

**CBER BLA Device Review Memorandum – Prefilled Syringe (PFS)**

**BLA STN 125835**

**MNEXSPIKE [COVID-19 Vaccine, mRNA]**

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

**1. BLA STN**

125835

**2. APPLICANT NAME**

ModernaTX, Inc.

**3. PRODUCT NAME/PRODUCT TYPE**

- Non-Proprietary/Proper/USAN: COVID-19 Vaccine, mRNA
- Proprietary Name: MNEXSPIKE

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

- General Description: RNA-lipid complex dispersion that contains RNA encoding the linked N-terminal domain and receptor-binding domain of the spike glycoprotein of the SARSCoV-2 virus, and four lipids that act as protectants and carriers of the RNA.
- Route of administration: Intramuscular injection
- Indication(s): Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

**5. COMBINATION PRODUCT INFORMATION**

- Type: 3: Prefilled Biologic Delivery Device/System (syringe)
- Biologic Constituent(s): vaccine
- Drug Constituent(s): n/a
- Device Constituent(s): syringe

**6. MAJOR MILESTONES**

- Filing Meeting: November 14, 2024
- Midcycle Internal Meeting: January 10, 2025
- Late Cycle Internal Meeting: March 14, 2025
- PDUFA Action Date: May 30, 2025

**7. QUALITY REVIEW TEAM**

<b>Reviewer/Affiliation</b>	<b>PFS-Relevant Subject Matter</b>
Alena Dabrazhynetskaya, PhD CBER/OVRR/DVP/LDNAV	Product compatibility, drug product quality attributes including sterility and endotoxin, container closure considerations (e.g., extractables/leachables and toxicological risk assessment, particulates, light protection)
Swati Verma, PhD CBER/OVRR/DVP	

Reviewer/Affiliation	PFS-Relevant Subject Matter
Alla Kachko, PhD CBER/OCBQ/DMPQ/ARB  Ou (Olivia) Ma CBER/OCBQ/DMPQ/MRB2  Cheryl Hulme CBER/OCBQ/DMPQ/PRB	Container closure integrity testing, aseptic processing, sterilization, (b) (4), shipping validation (CCIT, plunger stopper movement), quality management system

## 8. INTRA- & INTER-CENTER CONSULTS

Reviewer/Affiliation	Topic	Agree with consult recommendations? (Yes/No)
Neha Kumar, CDER/OSE/OMEPRM/DMEPAI	Human factors, ICCR # <a href="#">01035795</a>	yes

## 9. SUBMISSION(S) REVIEWED

Date Received	eCTD Sequence	Amd (STN 2 <sup>nd</sup> /3 <sup>rd</sup> Level)	Comments
30 Sept 2024	0001	0	Original submission
07 Feb 2025	0022	21	Response to IR#15. Scope of review limited to manufacturers in Module 3.2.P.3.1.
03 March 2025	25	24	Response to IR#15. Scope of review limited to analytical methods and validation in Modules 3.2.P.5.2 and 3.2.P.5.3, as well as select documents in Module 3.2.R.
17 March 2025	34	33	Response to IR#27. Scope of review limited to deliverable volume SOP in Module 3.2.R.
31 March 2025	0039	38	Response to IR#33. Scope of review limited to container closure information in Module 3.2.P.7 and stability data in Module 3.2.P.8.
18 April 2025	0045	44	Response to IR#38 labeling comments. Scope of review limited to revised information in Section 16 of the draft USPI.
02 May 2025	0052	51	Response to device IR#44.
May 6, 2025	0054	53	Response to device IR#46.
May 13, 2025	0059	58	Response to device IR#49.

## 10. RELEVANT REFERENCED REGULATORY SUBMISSIONS

<b>Submission Type &amp; STN (Center)</b>	<b>Holder</b>	<b>Referenced Information</b>	<b>Letter of Authorization (Yes/No)</b>	<b>Comments/Status</b>
DMF (b) (4) (CDER)	(b) (4)	Plunger stopper	Yes	Review leveraged from BLA 125752/74, due to similar formulation, same route of administration, and same syringe component. No new memo generated
DMF (b) (4) (CDER)	(b) (4)	Syringe barrel assembly	Yes	Review leveraged from BLA 125752/74, due to similar formulation, same route of administration, and same syringe component. No new memo generated.
DMF (b) (4) (CDER)	(b) (4)	(b) (4) Gray elastomer formulation	Yes	No DMF review required, information pertinent to finished container closure component is provided in the BLA or another DMF

## 11. RELEVANT PRIOR INTERACTIONS

The mRNA-1283 vaccine PFS uses the same syringe components as the Spikevax™ (mRNA-1273, BLA 125752) and mRESVIA® (mRNA-1345, BLA 125796) vaccines which are approved in the US.

## 12. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

Moderna submitted a BLA for licensure of their COVID-19 Vaccine, mRNA (MNEXSPIKE), which is a vaccine in a 1 mL non-graduated pre-filled syringe. The scope of this review memo includes device evaluation of the pre-filled syringe (product description, evaluation of essential performance after manufacture, storage, and shipping, biocompatibility, control strategy, and quality management system (design controls and purchasing controls)). Review of information cross referenced to master files is leveraged from previous memos created for Moderna's previous BLAs with PFS. Shelf life from a device perspective is supported by testing after accelerated aging, and confirmatory evidence is being generated in ongoing stability studies. Based on the information provided in the application and leveraged from previous reviews of 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**

### **I. APPROVAL**

- No device-related PMCs

### **II. SIGNATURE BLOCK**

<b>Reviewer, Title, Affiliation</b>	<b>Concurrence</b>	<b>Signature and Date</b>
Andrea Gray, PhD Device Consult Reviewer CBER/ORO/DROP/RPB	-	
Heba Degheidy, MD, PhD, RAC Senior Advisor for Medical Devices CBER/ORO/DROP/RPB (for Cherie Ward-Peralta, MS, Branch Chief, CBER/ORO/DROP/RPB)	Concur [May 16, 2025]	

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### I. Product Description

#### A. Combination Product

The DP (mRNA-1283) is supplied as a sterile, single-dose, ready-to-use liquid solution at 10 µg/0.2 mL for intramuscular (IM) administration in a 1-mL prefilled syringe (PFS). Each PFS delivers 10 µg of RNA and 200 µg of total lipids as a white to off-white dispersion in preservative-free buffer containing (b) (4) mM Tris and (b) (4) g/L sucrose at pH (b) (4).

#### B. Drug/Biologic

Module 3.2.P.1 states “The Drug Product (DP) is an RNA-lipid complex dispersion that contains RNA, which encodes the linked N-terminal domain and receptor-binding domain of the spike glycoprotein of the SARSCoV-2 virus, and four lipids that act as protectants and carriers of the RNA. The four lipids are SM-102 ((b) (4)), a custom-manufactured, ionizable lipid), cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), and PEG2000-DMG (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000).”

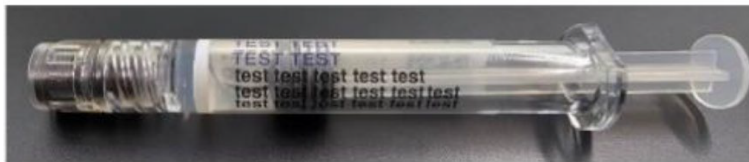
According to Table 6 in the PPQ Final Report RPT-19815 in Module 3.2.P.3.5, the density of the drug product is (b) (4).

**Reviewer Comment:** Refer to CMC memo for more drug product information.

### C. Syringe

From Module 3.2.R Regional Information - Prefilled Syringe Combination:

Figure 1: Image of PFS



<b>Components and Suppliers</b>	(b) (4): barrel, plunger rod, rigid cap (b) (4): plunger stopper (b) (4): tip cap
<b>Connection Type</b>	Luer
<b>Intended Connector(s)</b>	Needle
<b>Materials of Construction</b>	<p>From Module 3.2.R Regional Information - Prefilled Syringe Combination:</p> <p><u>Barrel</u>: Cyclic Olefin Copolymer (COC)*</p> <p><u>Rigid Cap</u>: Polycarbonate (PC) – (b) (4)</p> <p><u>Tip cap</u>: Bromobutyl Rubber (b) (4)</p> <p><u>Plunger stopper</u>: (b) (4) coated Bromobutyl Rubber ((b) (4))**</p> <p><u>Plunger rod</u>: Polypropylene (PP)</p> <p>*Per Document QER-12180 in Module 3.2.P.7, the syringe barrel lubricant is (b) (4).</p> <p>**Per EXT-19448 in Module 3.2.R, plunger stopper (b) (4) coating is (b) (4). The stoppers are also lubricated with (b) (4).</p>
<b>Dimensions</b>	Engineering drawings provided in Module 3.2.R
<b>Syringe Volume</b>	1 mL
<b>Fill Volume</b>	(b) (4) mL
<b>Sterilization Method</b>	<p><u>Syringe</u>: (b) (4) sterilization per (b) (4), sterility assurance lever (b) (4), received ready to use</p> <p><u>Plunger Stopper</u>: (b) (4) sterilization per (b) (4), sterility assurance lever (b) (4), received ready to use</p>
<b>Route of Administration</b>	Intramuscular injection
<b>Administration Site</b>	Injection site necessary for intramuscular injection of vaccines is common knowledge in the healthcare community per <a href="#">ACIP guidelines</a> .
<b>Target Tissue and Depth</b>	Target tissue and depth necessary for intramuscular injection of vaccines is common knowledge in the healthcare community per <a href="#">ACIP guidelines</a> .
<b>Type of Use</b>	Single use

<b>Storage Conditions and Proposed Expiry</b>	12 months -40°C to -15°C including up to 90 days of storage at 2°C to 8°C and up to 24 hours at room temperature (up to 25°C) to support administration of the vaccine at the point-of-care site.
<b>Intended User(s)</b>	Healthcare professionals
<b>Intended Use Environment</b>	Clinic
<b>Needle Length, Gauge, Tip Style</b>	No needle supplied with vaccine. Needle specifications necessary for intramuscular injection of vaccines is common knowledge in the healthcare community, per <a href="#">ACIP guidelines</a> .
<b>Markings</b>	n/a
<b>Reuse Durability</b>	n/a
<b>Safety Features</b>	n/a
<b>Automated Functions</b>	n/a

Module 3.2.R Regional Information - Prefilled Syringe Combination points out that “The mRNA-1283 vaccine PFS uses the same syringe components as the Spikevax™ (mRNA-1273) and mRNA-1345 mRESVIA® vaccines. Both have been approved and marketed in the United States (US).”

Moderna includes letters of authorization (LOAs) in Module 1.4.1 to reference the following master files:

- Drug Master File (DMF) # (b) (4) (3.1 Table of Contents of Module 3) for the syringe barrel, rigid tip cap, and plunger rod. (EXT-19247 LOA)
- DMF # (b) (4) (3.2.P.7 Master File Table of Contents; eCTD Document ID C\_STP) for the plunger (EXT-19245 LOA)
- DMF # (b) (4) (3.2.P.7) for the plunger elastomeric formulations, coatings, and films (EXT-19246 LOA).

**Reviewer’s Overall Assessment and Recommendations:** Product description information is acceptable from a device perspective.

## II. Manufacturing

### A. [Manufacturers](#)

From Module 3.2.P.3.1 (Amendment 21, Sequence 0022; emphasis added by reviewer):

<b>Facility</b>	<b>Responsibility</b>
(b) (4)	<b>Manufacturing of unlabeled drug product (UDP)</b> <b>In-process testing</b>

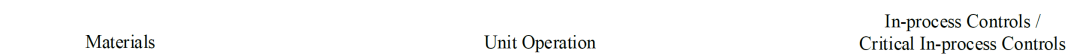
Facility	Responsibility
(b) (4)	(b) (4) <b>Assembly, label, and packaging of drug product</b> <b>In-process testing</b> Release and stability testing (b) (4)
(b) (4)	<b>Release and stability testing</b> (Particulate Matter, Bacterial Endotoxins, Sterility, (b) (4) <b>Container Closure Integrity, Deliverable Volume)</b>
Moderna Biotech Spain, SL Calle Julián Camarillo, 31, Planta 4a, Madrid 28037 Madrid, Spain	Batch certification <b>Release and stability testing</b> (Appearance, Total RNA content, Identity, mRNA Purity/Product Related Impurities, % RNA (b) (4) (b) (4) Lipid Identity/ content/ impurities, Particulate Matter, Bacterial Endotoxin, Sterility, <b>Deliverable volume)</b>
(b) (4)	(b) (4) <b>Frozen storage ( (b) (4) long-term)</b>
(b) (4)	Distribution
(b) (4)	Distribution

<sup>a</sup> (b) (4) is subcontracted by (b) (4)

## B. Manufacturing Process

From 3.2.P.3.3:

**Figure 1: Drug Product Process Flow Diagram <sup>(a)</sup>**



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

taken after assembly, labeling, and packaging. All samples undergo (b) (4) and are stored at (b) (4) prior to testing and/or stationing.”

**i. In Process Controls**

Table 2 in Module 3.2.P.3.3 lists in process controls, including the device-relevant controls related to filling excerpted below.

(b) (4)

(b) (4)

**Reviewer Comment:** Although container closure integrity (CCI) review is deferred to DMPQ, 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.

**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	Sample	Release Acceptance Criteria	Shelf-Life Acceptance Criteria	SOP*	Test Site*
Deliverable Volume	(b) (4)	For each of the (b) (4) syringes: (b) (4) 0.2 mL	For each of the (b) (4) syringes: (b) (4) 0.2 mL	(b) (4) Moderna: SOP-5183	(b) (4) Moderna Madrid
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4) EXT-25135	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4) EXT-25135	(b) (4)
Container Closure Integrity	(b) (4)	n/a	PASS	(b) (4): EXT-25134	(b) (4)

\*From Module 3.2.P.5.2

(b) (4)

**Reviewer Comment:** Review of container closure integrity (CCI) test method and validation is deferred to DMPQ.

Information on analytical method, validation, and justification for deliverable volume and (b) (4) in Modules 3.2.P.5.2, 3.2.P.5.3, and 3.2.P.5.7 are excerpted or summarized below.

### **Deliverable Volume**

Justification: Ensures that the device will eject the volume of product necessary for the intended dose.

Analytical Method: Per (b) (4). SOP-5183 is provided in Module 3.2.R of (Amendment 33, Sequence 0024). The test utilizes a (b) (4) with the assembled syringe (filled, stoppered barrel, plunger rod). The method conforms to (b) (4).

Verification/Validation: “The verification of the deliverable volume (b) (4) test method, in compliance with (b) (4) Verification of (b) (4) Procedures, was completed, demonstrating the suitability of this method at each testing site under the actual conditions of use. This method has additionally been verified by testing of the PPQ lots intended for registration.”

Module 3.2.R contains the following relevant documents:

- RPT-71378, October 5, 2020 (Amendment 24, Sequence 0025)
  - A (b) (4) method verification report for mRNA-1273. The methods included verification of SOP-0950 for container content per (b) (4) via direct comparison of the SOP and (b) (4) methods. Moderna determined the method was suitable and in harmony with the (b) (4) method.
- REC-2299, May 16, 2024 (Amendment 24, Sequence 0025)
  - A justification for non-verification of the (b) (4) test in mRNA syringes. The justification includes the information quoted above regarding (b) (4).
- RPT-17972, July 11, 2024 (Amendment 24, Sequence 0025)
  - A summary of the verification of (b) (4) test methods used for mRNA-1283 DP ((b) (4)). States, “Deliverable volume method (SOP-5183) was previously verified for mRNA (b) (4) DP (see RPT-17179), therefore as the method is not product-dependent (see AST-MEM-0244) no additional verification is needed.” Section 7.5 concludes that SOP-5183 conforms to the (b) (4).

(b) (4)

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

(b) (4)

(b) (4)

### III. Design Verification

Design verification information is provided in Module 3.2.R Regional Information - Prefilled Syringe Combination, which references several associated documents in the module.

Section 3.2.R.1.9 provides information on the PFS essential performance requirements, which Moderna identifies as deliverable volume (“expelled volume”<sup>(b) (4)</sup> 0.2 mL when tested at ambient temperatures”) and injections forces (<sup>(b) (4)</sup>). Moderna provides the following rationale for why tip cap removal force and needle cap removal force are not EPRs for this product: “Tip cap removal torque is not considered an EPR because the mRNA-1283 vaccine PFS is intended for the prevention of COVID-19 caused by SARS-CoV-2, rather than to treat an emergency, life-threatening condition. Therefore, the risk associated with tip cap removal is not expected to result in an unacceptable harm. A needle is not provided with the PFS; therefore, needle cap removal is not an applicable requirement or EPR for the PFS.”

Verification studies are described in Section 3.2.R.1.12. Moderna is leveraging some verification data from the development of the mRNA-1273 0.5 mL PFS. mRNA-1273 and mRNA-1283 have <sup>(b) (4)</sup> with differences being fill volume and concentration (mRNA-1283, 0.05 mg/mL). Moderna states “Elements that are agnostic to fill volume were previously tested during the development of the mRNA-1273 0.5 mL PFS and are applicable to mRNA-1283 0.2 mL PFS.”

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

This section refers to a Traceability Matrix (PLAN-0148, included in Module 3.2.R) for the design input requirements, design outputs, and references to design verification and validation evidence (test reports).

**Reviewer Comment:** Additional information is needed regarding the mRNA-1283 PFS and mRNA-1273 PFS lots used for design verification activities described in Section 3.2.R.1.12 in Module 3.2.R Regional Information - Prefilled Syringe Combination. Moderna should identify the lots, including which manufacturing process flow was used and duration of any (b) (4). **IR#44.1.**

**Information Request (IR)#44.1a**

**Date Sent:** April 29, 2025

**Date/Amd/eCTD Sequence Received:** May 2, 2025 / 51 / 0052

**IR Comment:** Table 5 in Module 3.2.R “Regional Information – Prefilled Syringe Combination” Section 3.2.R.1.12.1 contains design verification data for mRNA-1283 pre-filled syringe (PFS) and data leveraged from the development of mRNA-1273 PFS. Please address the following:

- a. We could not find sufficient information about the mRNA-1283 PFS and mRNA-1273 PFS lots that were tested. Please identify the lots (i.e., lot number) and provide additional information on the mRNA-1283 PFS and mRNA-1273 PFS lots associated with the data in Table 5, including manufacturing process flow (i.e., (b) (4)), duration of any (b) (4), and whether the samples were subject to assembly, labeling, and packaging steps. This is needed to further understand how the data applies to the output of your full commercial manufacturing processes.
- b. ...

**Applicant Response:** Table 1 identifies the mRNA-1283 and mRNA-1273 pre-filled syringe (PFS) lots used for design verification testing, including the corresponding lot numbers and manufacturing process details. Both mRNA-1283 and mRNA-1273 PFS lots were manufactured using the (b) (4) process flow, which included (b) (4) assembly, labeling, and packaging operations at the (b) (4) manufacturing site. The duration of (b) (4) was approximately (b) (4) for the mRNA-1283 lot and mRNA-1273 lot, respectively (Table 1). The duration of (b) (4)

Therefore, the design verification data generated using mRNA-1273 PFS (for elements that are agnostic of fill volume) and mRNA-1283 PFS (for CCI, label legibility, and essential performance requirements (b) (4) and Deliverable Volume) are applicable to the commercial manufacturing process for mRNA-1283.

*Information excerpted from table 1:*

Product	Process Flow	Lot Number	(b) (4)

<b>Information Request (IR)#44.1a</b>			
<b>Date Sent:</b> April 29, 2025			
<b>Date/Amd/eCTD Sequence Received:</b> May 2, 2025 / 51 / 0052			
Commercial Manufacturing mRNA-1283	Process Flow (b) (4)	n/a	(b) (4)
Design Verification mRNA-1283	Process Flow (b) (4)	Lot (b) (4)	(b) (4)
Design Verification mRNA-1273	Process Flow (b) (4)	Lot (b) (4)	(b) (4)
<b>Reviewer Comments:</b> The design verification samples are representative of the (b) (4) manufacturing process, with (b) (4). The duration of (b) (4) for test lots ( (b) (4) ) (b) (4) for the commercial process ( (b) (4) ). However, unlike some drug product critical quality attributes, the essential performance requirements (deliverable volume, injection forces) may be more impacted by (b) (4) than by (b) (4) duration. Therefore, the verification data (including after shipping and accelerated aging) is adequately representative of the commercial product. Also, it is noted that the verification data does not appear to overlap the PPQ data reviewed in <a href="#">Section II.B.C Batch Analysis</a> in this memo.			

**Reviewer's Overall Assessment and Recommendations:** Design verification information is sufficient. Leveraging of some mRNA-1273 PFS design verification data is acceptable.

#### IV. Design Validation

Design validation information is provided in Section 3.2.R.1.13 and Module 3.2.P.3.5. Moderna lists the following design validation activities:

- Establishing a plan for design validation and human factors.
- Defining the use specification (i.e., user needs, intended use, intended users).
- Human Factor comparative analysis (RPT-18233) was performed comparing the mRNA-1283 0.2 mL PFS presentation and the mRNA-1273 0.5 mL PFS presentation and supporting human factors validation study results.
- Summarizing human factors activities and design validation results in a Human Factors Usability Engineering Summary Report (RPT-18189), which is provided in 5.3.5.4 Other Study reports and related information.

Human factors data from mRNA-1273 is leveraged because “The intended user population, use environment, route of administration, and syringe components of the mRNA-1283 PFS are the same as the mRNA-1273 PFS... based on these similarities, design validation documentation and human factors testing of the mRNA-1273 PFS are suitable to be used to validate the mRNA-1283 PFS design and user interface associated with storage and administration.” Moderna concluded that “the studies validated that the mRNA-1283 vaccine PFS fulfills the defined user needs and that the intend-to-market user interface supports safe and effective use of the combination product for its intended uses, users, and use environments.”

**Reviewer's Overall Assessment and Recommendations:** Review of human factors information is deferred to the CDER HF consult.

## V. Biocompatibility

Section 3.2.R.1.11 in Module 3.2.R Regional Information - Prefilled Syringe Combination states “The syringe barrel, plunger rod, rigid cap, and tip cap have direct transient contact with intact skin surfaces. Based on the limited contact duration ( $\leq 24$  hours), chemical characterization testing was performed, and the relevant biological endpoints are cytotoxicity, sensitization, and irritation/intracutaneous reactivity. As presented in Table 4, the biocompatibility of components was verified using documentation provided by the component manufacturers and suppliers.”

Table 4 is recreated below:

Component	Material of Construction	Nature of Contact	Evaluation Performed	Results	Reference
Plunger rod	Polypropylene (PP)	Surface device Intact skin A – Limited ( $\leq 24$ hours)	Cytotoxicity	Acceptable	EXT-17330 Biocompatibility Statement Plunger Rod  DMF # (b) (4) (3.2.P.5.2.4 Results of the safety and toxicology tests)
Rigid cap	Polycarbonate (PC)	Surface device Intact skin A – Limited ( $\leq 24$ hours)	Cytotoxicity	Acceptable	EXT-12302 (b) (4) Syringe System Biocompatibility Testing  DMF # (b) (4) (3.2.P.5.2.4 Results of the safety and toxicology tests)
Syringe Barrel	Cyclic Olefin Copolymer (COC)	Drug Product Contact	The product extractables and leachables profile shall indicate no chemicals exceeding levels of toxicological concern.	Acceptable	Information provided in Module 3.2.P.2.4
Plunger	Halobutyl rubber with (b) (4) coating				
Tip Cap	Halobutyl rubber				

Moderna states “No data analysis was required because verification was performed via confirmation of manufacturer-supplied documentation.” Reference is made to the following:

- “DMF # (b) (4) (3.2.P.1.4 Materials, Components and Suppliers and 3.2.P.5.2.4 Results of the safety and toxicology tests) for the syringe barrel, rigid tip cap, and plunger rod (EXT-19247 LoA).
- DMF # (b) (4) (eCTD Document ID C\_BIO) for the plunger (EXT-19245 LoA)

- DMF # (b) (4) (3.2.P.7) for the plunger elastomeric formulations, coatings, and films (EXT-19246 LoA)."

**Reviewer's Overall Assessment and Recommendations:** Biocompatibility information is sufficient. The syringe components are identical to those used in mRNA-1273. Biocompatibility was assessed in detail in the device memo for BLA 125752/74 and the referenced master files and determined to be sufficient. Review of extractables and leachables information is deferred to CMC.

## VI. Sterilization

Module 3.2.P.7 states (emphasis added by reviewer)

(b) (4)

**Plunger stoppers** are received sterile and RTU. "(b) (4) **sterilization** of the plungers is performed according to (b) (4), to achieve the **sterility assurance level** of (b) (4)."

**Plunger rods** are received non-sterile.

Syringe Barrel Sterilization Site	Plunger Stopper Sterilization Site
(b) (4)	(b) (4)

**Reviewer's Overall Assessment and Recommendations:** Sterilization information is adequate. Review of drug product sterility and endotoxin levels is deferred to CMC and DBSQC review. Review of sterilization validation and sites is deferred to DMPQ.

## VII. Control Strategy

Essential Performance Requirement	Control Strategy Description (e.g., incoming acceptance, in-process control, and/or release testing activities):
Dose Accuracy	In process control (fill (b) (4)), lot release testing (deliverable volume (b) (4)), design verification (see <a href="#">Section III</a> of this memo)
(b) (4)	Purchasing controls, incoming controls, lot release testing (b) (4), design verification (see <a href="#">Section III</a> of this memo)
(b) (4)	Purchasing controls, incoming controls, lot release testing (b) (4), design verification (see <a href="#">Section III</a> of this memo)

Module 3.2.P.7 states “DP container closure components are received, inspected, and released for use according to established procedures, which include review and acceptance of the manufacturer Certificate of Analysis, Certificate of Processing, Certificate of Compliance, BSE/TSE statement, and the performance of a quality control test plan that is component specific. Sterility is documented by supplier quality certificates, as applicable. (b) (4) references for each component are summarized in Table 2.”

The (b) (4) consensus standards references in Table 2 are as follows:

- Syringe: (b) (4)
- Plunger Stopper: (b) (4)

Module 3.2.P.7 also identifies the specifications tabulated below (tables recreated from the submission) for incoming syringe components (QC = quality control).

**Table 3 and 4: Specifications for 1-mL Long COC Syringe and 1-mL Long Plunger, Respectively**

QC Inspection/Method	Specification
(b) (4)	Conforms
	Conforms to drawing
	Conforms
	Conforms
	Conforms
	Conforms

**Table 5: Specifications for Plunger Rod**

QC Inspection/Method	Specification
(b) (4)	Conforms
	Conforms to drawing
	Conforms

**Reviewer’s Overall Assessment and Recommendations:** Control strategy is adequate from a device perspective.

## VIII. Packaging, Stability, Shipping

### A. Packaging

According to Module 3.2.P.7 (Amendment 38, Sequence 0039) PFS are packed in (b) (4) packed into a carton with a patient information leaflet (PIL) or prescribing information (PI). Cartons are placed into cases. “The carton configurations for mRNA-1283 DP are listed below:

- Carton of 1 single-dose PFS
- Carton of 1 single-dose PFS (b) (4)
- Carton of 2 single-dose PFS

- (b) (4)
- Carton of 10 single-dose PFS
- (b) (4)

The revised Prescribing Information in Amendment 44 (Sequence 0045), submitted in response to labeling comments in IR#38, indicates that Moderna (b) (4). The remaining packaging configurations are:

- Carton of 1 single-dose PFS
- Carton of 2 single-dose PFS
- Carton of 10 single-dose PFS

The Human Factors Usability Engineering Summary Report (RPT-18189) contains a depiction of the carton of 10 syringes:



## B. Stability

Proposed Shelf Life and Storage Conditions: **12 months at -40°C to -15°C including up to 90 days of storage at 2°C to 8°C and up to 24 hours at room temperature (up to 25°C)**

According to Section 3.2.R.1.12 in Module 3.2.R Regional Information - Prefilled Syringe Combination, design verification activities included testing after storage for (b) (4). Results are excepted from Table 5 below.

(b) (4)

(b) (4)

Additionally, Moderna states “ongoing stability studies that include (b) (4), deliverable volume, and container closure integrity testing are described in [Module] 3.2.P.8.1.”

**Reviewer Comment:** Moderna has not provided an explanation of how or a basis for why the accelerated aging conditions (b) (4) are representative of the real-time storage conditions and durations. See **IR#44.1b**. It is also not clear what lots were used for design verification. Moderna should identify the lots used for design verification activities described in Section 3.2.R.1.12 in Module 3.2.R Regional Information - Prefilled Syringe Combination, including which manufacturing process flow was used and duration of any (b) (4). See **IR#44.1a** in [Section III. Design Verification](#) in this memo.

**Information Request (IR)#44.1b**

**Date Sent:** April 29, 2025

**Date/Amd/eCTD Sequence Received:** May 2, 2025 / 51 / 0052

**IR Comment:** Table 5 in Module 3.2.R “Regional Information – Prefilled Syringe Combination” Section 3.2.R.1.12.1 contains design verification data for mRNA-1283 pre-filled syringe (PFS) and data leveraged from the development of mRNA-1273 PFS. Please address the following:

- a. ...
- b. Table 5 includes verification data for samples subjected to accelerated aging for (b) (4). However, you did not indicate what real time conditions and durations these accelerated aging parameter represent. Please state the equivalent real time aging conditions and duration, how the accelerated aging conditions were selected, and a comparison to the proposed shelf life conditions (i.e., 12 months at -40°C to -15°C including up to 90 days of storage at 2°C to 8°C and up to 24 hours at room temperature (up to 25°C) to support administration of the product at the point-of-care site). This is needed to understand how the data you provided demonstrate that device performance is maintained over the proposed shelf life.

**Applicant Response** (emphasis added by reviewer): Accelerated aging conditions are based on (b) (4)

(b) (4)

(b) (4)

**Reviewer Comments:** Response is acceptable. (b) (4) is an FDA recognized standard. The PFS components used in this product are also used in

**Information Request (IR)#44.1b**

**Date Sent:** April 29, 2025

**Date/Amd/eCTD Sequence Received:** May 2, 2025 / 51 / 0052

*Moderna's other approved vaccines, which have the same long term storage condition. This product experience mitigates concerns that the current vaccine in PFS would not meet functional performance requirements at expiry. Additionally, the essential performance requirements are being evaluated in the ongoing PPQ stability studies.*

The PFS lots below were used for stability testing described in Module 3.2.P.8.1 and include data for device-relevant metrics. Timepoints are in months. All samples met acceptance criteria (see [Section II.B.ii](#) in this memo). Moderna states in Module 3.2.P.8.1 that they did not observe any trends in (b) (4) or deliverable volume. Latest available timepoints are extracted from Module 3.2.P.8.3 that was updated in Amendment 38 (Sequence 0039), in response to CMC IR#33. In this response, Moderna clarified that all lots were made with Process Flow (b) (4) and also provided the (b) (4) time for each lot.

ID	CMO Lot#	Lot Type	Date of Manufacture	Fill Volume (mL)	UDP (b) (4)	Manufacturing Site	Temperature*	Duration	Latest timepoint available – Deliverable Volume	Latest timepoint available (b) (4)	Latest timepoint available – CCIT
(b) (4)	(b) (4)	PPQ	(b) (4)	(b) (4)	(b) (4)	(b) (4)	-25°C to -15°C 2°C to 8°C 23°C to (b) (4)°C	12 (b) (4) (b) (4)	6 (b) (4) complete	6 (b) (4) complete	6 (b) (4) complete
		PPQ					-25°C to -15°C 2°C to 8°C 23°C to (b) (4)°C	12 (b) (4) (b) (4)	6 (b) (4) complete	6 (b) (4) complete	6 (b) (4) complete
		PPQ					-25°C to -15°C 2°C to 8°C 23°C to (b) (4)°C	12 (b) (4) (b) (4)	6 (b) (4) complete	6 (b) (4) complete	6 (b) (4) complete
		PPQ					(b) (4) °C -25°C to -15°C 2°C to 8°C 23°C to (b) (4)°C	(b) (4) (b) (4) (b) (4)	1 1 3 complete	1 1 3 complete	1 1 3 complete
		PPQ					(b) (4) °C -25°C to -15°C 2°C to 8°C 23°C to (b) (4)°C	(b) (4) (b) (4) (b) (4)	1 1 3 complete	1 1 3 complete	1 1 3 complete
		PPQ					(b) (4) °C -25°C to -15°C 2°C to 8°C 23°C to (b) (4)°C	(b) (4) (b) (4) (b) (4)	1 1 3 complete	1 1 3 complete	1 1 3 complete

According to Module 3.2.P.8.1, for **end-to-end stability testing**, samples from PPQ lots at -25°C to -15°C will be moved to storage at 2°C to 8°C at the (b) (4) timepoints and will be considered the “initial” timepoint for the 2°C to 8°C study, which will evaluate (b) (4), deliverable volume, and container closure integrity at 1, 2, 3, (b) (4) months. Additionally, samples at 2°C to 8°C will be moved to storage at 23°C to (b) (4)°C at the (b) (4) timepoints and will be considered the “initial” timepoint for the 23°C to (b) (4)°C study, which will evaluate (b) (4), deliverable volume, and container closure integrity at 24 hours.

In the response to CMC IR#33, Moderna states (emphasis added by reviewer) “An **end-to-end stability study has been initiated for a representative development lot stored in the commercial container closure (COC PFS)**. This lot has been stored at -25°C to -15°C for 3 and 6 months (**sublots lot (b) (4)**, respectively) and then transferred for storage at 2°C to 8°C for 3 months followed by 24 hours at 23°C to (b) (4)°C. All available data for these lots are within specifications over the shelf-life storage conditions and no unexpected trends have been observed. This data continues to support the proposed shelf life for mRNA-1283 DP. An additional subplot is being stored at -25°C to -15°C for (b) (4) months and will be subsequently transferred to 2°C to 8°C for 3 months followed by 24 hours at 23°C to (b) (4)°C to cover the proposed shelf life for mRNA- 1283 DP. **This study is expected to be completed by the end of Q3 2025.**”

In Module 3.2.P.8.2, Moderna “commits to placing a minimum of (b) (4) on stability annually. If a seasonal change is made to the DP, a lot of the new seasonal DP will be placed on stability. No additional lots of the previous season's DP will be placed on stability.” These stability studies will be end-to-end studies (LDP stored for 9 months at -25°C to -15°C, then 3 months at 2°C to 8°C, then 24 hours at 23°C to (b) (4)°C). (b) (4), and container closure integrity will be evaluated at the initial timepoint and end timepoint of each storage condition.

### C. Shipping

According to Section 3.2.R.1.12 in Module 3.2.R Regional Information - Prefilled Syringe Combination, design verification activities included testing after exposure to simulated transit conditions (at (b) (4) °C). “Simulated transit conditioning was conducted in accordance with (b) (4) ... To simulate domestic or international transportation, the PFS samples were packaged in shipper boxes per the proposed commercial packaging configuration.”

**Reviewer Comment:** (b) (4) is an FDA-recognized standard. (b) (4) is for simulating (b) (4), and involves the following stages: (b) (4)

Results are excerpted from Table 5 below. For rationales and test methods, see [Section III Design Verification](#) or [Section VIII.B Stability](#) in this memo.

(b) (4)

**Reviewer Comment:** *It's not clear what lots were used for this testing. See **IR#44.1a** recommended in [Section III. Design Verification](#) in this memo.*

**Reviewer's Overall Assessment and Recommendations:** Packaging, stability, and shipping information is sufficient from a device perspective. Real time stability studies are on-going and will confirm results of accelerated aging testing for dose accuracy and injection forces.

**IX. [Comparability Protocols](#)**

None submitted.

**X. [Quality Management System](#)**

**Site:** "ModernaTX Sites" (from Module 3.2.R)

**Reviewer Comment:** *Based on this wording, it appears the information below might only apply to Moderna Biotech Spain, SL, Calle Julián Camarillo, 31, Planta 4a, Madrid, 28037 Madrid, Spain.*

Quality management system information is discussed in Module 3.2.R Regional Information - Prefilled Syringe Combination. Section 3.2.R.1.7.1 states “ModernaTX has implemented a Quality Management System (QMS) that applies to all ModernaTX personnel and sites that perform applicable regulated activities... To comply with 21 CFR Part 4, Subpart A, ModernaTX has implemented a streamlined approach based on drug cGMPs of 21 CFR Parts 210, 211, and 600-680 with the addition of the following provisions of the Quality System Regulation:

- 21 CFR 820.20 Management responsibility.
- 21 CFR 820.30 Design Controls.
- 21 CFR 820.50 Purchasing Controls.
- 21 CFR 820.100 Corrective and Preventive Action.”

Device GMP Requirement	Summary
21 CFR 820.20 Management Responsibility	<b>Deferred to OCBQ/DMPQ review.</b>
21 CFR 820.30 Design Controls	Summarized in Section 3.2.R.1.7.2 and covers design and development planning, design inputs, design outputs, design verification and validation, design review, design transfer, design changes, and design history file. Notably, Moderna states “Documents supplied by contract manufacturers were leveraged to fulfill design outputs as appropriate.”
21 CFR 820.50 Purchasing Controls	Summarized in Section 3.2.R.1.7.4 and describes a supplier management program and a materials management process.
21 CFR 820.100 Corrective and Preventive Actions	<b>Deferred to OCBQ/DMPQ review.</b>
21 CFR 820.170 Installation	N/A
21 CFR 820.200 Servicing	N/A

**Reviewer Comment:** In response to the question “What facility information should I list in Module 3?”, the FDA guidance “Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers” states “For each facility manufacturing a single entity or co-packaged combination product that is subject to 21 CFR Part 4, identify which CGMP operating system approach is established.” Additionally, the FDA guidance “Current Good Manufacturing Practice Requirements for Combination Products” states “Combination product manufacturers who are required to address CGMP issues as part of premarket review should identify in premarket submissions whether they are operating under a streamlined approach, and if so, whether it is a drug CGMP-based or device QS regulation-based streamlined approach... For NDAs, BLAs and ANDAs, the CGMP approach should be described in

*the Common Technical Document.” Section 5 of the FDA guidance “eCTD Technical Conformance Guide” states Module 3.2.P.3.1 should include the following information:*

- “For each facility that is subject to 21 CFR part 4, identify whether it follows the combination product streamlined manufacturing approach and identify the base set of regulations (i.e., 21 CFR 211 or 820).”*
- “Provide a detailed list of all manufacturing facilities; what activities occur at the site (e.g., assembly, filling, sterilization, testing, other); what constituents are at the site (e.g., drug only, device only, both drug and device). For the facilities that have both the drug and device, identify which combination product operating system is used at the site.”*

*No quality management operating system information was submitted for the other manufacturing sites. The (b) (4) sites conduct manufacturing activities for the finished single-entity combination product and are therefore subject to the requirements in 21 CFR Part 4 (i.e., must demonstrate compliance with drug, biologic, and device GMPs, following a streamlined approach if desired). See IR#46.2.*

**Information Request (IR)#46.1**

**Date Sent:** May 2, 2025

**Date/Amd/eCTD Sequence Received:** May 6, 2025 / 53 / 0054

**IR Comment:** The FDA guidance “Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers” states “For each facility manufacturing a single entity or co-packaged combination product that is subject to 21 CFR Part 4, identify which CGMP operating system approach is established.” Additionally, the FDA guidance “Current Good Manufacturing Practice Requirements for Combination Products” states “Combination product manufacturers who are required to address CGMP issues as part of premarket review should identify in premarket submissions whether they are operating under a streamlined approach, and if so, whether it is a drug CGMP-based or device QS regulation-based streamlined approach... For NDAs, BLAs and ANDAs, the CGMP approach should be described in the Common Technical Document.” In Module 3.2.R Regional Information - Prefilled Syringe Combination, you describe the quality management for Moderna manufacturing sites. However, you have not provided this information for the other manufacturing sites listed in Module 3.2.P.2.1. As discussed in the guidance documents cited above, please identify the CGMP operating system approach in place at each manufacturing site. If a site is utilizing a streamlined approach described in 21 CFR Part 4.4(b), please identify the elected approach.

**Applicant Response:** Per an email dated 05 May 2025 from FDA (Donna Elhindi), a response to Item #2, regarding the CGMP operating system approach in place at each manufacturing site, is no longer required.

**Reviewer Comments:** This was discussed with DMPQ on May 5, 2025. DMPQ clarified that the contract manufacturer site GMP operating systems and the responsibilities of each part are defined in Moderna’s quality agreement at each site. Additionally, the (b) (4) sites are also utilized to manufacture mRNA-1273 DP in 125752. The DMPQ review memo for that supplement states “The (b) (4) corporate quality policies and procedures as well as regulatory requirements,

**Information Request (IR)#46.1**

**Date Sent:** May 2, 2025

**Date/Amd/eCTD Sequence Received:** May 6, 2025 / 53 / 0054

*including GMP apply to all (b) (4) sites. Information related to the QS regulations § 820.20 - Management responsibility, §820.30 – Design controls, § 820.50 - Purchasing controls, and § 820.100 – Corrective and preventive action has been reviewed and deemed acceptable (BL 125752/74, approved on September 11, 2023).” The (b) (4) sites currently have applicable device QS regulations in place.*

*Therefore, this comment of IR#46 was retracted via email on May 5, 2025.*

**Reviewer’s Overall Assessment and Recommendations:** QMS information is sufficient from the device perspective. Defer to DMPQ.