basis of accelerated aging calculation, and test methods. Ideally, Applicant should provide the complete test report for the verification testing. See **IR#52.3a**.*

Information Request (IR)#52.3
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

IR Comment: You provided design verification information in Module 3.2.R.1 Device Information. According to Table 2, you evaluated(b) (4), expelled volume, (b) (4) e on baseline samples (time =(b) (4) and samples subjected to accelerated aging equivalent to over (b) (4) of aging at (b) (4). You also state that you are leveraging component level design verification from the supplier (b) (4)). Please address the following:

a. Please provide additional information on the design verification testing performed by Novavax, including but not limited to sample size, batch(es) identification, basis of accelerated aging calculation (e.g., per (b) (4)), and test methods. This information is needed to fully determine the adequacy of the verification data and clarify whether it overlaps with any of the Batch Analysis data provided in Module 3.2.P.5.4.
b. …

Applicant Response (emphasis added by reviewer): Functional performance of the PFS to ensure the DP can be delivered to the patient was verified by measuring (b) (4) **, expelled volume,**(b) (4) as part of a design verification study. The design verification study was performed on an **accelerated basis** – samples were aged at (b) (4) and (b) (4) prior to testing at the timepoints specified in the table below. Sample size and test method are also given in the table below. The **test methods were developed and validated by** (b) (4) **and conform to**(b) (4) , as appropriate.

(b) (4)

Testing was performed using material from (b) (4) lots: Lot (b) (4) manufactured at the Serum Institute of India and Lot (b) (4) manufactured at (b) (4) The **lot produced at** (b) (4) **uses equivalent components and the same drug product formulation as fully finished product** manufactured at Serum Institute of India product and therefore is **representative of the final product configuration**.

Information Request (IR)#52.3
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

An accelerated aging factor (AAF) in accordance with (b) (4) is calculated using the accelerated aging (b) (4) and the (b) (4)

(b) (4)

Therefore, the simulated real time is significantly greater than the expected shelf-life of the drug product.

In addition to the accelerated design verification study described above, a **PFS stability study is being performed using Process Performance Qualification (PPQ) run material** manufactured as fully finished commercial specification product. The study includes testing for (b) (4) PPQ batches manufactured at Serum Institute of India ((b) (4)). The study includes (b) (4) **and container closure integrity** (b) (4) **)**. Functional testing is **performed by**(b) (4) **using the same validated test methods as identified above.**

Reviewer Comments*: Response is* ***acceptable****. The lots used for the described verification study do not appear to overlap with the PPQ lots reviewed in Section II of this memo.*

(b) (4) , and expelled volume were also evaluated as part of PPQ (see Section II.B.iii Batch Analyses in this memo).

Applicant states “A Design Requirements Traceability Matrix, summarized in Table 3, is used to demonstrate traceability between the Design Input Requirements, the Design Outputs, the Design Verification, and Risk Control Measures.”

Reviewer Comment*: Many of the design inputs in the traceability matrix in Table 3 are ambiguous. Design inputs should be measurable, including acceptable ranges and limits, and should not be ambiguous, conflicting, or incomplete (21 CFR 820.30(c)). It’s possible that Table 3 was intended to be a high-level summary of design input and output information. Applicant should clarify whether Table 3 is a high-level summary of the traceability matrix included in their Design History File (DHF), or an exact copy.*

*Applicant should examine their design control documentation and redefine their design inputs and outputs as necessary to ensure accurate and consistent control of the combination product design. Applicant should also confirm that their design control procedures include means to address incomplete, ambiguous, or conflicting requirements. See **IR#52.4**.*

Information Request (IR)#52.4 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: Module 3.2.R.1 Device Information states "A Design Requirements Traceability Matrix, summarized in Table 3, is used to demonstrate traceability between the Design Input Requirements, the Design Outputs, the Design Verification, and Risk Control Measures." Many of the design inputs listed in the traceability matrix in Table 3 are ambiguous. For example, one design input states "The PFS shall function for the intended medication." As discussed in the FDA "Design Control Guidance for Medical Device Manufacturers" (https://www.fda.gov/media/116573/download), design inputs should be measurable, including acceptable ranges and limits, and should not be ambiguous, conflicting, or incomplete (21 CFR 820.30(c)). As you state that Table 3 is a "summary", please address the following to support the adequacy of these aspects of your design controls: a. Please confirm that the traceability matrix included in your Design History File (DHF) contains detailed design inputs that are measurable using an objective method of analysis, including acceptable ranges and limits, and are not ambiguous, conflicting, or incomplete. b. Please confirm that the traceability matrix included in your DHF contains design outputs that refer to specific product specification documents (i.e., more detailed than "Syringe barrel specifications"). c. Please confirm that your design control procedures include means to address incomplete, ambiguous, or conflicting requirements, as required by 21 CFR 820.30(c). We recommend that you provide a copy of the traceability matrix included in your DHF in your response to this comment. Please note you do not need to provide your entire DHF, design control procedure, or other design control documents in response to this comment.
Applicant Response: a. Table 3 is intended to provide a high-level summary of the design inputs. Novavax has developed design inputs that are measurable using an objective measure of analysis and that are not ambiguous, conflicting or incomplete. QAG_09943 (Design Input Requirements) defines design input requirements while QAG_09844 (Traceability Matrix) documents the traceability of design input requirements to design output and design verification results. b. Novavax confirms the traceability matrix (QAG_09844) provides references to specific product specification documents.

Information Request (IR)#52.4 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
c. Novavax's design control procedures require that design input requirements to be complete, unambiguous, and verifiable, free of conflicting requirements. QAG_09844 (Traceability Matrix) is provided.
Reviewer Comments: *Responses are* ***acceptable****. The referenced design input and traceability documents are indeed more detailed than the summary table provided in the BLA, and appear to be sufficiently clear, measurable, non-conflicting, and complete.*

(b) (4)

Reviewer's Overall Assessment and Recommendations*:* Design verification information provided in the BLA and in response to IR#52 is acceptable from a device perspective.

IV. Design Validation

Module 3.2.R.1 Device Information states "Design validation was primarily achieved through the selection of an off-the-shelf PFS system from an established supplier (see

DMF (b) (4) and the design verification activities. Design Validation is also supported by a clinical evaluation report (CER)."

***Reviewer Comment**: The sponsor is relying on the clinical evaluations to demonstrate device validation. Evaluation of clinical data is deferred to the clinical review team. However, sponsor should ensure their design history file (DHF) contains a URRA.*

Information Request (IR)#52.5 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: Module 3.2.R.1 Device Information states "Design validation was primarily achieved through the selection of an off-the-shelf PFS system from an established supplier (see DMF (b) (4)) and the design verification activities. Design Validation is also supported by a clinical evaluation report (CER)." "Validation" is defined in 21 CFR 820.3(z)(2) as "establishing by objective evidence that device specifications conform with user needs and intended use(s)." The FDA guidance "Current Good Manufacturing Practice Requirements for Combination Products" (https://www.fda.gov/media/90425/download) states "Design validation… includes testing of production units or their equivalents (with appropriate justification) under actual or simulated use conditions... Design validation activities, for example, may include simulated use testing or clinical/nonclinical evaluation, including human factors and software validation." Please provide additional summary of your objective evidence of design validation (i.e. regarding the referenced CER and your use related risk assessment (URRA)).
Applicant Response: Design validation demonstrating the PFS design conforms to the user needs was performed through a combination of literature review, anthropometric and human strength data, and simulated bench testing using production devices. It is noted that the safety and efficacy of delivering our Drug Product through intramuscular injection (IM) has been established through prior clinical trials with the drug product in vials using equivalent hypodermic needles for the injection. A clinical evaluation was performed based on a comprehensive analysis of available clinical data, non-clinical data, post-market surveillance data; including clinical investigation study data relevant to the intended purpose of the PFS. All available Adverse Event (AE) data reported for similar vaccines delivered through IM injection and marketed in prefilled syringes for the USA and EU markets were examined. Database searches included a broad patient age range from pediatric to elderly and included many marketed vaccines available in vials and prefilled syringes. None of the identified reports or publications reviewed raise any specific concerns regarding the safe and effective use of prefilled syringes for vaccine administration via IM. Results from the clinical evaluation were used as inputs to inform the risk analysis performed in accordance with (b) (4). The risk analysis includes design risks, use-related risks, and manufacturing risks. The risk analysis and assessment results for the Novavax Covid-19 Vaccine in a Prefilled Syringe indicate that the residual risks

Information Request (IR)#52.5 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
for the intended use of the product have been reduced to as low as possible and are outweighed by the product's benefits. Based on the defined user needs and the risk assessment results, design inputs were defined to ensure the user needs are met. The PFS format is a well-established, standard of care technology with a simple, intuitive interface. Compliance to the (b) (4) ensures users can attach required needles with standard design Luer connections. Bench testing of production product was performed to confirm the delivered dose, the (b) (4) are within user capability based on anthropometric and human strength data from the literature. Delivery of medicinal products through syringe delivery systems via IM injection is covered by the training of the health care professional. As described above, no new or unique failure modes – including use-related risks – have been identified for Novavax's Drug Product within a PFS. Based on the above activities and results, no specific usability testing or clinical investigation is required to support design validation of the PFS system for Novavax's Drug Product.
***Reviewer Comments**: Response is **acceptable**. The vaccine was previously authorized for use under an Emergency Use Authorization (EUA). There are no differences between the overall design and use of the authorized PFS product and the PFS product in this BLA. Therefore, there are no new concerns regarding ability of the PFS to meet user needs.*

***Reviewer's Overall Assessment and Recommendations**:* Design validation information is sufficient from a device perspective. Review of clinical performance deferred to the clinical review team.

V. Biocompatibility

Refer to Section I.C of this memo regarding the materials of construction for the syringe components.

Table 3 in Module 3.2.R.1 Device Information includes a user requirement that "User contact areas and container closure of the drug delivery system must be made of materials that are compatible with the drug product, biocompatible, and meet all regulatory requirements for primary packaging systems." The associated "design inputs" are:

1. The fluid-contacting components of the DP (Drug Products) manufacturing process and primary container components shall have an acceptable leachable profile based on a toxicological risk assessment.
2. The components of the PFS shall comply with (b) (4) requirements
3. The PFS shall meet (b) (4) . Clause (b) (4) – Type (b) (4) Glass

4. The elastomeric closures shall comply with applicable biological and physicochemical requirements.

The associated design outputs are "Syringe Barrel Specifications, Plunger Specifications, Plunger Rod Specifications, Section 3.2.P.2.4 Container Closure System". (b) (4) DMF (b) (4) and a link to the associated LOA are listed as the "design verification/validation" for requirements 2 through 3 in the list above.

Reviewer Comment*: The syringe components are off the shelf items commonly used in many approved PFS products. The biocompatibility of the syringe barrel assembly and tip cap elastomer can be leveraged from the review of BLA* (b) (4) *and BLA* (b) (4) *The biocompatibility of the plunger stopper can be leveraged from DMF* (b) (4) *(see separate DMF memo). Regardless, Applicant should still provide a biocompatibility statement from the supplier* (b) (4)*, as objective evidence that they have documentation in their records that ensures the design input is satisfied. See* ***IR#52.6****.*

Information Request (IR)#52.6 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: Table 3 in Module 3.2.R.1 Device Information includes user needs and design inputs related to biocompatibility of the PFS components. You cite the referenced DMF (b) (4) as the corresponding design verification. "Verification" is defined in 21 CFR 820.3(aa) as "confirmation by examination and provision of objective evidence that specified requirements have been fulfilled." Reference to the DMF alone is not sufficient to demonstrate that you have objective evidence that the design input is met. Please provide supplier-provided documentation (e.g., supplier biocompatibility summary) that demonstrates you have objective evidence that design inputs regarding biocompatibility have been met.
Applicant Response (emphasis added by reviewer): The PFS supplier, (b) (4) (b) (4) component testing is applicable to Novavax's PFS DP for the following reasons: • In their testing and evaluations, (b) (4) has included their component manufacturing processes, including packaging and sterilization. • Novavax's DP manufacturing processes associated with the (b) (4) PFS do not include any added materials and are designed to minimally handle and process the components. Fill and finish processes are performed in an aseptic environment using (b) (4) processing systems with no . The documents that provide a summary of the biocompatibility evaluations for the syringe barrel, plunger stopper, and plunger rod are provided below. QAG_27309 Ver 1.0 is a (b) (4) summary report that documents (b) (4) application of (b) (4) for the **syringe barrel**, including material characterization, biological testing strategy, and a summary of testing.

Information Request (IR)#52.6
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

QAG_28191 Ver 1.0 is a (b) (4) summary report that documents (b) (4) application of (b) (4) for the **plunger stopper**, including material characterization, biological testing strategy, and a summary of testing.

QAG_26903 Ver 1.0 is a (b) (4) document that provides certification that the **plunger rod** has been evaluated and tested in accordance with (b) (4) for a surface contacting device in contact with for a limited exposure.

Reviewer Comments: *Response is* ***acceptable****.*
From ***QAG_27309****:*
Studies results summary for TA 16-6200-014-A (b) (4) *glass syringe, polycarbonate luer lock adaptor, and polypropylene rigid cap): Qualification of the* ***borosilicate glass barrel, lubricant, polycarbonate luer lock adaptor, and polypropylene rigid cap****.*

(b) (4)

Information Request (IR)#52.6
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

(b) (4)

QAG_26903 *is a Materials Of Concern And Safety Information document. It states "The product is classified per* (b) (4) *as surface contacting device in contact with intact skin, for a limited exposure and complies with the appropriate requirements of the following standard:*
- (b) (4) *standard "Biological Evaluation of Medical Devices" - Part 1: 2018 Evaluation and testing within a risk management process."*

The plunger rod is non-patient/product contacting. It is potentially health care provider-contacting, but the contact (direct, intact skin) duration is transient. Statement of compliance from the manufacturer is sufficient.

Reviewer's Overall Assessment and Recommendations*:* Biocompatibility information provided in the BLA, in response to IR#52, leveraged from (b) (4) and (b) (4), as well as information provided in the referenced DMF are acceptable from a device perspective. Review of extractables and leachables (E/L) evaluation from a container closure perspective is deferred to CMC.

VI. Sterilization

The syringe barrel assemblies and plunger stoppers are provided sterile, clean, and ready to fill. Section 6 of the supplier document S_EXT_04084 provided in response to IR#52.3b states the following regarding sterility and endotoxin for syringe barrel assemblies:

"6.2 Sterility
- The barrels are sterilized with (b) (4) to a (b) (4) using a validated sterilization method in accordance with (b) (4) (2018).
- All design control activities are performed on final products (b) (4) which mitigates the risk of compromising safety and performance through sterilization process.
- Sterility Tests are conducted in accordance with the (b) (4)
- EO residuals are tested in accordance with (b) (4)

6.3 Pyrogenicity/Endotoxins
- (b) (4) performs endotoxin tests and ensures the limit value (b) (4)
- (b) (4) extraction method complies with the (b) (4) (Dec 2017).
- (b) (4) testing method is compliant with the (b) (4) method c) (Jan 2018), (b) (4) (May 2018) and (b) (4) (April 2016).
- (b) (4) sample preparation is based on the documents mentioned in annex D.1 given for information.
- For manufacturing of subassembled syringes, the process is adapted to remove pyrogenic agents and is validated to ensure a (b) (4) endotoxin reduction."

As evidenced in QAG_29821 and QAG_27852 in Module 3.2.P.7, the type of information above is included in the certificates for each lot of (b) (4) syringes and plunger stoppers, and verification of this information is included to some extent in the SIIPL incoming material assessment.

(b) (4)

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

***Reviewer Comment**: Applicant's incoming material assessments for barrels include sterility and endotoxin, but do not include sterilization residuals. Similarly, the plunger stoppers acceptance criteria do not appear to include endotoxin. As these are related to safety of using these components in the final product, Applicant should include checking incoming barrel assembly and plunger stopper certificates for verification of sterilization residuals and endotoxin, respectively. See **IR#59**.*

Information Request (IR)#59
Date Sent: March 4, 2025
Date/Amd/eCTD Sequence Received: March 7, 2025/85/0087

IR Comment: Document QAG_29821 in Module 3.2.P.7 contains SIIPL Analytical Reports and associated supplier certificates for incoming syringe barrel assemblies and plunger stoppers. Please address the following:

- It appears that the SIIPL incoming material assessments for the syringe barrel assemblies do not include assessment of sterilization residuals (b) (4) , although the supplier certificate includes this information. Assessment of sterilant residuals is an important safety concern because high residual levels can lead to adverse events including tissue injury. To ensure risk of introducing high levels of sterilant residuals into your product via container closure components is adequately mitigated, please include a specification and acceptance criterion for sterilant residuals (e.g., via supplier certificate examination) in the SIIPL incoming material assessments for the syringe barrel assemblies.
- It appears that the SIIPL incoming material assessments for the plunger stoppers do not include assessment of endotoxin, although the supplier certificate includes this information. Assessment of endotoxins is an important safety concern because high levels of endotoxins can cause an inflammatory response. We acknowledge that you have established final product specification and acceptance criterion for endotoxins. However, to ensure risk of introducing endotoxins into your product via container closure components is additionally mitigated, please include a specification and acceptance criterion for endotoxins (e.g., via supplier certificate examination) in the SIIPL incoming material assessments for the plunger stoppers.

Applicant Response:
Novavax agrees to include a specifications and acceptance criterion for sterilant residuals on the incoming material assessment requirements for the syringe barrel assemblies as summarized below:
• Residual (b) (4) dosage: (b) (4) or less
• Residual (b) (4) dosage: (b) (4) or less
• Residual (b) (4) dosage: (b) (4) or less
These acceptance criteria will be assessed via supplier certificate examination.

Novavax agrees to include a specification and acceptance criterion for endotoxins in the SIIPL incoming material assessment for the plunger stoppers according to (b) (4) as follows:
• Bacterial endotoxins: No more than (b) (4) EU/plunger stopper

Information Request (IR)#59 **Date Sent**: March 4, 2025 **Date/Amd/eCTD Sequence Received**: March 7, 2025/85/0087
This acceptance criteria will be assessed via supplier certificate examination.
Reviewer Comments*: Response is* ***acceptable****.*

The plunger rod is provided non-sterile.

Reviewer's Overall Assessment and Recommendations*:* Sterilization information sufficient from device perspective. Sterility and endotoxin levels of the drug product (PFS contents) deferred to CMC review.

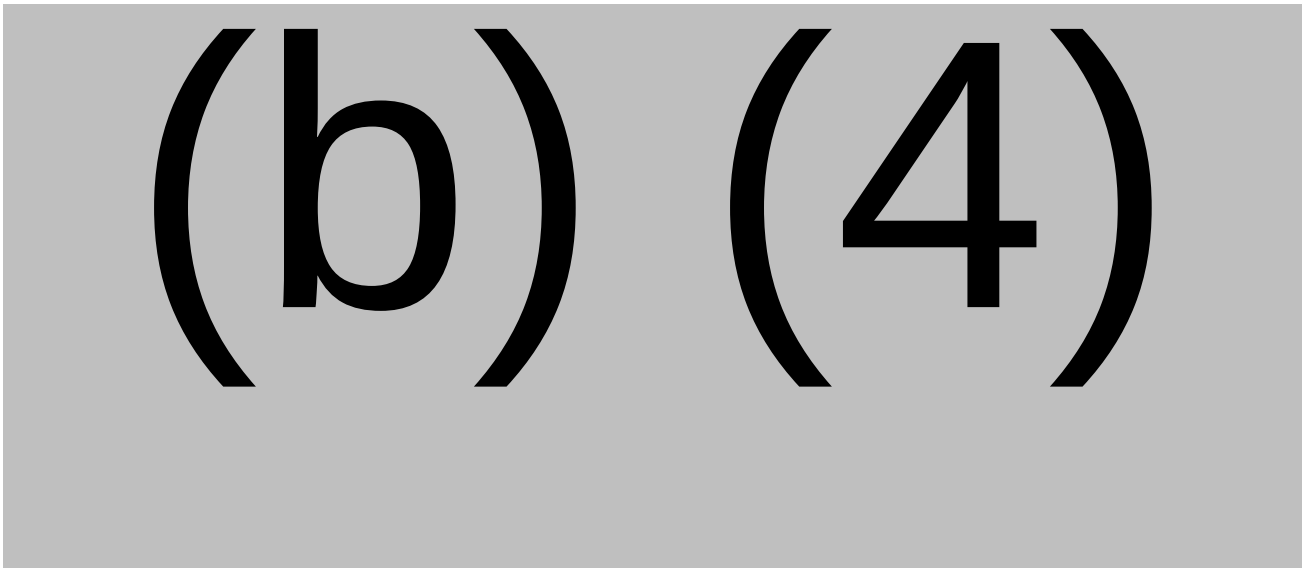
VII. Control Strategy

Essential Performance Requirement	Control Strategy Description (e.g., incoming acceptance, in-process control, release testing activities):
Dose accuracy (expelled volume)	Fill weight in process control (see Section II.B.i of this memo), final product release testing (see Section II.B.ii of this memo), stability program (see Section VIII.B and VIII.C of this memo)
(b) (4)	Design verification (see Section III of this memo), stability program (see Section VIII.B and VIII.C of this memo), purchasing controls (see Section X of this memo) and incoming acceptance activities (see below)

Material acceptance analytical reports and the associated certificates of conformance are included in Module 3.2.R.1 and 3.2.P.7:

- Syringe barrel assemblies and plunger stoppers: QAG_29821
- Plunger rods: QAG_27852, QUG_27958

Notably, the syringe barrel assembly SIIPL analytical report includes the following:



Reviewer's Overall Assessment and Recommendations*:* Control strategy to ensure final product meets its essential performance requirements is sufficient from device perspective.

VIII. Packaging, Stability, Shipping

A. Packaging

Module 3.2.P.3.3 Section 2 Step (b) (4) states "pre-filled syringes are then placed and sealed into blister packages. Ten syringes in blister packages are then placed into a pre-printed folding boxboard carton… The cartons are then placed into (b) (4)

Reviewer Comment*: Sponsor should provide a picture or diagram of the proposed packaging configuration to assist the reviewer with visualization of the final product. See* ***IR#52.8*** *in Section VIII.C of this memo.*

B. Stability

Proposed Shelf Life and Storage Conditions: 3 months at 2-8°C

Section 3 of Module 3.2.P.8.1 states "Stability will continue to be monitored per the protocol described within and additional data will be provided as available to extend shelf-life."

Stability data reviewed here was submitted in Sequence 0047.

The following PFS batches (all manufactured at (b) (4) Floor (b) (4)) were put on stability under long-term (5 ± 3°C) conditions (stored (b) (4)):

- XBB.1.5 PPQ ((b) (4) µg/mL) (CCIT (no failures), (b) (4) at 0, 3, 6 ,9, (b) (4) months)
  - (b) (4) (6 months available)

    - (b) (4) (6 months available)
    - (b) (4) (6 months available)
- JN.1 PPQ ((b) (4) µg/mL) (CCIT (no failures), (b) (4) at 0, 3, (b) (4) months)
    - (b) (4) (3 months available)
    - (b) (4) (3 months available)
    - (b) (4) (3 months available)
- JN.1 (b) (4) µg/mL) (CCIT (no failures), (b) (4) at 0, 3, (b) (4) months)
    - (b) (4) months available)
    - (b) (4) months available)
    - (b) (4) months available)
    - (b) (4) months available)

*Only Relative Potency by (b) (4) reported for indicated batches at most recently available interval.

***Reviewer Comment**: CCIT is commonly used as a surrogate for dose accuracy (expelled volume, deliverable volume, etc.) in stability and shipping studies, with the rationale being that the volume is expected to remain unchanged if the closure integrity is maintained.*

The following PFS batches (all manufactured at (b) (4) Floor (b) (4)) were put on stability under accelerated (b) (4)) conditions (stored (b) (4)):

- XBB.1.5 PPQ (b) (4) µg/mL) ("report results" for CCIT, (b) (4) at 0, 3, 6 months)
    - (b) (4) (3 months available)
    - (b) (4) (3 months available)
    - (b) (4) (3 months available)
- JN.1 PPQ (b) (4) µg/mL) ("report results" for CCIT, (b) (4) at 0, 3, (b) (4) months)
    - (b) (4) (3 months available)
    - (b) (4) (3 months available)
    - (b) (4) (3 months available)
- JN.1 ((b) (4) µg/mL) ("report results" for CCIT, (b) (4) at 0, 3, (b) (4) months)
    - (b) (4) (2 months available)
    - (b) (4) (2 months available)
    - (b) (4) (2 months available)
    - (b) (4) (2 months available)

"Batches indicated with "A" are sublots for packaging purposes. The stability data reported corresponds to results for the entire batch."

Per the data tabulated in Module 3.2.P.8.3, all currently evaluated time points at which injection forces and CCIT were evaluated met the long-term acceptance criteria. Accelerated storage batches (which only have requirements of "report results") also met

the long-term storage acceptance criteria. Notably, however, accelerated storage lot (b) (4) is missing data for the initial timepoint (0 months). Applicant indicates there is an "Investigation ongoing into missed T0 testing."

The following commercial JN.1 ((b) (4) µg/mL) PFS batches (all manufactured at (b) (4) Floor (b) (4)) were put on stability under long-term (5 ± 3°C) conditions (stored (b) (4) but will not evaluate any device relevant metrics (i.e., only measures total protein content and relative potency): (b) (4)

Additional stability data for (b) (4) , expelled volume, (b) (4) after (b) (4) years accelerated aging is reported in the Design Verification section of Module 3.2.R.1 Device Information. See the review of this information in Section III. Design Verification in this memo.

Regarding the post-approval stability program, Applicant commits in Module 3.2.P.8.2 that (b) (4) batch of variant SARS-CoV-2 rS vaccine drug product from the manufacturing site(s) will be placed on stability each year… Stability studies will be conducted at 2 – 8°C (long term conditions) for the annual stability batch and under accelerated conditions at (b) (4) , if a significant change is made… In the event of any out of specification results, an investigation will be performed and any required actions in the marketplace will be communicated to the agency." Per Table 1 in this module, the long-term stability batches will be evaluated for injection forces and CCIT per the release specifications at 0, (b) (4) months. Accelerated stability studies will not include evaluation of (b) (4) and CCIT.

Reviewer Comment*: Applicant should clarify what they mean by (emphasis added by reviewer) "Stability studies will be conducted… under accelerated conditions at (b) (4) **, if a significant change is made**." Applicant should acknowledge that new stability data (e.g., long term stability) may be needed to support certain changes to the syringe components. See **IR#52.8**.*

Information Request (IR)#52.8 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: In Module 3.2.P.8.2, you state that (b) (4) batch of variant SARS-CoV-2 rS vaccine drug product from the manufacturing site(s) will be placed on stability each year… Stability studies will be conducted at 2 – 8°C (long term conditions) for the annual stability batch and under accelerated conditions at (b) (4) , if a significant change is made." Please address the following: a. It is not clear what scope of "significant changes" would require only accelerated stability data. Please clarify the scope of "significant changes". b. The proposed accelerated stability studies will not include evaluation of (b) (4) or container closure integrity. Please be advised that new

Information Request (IR)#52.8 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
stability data (e.g., long-term stability) may be needed to support certain changes to syringe components.
Applicant Response: a. Novavax would like to clarify that stability studies will be conducted at both 2 – 8°C (long term conditions) and (b) (4) (accelerated conditions) if a significant change is made on a case-by-case basis. Stability studies will be conducted at only 2 – 8°C (long term conditions) for the annual stability batch if there are no significant changes. Section 3.2.P.8.2 is revised and provided in this response to provide further clarification. b. Novavax would like to clarify that stability studies at long-term storage conditions will always be conducted for annual commitment batches and include both CCIT and (b) (4) as outlined in 3.2.P.8.2. In the case of significant change, assessed on a case-by-case basis, accelerated studies will be run in addition to long-term.
Reviewer Comments: *Response is* ***acceptable****.*

C. Shipping

Table 3 in the Design Verification section in Module 3.2.R.1 Device Information contains the following design input: "The PFS shall meet functional and performance requirements after shipping (air, sea, and truck)." The design verification column listed for this input refers to Module 3.2.P.2.4 Container Closure System. Section 2 of Module 3.2.P.2.4 Container Closure System refers to the following documents:

- QAG_04613 (Shipping Validation Master Plan)
- QAG_21686 (Validated Shipping System List)
- QAG_26835 (Shipping Evaluation of SARS CoV-2 rS (Vaccine Drug Product in PFS Finished Good Presentation at SIIPL).

At the time of submission of Sequence 0044, Applicant stated "an (b) (4) study for the PFS DP is on-going and will be assessed per QAG_26835."

In Sequence 0053, Applicant submitted Technical Report QAG_30321 entitled "Summary Report for QAG_26835 Shipping Evaluation of SARS CoV 2-rS (Vaccine) Drug Product in PFS Finished Good Presentation at SIIPL".

The study utilized representative SARS-CoV-2 rS Omicron Variant (XBB.1.5) PFS finished goods, (b) (4)

Notably, the test article packaging configuration differs from the planned future commercial configuration. Section 2 of the report states (emphasis added by reviewer)

"Currently, SIIPL has a **standard PFS packaging** consisting of a (b) (4) For **2024**, Novavax will use a slightly different finished goods package that includes (b) (4) **SIIPL** (b) (4) For **2025**, Novavax will use a slightly different finished goods package that includes (b) (4) The main difference between the standard SIIPL blister pack and the (b) (4) PFS blister pack strip is that **the standard SIIPL blister pack is** (b) (4) . The Novavax configuration for 2025 requires change parts which are on order but will be available for validation in Q1 of 2025. The **SIIPL standard packaging configuration reasonably approximates Novavax's ultimate finished goods packaging**."

***Reviewer Comment**: The rationale for the applicability of the shipping study results to planned 2025 packing configuration appears reasonable. However, it would help for the Applicant to provide images comparing each level of the packing configuration (i.e., blisters, cartons, shippers, pallets). See **IR#52.9**.*

Information Request (IR)#52.8 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: In Sequence 0053, you submitted Technical Report QAG_30321 entitled "Summary Report for QAG_26835 Shipping Evaluation of SARS CoV 2-rS (Vaccine) Drug Product in PFS Finished Good Presentation at SIIPL". In the Background section of the report, you indicate that the finished goods used in the shipping validation study (b) (4)) is different from the planned 2025 packaging configuration (b) (4) . While the rationale for applicability of the shipping study results to the planned 2025 packing configuration appears generally reasonable, please also provide images comparing each level of the packing configurations (i.e., blisters, cartons, shippers, pallets). This is being requested to fully understand the rationale for applicability of the shipping validation results.
Applicant Response (emphasis added by reviewer): Novavax acknowledges the request to provide images comparing each level of the packaging configuration to enable full understanding of the comparison risk assessment rationale. Reference the following background summary of the Shipping (b) (4) Study History and PFS Packaging Progression, the Commitment to repeat Shipping (b) (4) Study with JN.1 PFS packaged in (b) (4) Carton, and images comparing each level of the packaging configuration (i.e. blisters, cartons, shippers, pallets). Shipping (b) (4) Study History and PFS Packaging Progression QAG_26835 was designed to perform an (b) (4) study on XBB.1.5 PFS samples. XBB.1.5 PFS were packaged in a (b) (4) Refer

Information Request (IR)#52.8
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

to Image 1 below for images and drawings for XBB.1.5 PFS mono carton with blister, an outer carton, a shipper and a pallet.

Due to occurrences of out-of-specification results for Matrix C and Total Protein Content on the XBB.1.5 samples, amendment protocol QAG_26835-AMD-01 was developed to perform testing on the designated seasonal variant JN.1 PFS samples. At this time of testing, commercial JN.1 PFS material was planned to be packaged in a 10 × 1 carton. JN.1 PFS samples were packaged in a mono blister individually packaged in a 10 × 1 carton. (b) (4) cartons were packaged in a shipper.(b) (4) shippers were placed on a pallet for commercial shipment. Refer to Image 2 below for images and drawings for JN.1 PFS individual blister with 10 × 1 carton, shipper and pallet.

For the 2025 COVID season, the PFS packaging will be updated to a(b) (4) carton packaging configuration. The packaging will take place with a (b) (4) configuration, meaning(b) (4) perforated blisters of(b) (4) PFS are packed in a carton, containing molded syringe trays with a pull-back/semi-resealable cover. Each shipper will contain (b) (4) cartons.(b) (4) shippers will be placed on a pallet to be ready for commercial shipment. Refer to Image 3 below for images and drawings for Year-2025 variant PFS perforated blisters, (b) (4) carton, shipper and pallet.

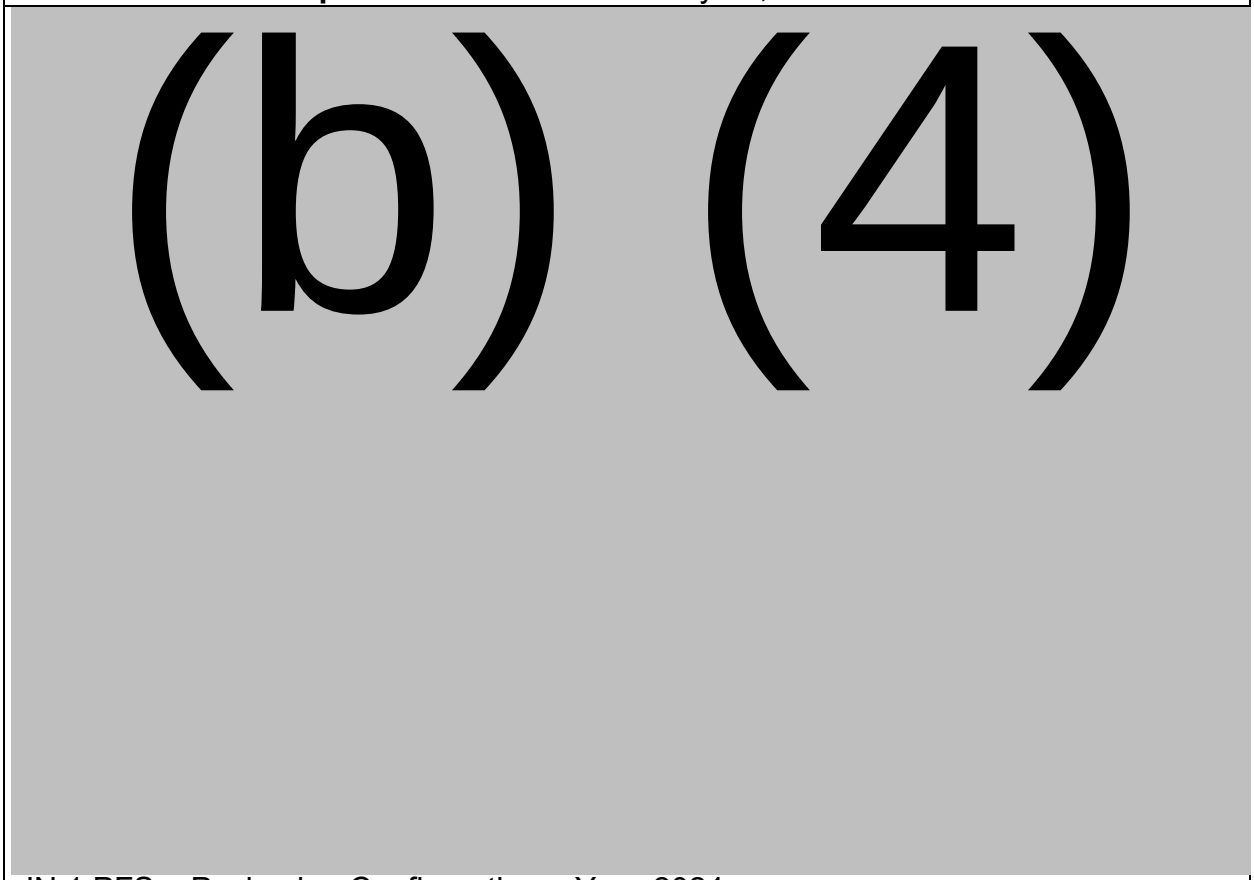
Commitment to repeat Shipping (b) (4) Study with JN.1 PFS packaged in (b) (4) Carton

Reference is made to CBER's Comments received February 23, 2025, regarding the Shipping Validation studies submitted to BLA 125817 (Amendment 51; SN 0053). **Novavax is committed to repeat the Shipping** (b) (4) **Study for JN.1 PFS packaged in the new** (b) (4) **Carton Packaging Configuration.** Upon successful completion of the re-execution of the JN.1 study, a **summary report will be generated and results comparable to the relative potency at release will be provided to the agency targeting completion by the end of July-2025**.

XBB1.5 PFS – Packaging Configuration – Year-2023

XBB.1.5 PFS was packaged in a Mono carton individually and (b) (4) mono cartons were inserted into an outer carton. (b) (4) outer cartons were placed in a shipper (b) (4) outer carton × (b) (4) PFS = (b) (4) PFS per shipper).

Information Request (IR)#52.8
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079



JN.1 PFS – Packaging Configuration – Year-2024.
JN.1 PFS was packaged in a (b) (4) Carton; (b) (4) PFS were in individual blisters. Each (b) (4) Carton carried (b) (4) PFS, in individual blister. (b) (4) Cartons were placed in a shipper (b) (4) cartons × (b) (4) PFS = (b) (4) PFS per shipper)

Information Request (IR)#52.8
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

(b) (4)

Year-2025 Variant PFS – Packaging Configuration – Year-2025.
The designated variant for Year-2025 will be packaged in the carton packaging configuration. The packaging will take place with a configuration, meaning perforated blisters of PFS are packed in each carton, containing molded syringe trays with a pull-back/semi-resealable cover. Each shipper contains eighteen cartons cartons × PFS = PFS per shipper)

Information Request (IR)#52.8
Date Sent: February 20, 2025
Date/Amd/eCTD Sequence Received: February 27, 2025/77/0079

(b) (4)

Reviewer Comments: *The provided images do not raise any concerns about the leveraging of the current data to support the proposed commercial packaging configuration. Notably, the referenced out of specification results mentioned above were not for the device essential performance requirements (expelled volume,* (b) (4) *. According to the response (Amd 51, Seq 0053) to CMC comments dated February 23, 2025, "Novavax will repeat the shipping validation study with a minimum of* (b) (4) *commercial-representative lots of the JN.1 DP (PFS presentation). Due to the age of the recently manufactured DP lots, we are planning on using upcoming* (b) (4) *µg/mL formulation target JN.1 batches planned for manufacturing in the beginning of* (b) (4) *. Upon successful completion of the re-execution of the JN.1 study, a summary report will be generated and results comparable to the relative potency at release will be provided to the Agency, targeting submission by the end of July 2025." The CMC comments indicated the reports could be provided as a product correspondence.* ***The currently provided data is sufficient to support approval from a device perspective, and the additional data the Applicant commits to submitting will provide further evidence that essential performance requirements are maintained after shipping.***

Test articles were manufactured and manually packed into cartons and shippers by SIIPL. (b) (4) shippers were created:

- (b) (4)

***Reviewer Comment**: Based on an internet search,* (b) (4) *is a testing laboratory in India.*

(b) (4) subjected test sample shippers to simulated shipping and distribution testing per (b) (4) , Distribution (b) (4) and Assurance Level (b) (4)

- (b) (4)

(b) (4) performed visual inspections after exposure to the test sequence:

- (b) (4)

Test samples were then returned to SIIPL performed DP quality testing, including the following device-relevant metrics:

- (b) (4)

Acceptance criteria were:

- (b) (4)
- (b) (4)
- CCIT: (b) (4) should be observed, and no leak should be detected."

***Reviewer Comment**: CCIT is commonly used as a surrogate for dose accuracy (expelled volume, deliverable volume, etc.) in stability and shipping studies, with the*

rationale being that the volume is expected to remain unchanged if the closure integrity is maintained.

SIIPL pooled together the syringes from the (b) (4) test sample shippers and pulled random samples for each test. SIIPL also took random samples from the Control Samples and the Conditioned Control Samples for each test.

According to Table 5 in the report, all (b) (4) boxes, (b) (4) cartons, and (b) (4) PFS met visual inspection acceptance criteria. According to Table 6 in the report, all PFS samples from the test shippers subjected to simulated shipping and distribution met acceptance criteria for (b) (4) (maximum (b) (4) and CCIT.

***Reviewer Comment**: Table 6 reports "not tested" for (b) (4), and CCIT for the control shipper and conditioned control shipper. According to the table, the lot used for this testing was batch (b) (4), which according to Module 3.2.P.8, was one of the XBB.1.5 PPQ lots placed on long term and accelerated storage stability. The initial timepoints (0 months) for this lot met acceptance criteria for (b) (4) and CCIT, and those results ((b) (4), CCIT: no failures) can be leveraged as a control value for the shipping study test samples.*

Notably, JN.1 samples were also included in the shipping study as part of QAG_26835-AMD-01, but were only evaluated for total protein content, relative potency, Matrix A content, and Matrix B content.

***Reviewer Comment**: As the PFS presentation is consistent between the XBB.1.5 DP and JN.1 DP, the XBB.1.5 PFS results for (b) (4) and CCIT are leverageable for JN.1 PFS, from a device perspective.*

Section 9 contains "Exceptional Condition Reports and Protocol Amendments", which includes the following regarding CCIT (emphasis added by reviewer): "Post-simulated shipping testing included container closure integrity testing (CCIT) by (b) (4) using a previously validated test method. Sample preparation for this testing by (b) (4) included (b) (4) DEV-24-008E for further details). It was concluded that there was **no impact as all test sample results were observed to be valid and passing**. The (b) (4) (which was previously validated)."

***Reviewer Comment**: Rationale appears reasonable from device perspective as far as results interpretation. Defer to (b) (6).*

The report conclusions include that "Functional performance assessments, such as container closure integrity (CCI) and syringe plunger testing, validated that the product remains physically and functionally intact post-shipping."

***Reviewer's Overall Assessment and Recommendations**:* Packaging, stability, and shipping information provided in the submission and in response to IR#52 are sufficient from a device perspective.

IX. Comparability Protocols

None submitted.

***Reviewer's Overall Assessment and Recommendations**:* n/a

X. Quality Management System

Section 4 of Module 3.2.P.3.3 states "The SARS-CoV-2 rS Protein (COVID-19) Nanoparticle Vaccine in the PFS was developed and is manufactured per FDA regulation, 21CFR Part 4, cGMP Requirements for Combination Products. Since Novavax and our contract manufacturing organization (CMO) have drug/biologic cGMP processes in place, device-specific cGMP requirements were incorporated using the drug cGMP-based streamlined approach prescribed by 21 CFR 4.4(b)(1)."

Additional information is provided in Module 3.2.R.1 Device Information.

Device GMP Requirement	Responsible Firm(s):	Summary
21 CFR 820.20 Management Responsibility	Novavax and Serum Institute of India	**Deferred to** (b) (6) **review.**
21 CFR 820.30 Design Controls	Novavax and Serum Institute of India	From Module 3.2.R.1: "21 CFR 820.30 Design Controls. Novavax has developed a Policy for Combination Products (P_POL_01746) that establishes Novavax's approach to device development and establishment and maintenance of design controls for vaccine combination product development. The design control process is governed by P_SOP_01284, Design Control Procedure for Combination Products." Novavax provides additional information regarding design inputs, design outputs, design verification, design validation, design transfer, design changes, and risk management in this Module section. ***Reviewer Comment**: Also refer to Section III and Section IV of this memo.*

Device GMP Requirement	Responsible Firm(s):	Summary
21 CFR 820.50 Purchasing Controls	Novavax and Serum Institute of India	From Module 3.2.R.1: "21 CFR 820.50 Purchasing Controls. Purchasing controls are defined in Section 7.6 of the Novavax Corporate Quality Manual (P_QM_00857) and meet the requirements of 21 CFR 820.50." ***Reviewer Comment**: This statement does not sufficiently describe how the content of the referenced Quality Manual meet the requirements of 21 CFR 820.50. See **IR#52.7**.*
21 CFR 820.100 Corrective and Preventive Actions	Novavax and Serum Institute of India	**Deferred to** (b) (6) **review.**
21 CFR 820.170 Installation	N/A	N/A
21 CFR 820.200 Servicing	N/A	N/A

Information Request (IR)#52.7 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
IR Comment: In Module 3.2.R.1 Device Information, you state that "Purchasing controls are defined in Section 7.6 of the Novavax Corporate Quality Manual (P_QM_00857) and meet the requirements of 21 CFR 820.50." To demonstrate that the requirements of 21 CFR 820.50 are met, please provide additional summary of the purchasing control procedures (e.g., conformance to specified requirements, quality agreements, notification of changes) in the referenced quality manual. Please note you do not need to provide a copy of the quality manual in the response to this comment.
Applicant Response: Novavax's Corporate Quality Manual (P_QM_00857) outlines at a high level the management of outsourced activities and purchased materials and highlights processes designed to ensure that all products or services procured for use in manufacturing conform to specified requirements. In the next level below of document hierarchy are the Corporate Supplier Quality Management Policy (P_POL_06545) and the Supplier Qualification Program (P_SOP_00327). These documents provide more details on the processes for evaluating, qualifying, re-evaluating, and discontinuing suppliers and contracted/consulted organizations

Information Request (IR)#52.7 **Date Sent**: February 20, 2025 **Date/Amd/eCTD Sequence Received**: February 27, 2025/77/0079
engaged in Good Manufacturing Practice (GxP) processes, systems, and applications. The supplier evaluation process includes comprehensive assessments such as questionnaires and audits to evaluate and select suppliers, contractors, and consultants (suppliers) based on their ability to conform to specified and quality requirements, and the identification of relationships that require the establishment of Quality Agreements with suppliers. In addition, notification and approval of any changes that may affect the quality of Novavax products and/or processes is agreed to in either a change notification agreement or the Quality Agreement. The supplier evaluation process also requires the establishment and maintenance of data for acceptable suppliers and the re-evaluation of a supplier at a predetermined frequency and whenever significant changes occur. The details outlined in these documents ensure the requirements of 21 CFR 820.50 are adequately met for suppliers utilized by Novavax.
Reviewer Comments*: Response is* ***acceptable****.*

Reviewer's Overall Assessment and Recommendations*:* QMS information provided in the BLA and in response to IR#52 are acceptable from a pre-market review perspective, for the items with the purview of the device reviewer. Evaluation of compliance determined by inspection is deferred to (b) (6).