

CBER BLA Device Review Memorandum – Prefilled Syringe (PFS)

BLA STN 125796

MRESVIA (RSV Vaccine, mRNA-1345)

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

1. **BLA#:** STN 125796

2. **APPLICANT NAME:** ModernaTx, Inc

3. **PRODUCT NAME/PRODUCT TYPE**

- Non-Proprietary/Proper/USAN: RSV-Vaccine, mRNA-1345
- Proprietary Name: MRESVIA

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

- General Description: sterile white to off-white suspension for intramuscular injection contained in a single-dose pre-filled syringe
- Route of administration: Intramuscular Injection
- Indication(s): Active immunization for the prevention of lower respiratory tract disease (LRTD) (b) (4) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older

5. **COMBINATION PRODUCT INFORMATION**

- Category: Biologic-Device
- Type: Type 3: Prefilled Biologic Delivery Device/System
- Biologic Constituent(s): Vaccine
- Drug Constituent(s): N/A
- Device Constituent(s): Prefilled Syringe

6. **MAJOR MILESTONES**

- Filing Meeting: October 26, 2023
- Midcycle Internal Meeting: December 20, 2023
- Late Cycle Internal Meeting: March 4, 2024
- PDUFA Action Date: May 10, 2024 (Major Amendment received February 26, 2024, letter issued: March 7, 2024, reconsidered by IOD and reconsideration letter sent April 11, 2024, reverting ADD to original date)

7. **QUALITY REVIEW TEAM**

Reviewer/Affiliation	PFS-Relevant Subject Matter
Judy Beeler CBER/OVRR/DVP	CMC (Extractables and Leachable, Toxicological Risk Assessment, Biologic Compatibility)
Iryna Zubkova CBER/OCBQ/DMPQ	Container Closure Integrity, Shipping Validation

8. **INTER-CENTER CONSULTS**

Reviewer/Affiliation	Topic	In agreement with consult recommendations (Yes/No)
Avani Bhalodia CDER/OSE/OMEPRM/DMEPA1	Human Factors	Yes

9. SUBMISSION(S) REVIEWED

Date Received	eCTD Sequence	Submission (STN 2nd Level)	Comments
June 29, 2023	0001	0	Original submission
January 26, 2024	0025	24	Response to Information Request (IR)#18 (device IR)
January 28, 2024	0040	39	Response to IR#23 (CMC IR)
April 5, 2024	0055	54	Response to IR#35 (CMC IR)
April 25, 2024	0058	57	Response to IR#38 (device IR)
April 29, 2024	0065	64	Response to IR#43 (Labeling IR)

10. RELEVANT REFERENCED REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Information	Letter of Authorization	Comments/Status
DMF (b) (4)	(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)	(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)	(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
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11. RELEVANT PRIOR INTERACTIONS

Moderna had a CMC-Specific Type B pre-BLA Meeting interaction with FDA under IND 23342.73 (written responses dated April 6, 2023). Question 4 asked “Does the Agency agree with the Applicant’s approach to mRNA-1345 combination product design verification, design validation and human factors?” FDA responded, “Your general approaches for mRNA-1345 combination product design verification, design validation and human factors appear acceptable”, and also provided some specific recommendations regarding justifications for leveraging data from another product, requested documentation (e.g., traceability matrix), appropriate use of consensus standards, essential performance requirements (EPRs; e.g., EPR identification, control strategy, shelf life), and appropriate use of master files.

12. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Moderna submitted BLA 125796 for licensure of their mRNA-based RSV vaccine (mRNA-1345, MRESVIA), which consists of a non-graduated 1 mL Cyclic Olefin Copolymer (COC) Luer-lock pre-filled syringe (PFS) containing a single-dose suspension of the mRNA-1345 drug product. The scope of this review memo includes: PFS description, PFS design verification (including device essential performance, e.g., deliverable volume, (b) (4)), verification of device essential performance over the proposed shelf life and after shipping, control strategy to ensure the final combination product meets essential performance requirements, PFS biocompatibility, and compliance with applicable device quality system regulations (design controls regulations (21 CFR 820.30), purchasing control regulations (21 CFR 820.50)). Review of information cross referenced to master files is leveraged from recent reviews in support of similar previous submissions, which are documented in separate memos available in the master file’s record. Based on the information provided in the application and cross-referenced master files, as well as additional information submitted interactively, I recommend that the BLA can be approved from a device/combination product perspective.

B. RECOMMENDATION: Approval

I. APPROVAL

- Comparability protocols in Module 3.2.R related to addition of a glass syringe presentation as well as identification of additional syringe component suppliers are approval from a device perspective.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Signature and Date
Andrea Gray, PhD Device Consult Reviewer CBER/ORO/DROP/RPB	
Sonday Kelly, MS, RAC, PMP Division Director CBER/ORO/DROP (for Cherie Ward-Peralta, MS, Branch Chief, CBER/ORO/DROP/RPB)	

Table of Contents

I. Contents

II. Product Description	1
A. Combination Product.....	2
B. Drug/Biologic.....	2
C. Syringe	2
III. Manufacturing.....	4
A. Manufacturers	4
B. Manufacturing Process	5
i. In Process Controls	7
ii. Final Product Specifications	7
iii. Batch Analyses	8
C. Process Validation	10
i. Fill Weight	10
ii. Process Flow 1.....	11
IV. Design Verification	13
V. Biocompatibility	20
VI. Sterilization.....	22
VII. Control Strategy	22
VIII. Packaging, Stability, Shipping	23
A. Packaging	23
B. Stability.....	24
C. Shipping	31
IX. Comparability Protocols.....	35
X. Quality System	37
XI. Appendices.....	38
A. Appendix 1 – Engineering Drawings	38
B. Appendix 2 – Relevant Comments and Responses: CMC IR#23 (Amendment 39, Sequent 0040); CMC IR#35 (Amendment 54, Sequence 0055).....	42
i. Comment 14.....	42
ii. Comment 17.....	42
iii. Comment 19	43
iv. Comment 23	44
v. Comment 26.....	45
vi. Comment 27	45
vii. Comment 28	45
viii. Comment 29	46
ix. Comment 30	47

II. Product Description

A. Combination Product

According to Module 2.3.1, “The mRNA-1345 DP is supplied as a sterile, single-dose, ready-to-use liquid solution at 0.10 mg/mL for intramuscular (IM) administration in a 1-mL prefilled syringe (PFS).”

B. Drug/Biologic


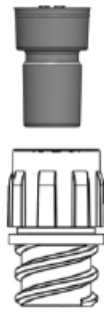


Module 3.2.P.2.2 states, “mRNA-1345 DP (encompassing UDP-100-AR02 and LDP-100-AR02) is a lipid nanoparticle (LNP) dispersion that contains an mRNA that encodes for the RSV F glycoprotein stabilized in the prefusion conformation. mRNA-1345 DP contains LNP-100-AR02 at a total RNA of 0.10 mg/mL in 20 mM tromethamine (Tris), (b) (4) mM acetate, 87 g/L sucrose, (b) (4).”

C. Syringe

From Module 3.2.R Regional Information – Prefilled Syringe:



Excerpted from Table 2 of Module 3.2.R Regional Information – Prefilled Syringe:

Component	Illustration ^(a)	DMF# (Location in DMF)
Syringe Barrel		(b) (4) (3.2.P.1 Description and Composition)
Rigid Tip Cap		(b) (4) (3.2.P.1 Description and Composition)
Plunger (stopper)		Plunger: (b) (4) (eCTD Document ID C_STP) Formulation, Coatings, Films: (b) (4) (3.2.P.7)
Plunger Rod		(b) (4) (3.2.P.1 Description and Composition)

^a Technical drawings are provided [Appendix 1](#) of this memo, excerpted from the attachments in 3.2.P.7 Container Closure System.

Components and Suppliers	(b) (4) : syringe (TOPPAC syringe with integrated Luer Lock (LL), tip cap, and rigid cap), plunger rod (b) (4) : tip cap (via (b) (4)) (b) (4) : plunger stopper
Connection Type	Luer
Intended Connector	Needle
Materials of Construction	Barrel with integrated LL*: Cyclic Olefin Copolymer (COC) Lubricant*: Reactive multicomponent polydimethylsiloxan system with EP-grade silicon oil: (b) (4) Rigid Cap: Polycarbonate (PC) – (b) (4) Tip Cap*: Bromobutyl Rubber (b) (4) Plunger stopper*: (b) (4) coated bromobutyl rubber ((b) (4)) Plunger Rod: polypropylene (PP) *Drug product contacting
Dimensions	See engineering drawings in Appendix 1 of this memo
Syringe Volume	1 mL
Fill Volume	(b) (4) mL
Sterilization Method	(b) (4)
Injection Site	Intramuscular – injection site necessary for intramuscular administration of vaccines is common knowledge in healthcare community and described by ACIP guidelines .
Injection Tissue and Depth	Injection tissue and depth necessary for intramuscular administration of vaccines is common knowledge in healthcare community and described by ACIP guidelines .
Type of Use	Single use
Storage Conditions and Proposed Expiry	18 months when stored at the long-term storage condition of -40°C to -15°C including up to 30 days of storage at 2°C to 8°C and up to 24 hours at room temperature (15°C to 25°C) to support administration of the vaccine at the point-of-care site.
Intended User(s)	Healthcare professional
Intended Use Environment	Clinic
Needle Length, Gauge, Tip Style	Needle not provided; needle specifications necessary for intramuscular administration of vaccines is common knowledge in the healthcare community and described by ACIP guidelines .
Markings	None

Reuse Durability	n/a
Safety Features	n/a
Automated Functions	n/a

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

III. Manufacturing

A. Manufacturers

From Module 3.2.P.3.1 (Amendment 39, Sequence 0040):

Facility	Responsibility
(b) (4) In-process testing: (b) (4) Release and stability testing (bacterial endotoxins, sterility, (b) (4) Stability (container closure integrity)	(b) (4) Manufacture
(b) (4) Distribution	
(b) (4) Distribution	
ModernaTX, Inc. (ModernaTX (b) (4)) Batch Release Combination product development and lifecycle	
(b) (4) Assembly, labelling, and packaging Release and stability testing: Appearance, Total RNA content, Identity, Purity and product-related Impurities,	(b) (4)

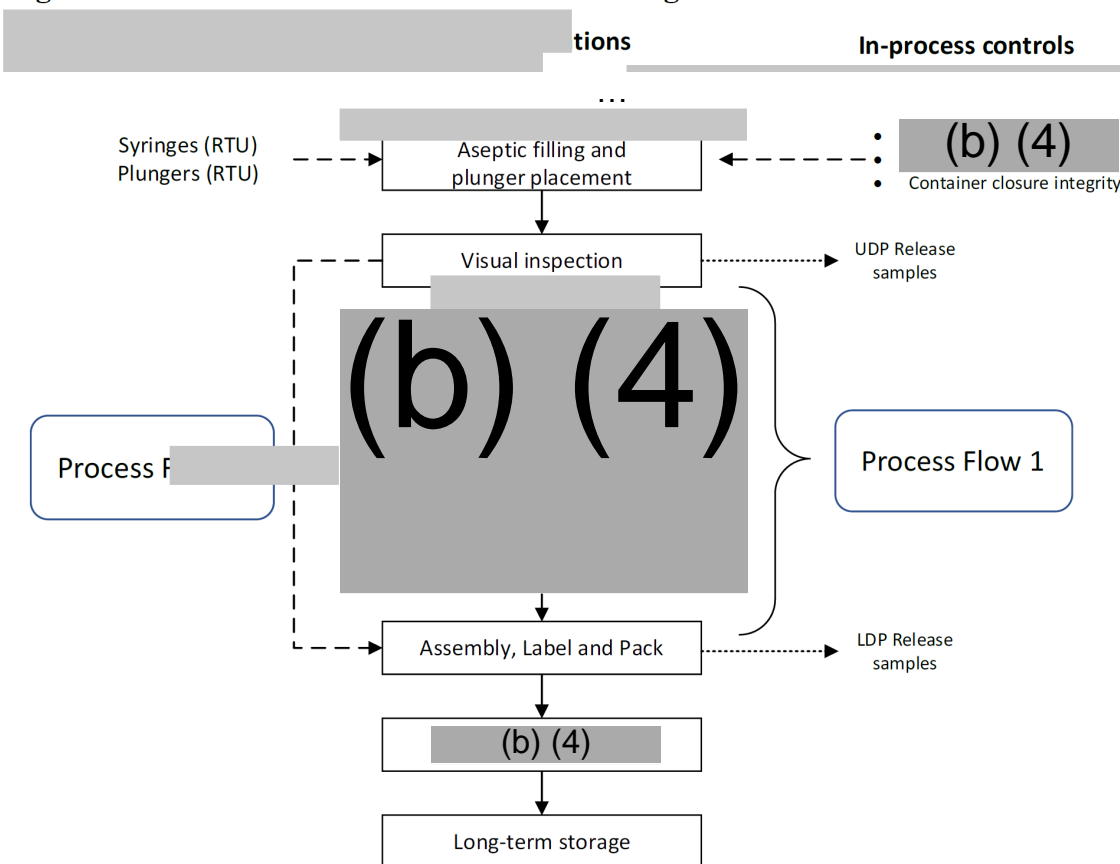
	(b) (4) , Lipid Identity/ Content/Purity.
(b) (4)	(b) (4) Frozen Storage ((b) (4))

* Subcontracted by (b) (4)

B. Manufacturing Process

The process flow diagram below is provided in Module 3.2.P.3.3. Only portions relevant to the syringe component (i.e., filling and subsequent downstream process steps) are shown given the scope of this review memo.

Figure 1: UDP-100-AR02 Process Flow Diagram^(a)



Abbreviations: (b) (4) LDP = labeled drug product; LNP = lipid nanoparticles; RTU = ready to use; UDP = unlabeled drug product

^a Process Flow 1 is shown as the main process flow. Process Flow 2 is shown with dashed arrows. Critical controls are highlighted in bold.

Process Flow 1 versus Process Flow 2: Module 3.2.P.3.3.1 states, “Two manufacturing process flows have been designed. The primary process flow (Process Flow 1, main

PFD), wherein (b) (4) prefilled, inspected syringes undergo an (b) (4) prior to assembly, label, and pack activities. The (b) (4) step is included to allow flexibility in the scale of label and pack operations. Process Flow 2 is forward processed without the (b) (4) (indicated with a dashed arrow)."

Aseptic Filling and Plunger Placement: Syringes and plungers are received pre-sterilized and ready for filling. Nested syringes are debagged and the (b) (4) cover and inner liner are removed prior to introduction to the filling area. During filling, (b) (4) in process controls are performed periodically during the filling process with measurement of the (b) (4). Plungers are placed immediately after filling, with plunger placement in-process controls (b) (4) performed periodically during the filling process.

Visual Inspection: "All syringes undergo 100% manual or automated visual inspection at controlled (b) (4) conditions. After completion of visual inspection, an acceptable quality limit sample set is manually inspected for the lot using a qualified operator."

(b) (4) (Process Flow 1): "(b) (4) PFS kept in the (b) (4) configuration within nested tubs are transferred at (b) (4) to (b) (4) and then moved to (b) (4) units" (b) (4).

(b) (4) (Process Flow 1): (b) (4) PFS in nested tubs are (b) (4) until required for assembly, label, and pack operations.

Reviewer Comment: Moderna did not state the maximum duration of the (b) (4) for Process Flow 1. See Moderna's response to IR#18.1 below, in which they proposed a maximum (b) (4) duration of (b) (4).

(b) (4) Syringes (Process Flow 1): "(b) (4) unlabeled PFS in tubs are transferred at (b) (4) to (b) (4) for (b) (4), assembly, label and pack. (b) (4) unlabeled PFS in tubs are transferred to a controlled environment and held for a minimum duration to ensure completion of (b) (4) process" (b) (4).

Assembly, Label and Pack: Plunger rods are inserted into syringes, and then syringes are labeled (automated). Labeled syringes are placed in "thermoformed trays and sealed. After sealing, the syringes are processed by a cutting station into blisters. The blisters are then packaged into cartons (multi-syringe pack) ... Cartons are placed into the shipping cases. These steps are performed at (b) (4)."

(b) (4): Packaged syringes are transferred at (b) (4) to (b) (4) and then moved to (b) (4) units (b) (4).

Syringes Storage: "The (b) (4) syringes in cases are transferred to the long-term storage condition."

Release Testing: Unlabeled drug product (UDP) samples for product quality and release testing are taken after visual inspection (before (b) (4)). Stability samples may also be taken at this point. Labeled drug product (LDP) samples for product quality release testing (identity) are taken after packaging.

Reviewer Comment: The information above is from the original submission. Minor revisions to Module 3.2.P.3.3 were introduced in response to **CMC IR#23** (Amendment 39, Sequence 0040), including the following:

- Clarification that (b) (4) syringes are transferred from (b) (4) to (b) (4) for (b) (4) before assembly, labeling, and packing.
- Clarification that (b) (4) syringe storage are at (b) (4)
- Clarification regarding release testing that “Both UDP and LDP release and stability samples undergo (b) (4) at (b) (4) and are stored at (b) (4) prior to testing or stationing.”

i. In Process Controls

Device-relevant in-process controls are excerpted below from Table 4 of Module 3.2.P.3.4.

Process Step	Critical In-Process Control	Acceptance Criteria	Rationale
Filing	(b) (4)	(b) (4)	To achieve target deliverable volume

(c) (b) (4) is based on site-specific fill capability and is monitored on-line during the filling process.

ii. Final Product Specifications

Device-relevant in-process controls are excerpted below from Table 1 of Module 3.2.P.5.1.

Test Method	Sample	Release Acceptance Criteria	Shelf-Life Acceptance Criteria
Deliverable Volume by (b) (4)	UDP	For each of the 5 syringes: ≥ 0.5 mL	n/a
(b) (4)	UDP	(b) (4)	(b) (4)
(b) (4)	UDP	(b) (4)	(b) (4)

The test methods for (b) (4) and (b) (4) are described in Module 3.2.P.5.2: “(b) (4) and (b) (4) are determined using a (b) (4) equipment on a defined number of syringes. The analysis consists of (b) (4)”

(b) (4)

(b) (4) in-house method is referred to as SOP CC-188 and is provided in Document EXT-18755 in Module 3.2.R. In the justification for this specification in Module 3.2.P.5.6, Moderna states “ (b) (4) and (b) (4) methods are functionality tests according to (b) (4) and based on simple instrumental determination in line with (b) (4).” Additionally, Moderna explains that the acceptance criterion ((b) (4)) is based on data for “ (b) (4) (b) (4) obtained by (b) (4) (b) (4) . Those studies determined that

iii. Batch Analyses

Module 3.2.P.5.4 contains data for the PPQ batches (commercial scale) tabulated below.

PPQ lot identification is excerpted below from Table 1

UDP-ID	Lot (CMO Lot)	DOM ^(a)	Manufacturer	Use
UDP-100-AR02	(b) (4)	(b) (4)	(b) (4)	PPQ comparability, stability
UDP-100-AR02	(b) (4)	(b) (4)	(b) (4)	PPQ comparability, stability
UDP-100-AR02	(b) (4)	(b) (4)	(b) (4)	PPQ comparability, stability

^(a) the date of manufacturing presented is for the UDP

Device-relevant results are excerpted below from Table 2:

Test Method	Acceptance Criteria	(b) (4)	(b) (4)	(b) (4)
Deliverable Volume by	For each of the 5 syringes: ≥ 0.5 mL	(b) (4)	(b) (4)	(b) (4)

Test Method	Acceptance Criteria	(b) (4)	(b) (4)	(b) (4)
(b) (4)				
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Reviewer Comment: Data is also provided from other batches manufactured for clinical trial use that were manufactured in 2020, 2021, and 2022. However, no device-relevant metrics were evaluated for these lots as, according to Module 3.2.P.5.6, “Prior to the commercial-scale production, mRNA-1345 was only produced in (b) (4).” Therefore, data from those lots are not reviewed here.

Additionally, the data above was generated using UDP samples, which are taken during visual inspection and (b) (4), according to Module 3.2.P.3.3. Therefore, this data does not appear to represent worse case samples (i.e., samples that have been subjected to maximum durations of the following sequence: (b) (4) (Process flow 1)). Moderna should clarify the manufacturing process flow for these commercial registration lots, including duration of any (b) (4). See **IR#18.1** below.

Information Request #18.1 Date Sent: January 12, 2024 Date/Sequence Received: January 26, 2024/0025	
IR Comment	Module 3.2.P.3.3 describes two alternative manufacturing process flows, where Process Flow 1 includes an additional (b) (4) between visual inspection and assembly, labeling, and packaging. However, you have not stated the maximum duration of the (b) (4) for Process Flow 1. Please state the maximum duration of the (b) (4) for Process Flow 1. Please also revise Table 4 in Section 3.2.P.2.3.2.1 Batch Genealogy and Lot History of Module 3.2.P.2.3.2 “Manufacturing Process Development – Manufacturing History” to identify the manufacturing process flow and duration of (b) (4) for each of the mRNA-1345 DP Commercial Scale lots. If this information is already included elsewhere in the application, please identify its location, and provide a corresponding hyperlink. This information is needed to determine whether you have provided adequate data for essential performance requirement (EPRs, i.e., (b) (4), deliverable volume, and container closure integrity (as an indicator of deliverable volume)) in your PPQ and stability studies product made using your commercial manufacturing process flows.

Applicant Response (emphasis added by reviewer)	<p>The Sponsor confirms that the maximum duration of the UDP (b) (4) [REDACTED] for Process Flow 1 is (b) (4) [REDACTED]. This information was added to an updated Section 3.2.P.3.3 included with this submission.</p> <p>All PPQ batches were manufactured using Process Flow 1. LDP lot (b) (4) [REDACTED] was generated for UDP lot (b) (4) [REDACTED] after (b) (4) [REDACTED] of UDP (b) (4) [REDACTED]. Table 4 in Section 3.2.P.2.3.2.1 has been updated with the above information.</p>
Reviewer Comments	<p><i>The sponsor adequately clarified the maximum (b) (4) [REDACTED] duration.</i></p> <p><i>The applicant did not adequately address the question regarding duration of (b) (4) [REDACTED] for the PPQ lots. LDP Lot (b) (4) [REDACTED] appears to be the lot that was used for the mock assembly, label, and pack study described in Module 3.2.P.2.3 Manufacturing Process Development {Process Characterization} and reviewed in Section III.C Process Validation in this memo. LDP lot (b) (4) [REDACTED] had an (b) (4) [REDACTED] of only (b) (4) [REDACTED], which is below the proposed maximum (b) (4) [REDACTED] duration of (b) (4) [REDACTED]. Additional data to support the proposed (b) (4) [REDACTED] duration was submitted in response to CMC IR#23 and is reviewed in Section III.C.ii Process Validation – Process Flow 1 in this memo.</i></p>

C. Process Validation

Process performance qualification (PPQ) was conducted in manufacturing the lots tabulated in Batch Analyses above.

(b) (4)

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

(b) (4)

IV. Design Verification

Design verification data is described in Module 3.2.R “Regional Information – Prefilled Syringe” Section 1.12. Moderna is leveraging data generated during development of other PFS products on their mRNA platform (mRNA-1273 (Spikevax) and (b) (4)) as (1) all three drug products have comparable physical and chemical properties, (2) the syringe components are identical, and (3) all three drug products are manufactured on the same filling and packaging lines with the same critical fill parameters. Memo PD-MEM-2401 Version 4.0 in Module 3.2.R “summarizes the impact of utilizing design verification, design validation, and usability data across the mRNA-1273 (and variants), (b) (4), and mRNA-1345 LNP-100 based vaccine PFS products that utilize identical syringe configurations.”

Reviewer Comment: Moderna provided adequate justification for applicability of mRNA-1273 (Spikevax) and (b) (4) PFS design verification data to the mRNA-1345 PFS.

Baseline (T=0) verification data is excerpted below from Table 6 of this section.

Test Performed	Sample Size	Acceptance Criteria (95% Confidence / 95% Reliability)	Rationale & Test Method	T=0 Results
(b) (4)				
Deliverable Volume (EPR)	(b) (4)	Expelled fluid shall be ≥ 0.5 mL when tested at ambient temperature	(b) (4)	Pass ^(a) Mean: (b) (4) Min: (b) (4) Max: (b) (4)
(b) (4)				

Test Performed	Sample Size	Acceptance Criteria (95% Confidence / 95% Reliability)	Rationale & Test Method	T=0 Results
(b) (4)				
Product Label Visual Inspection	n/a	Product labeling shall remain intact and legible when shipped and stored at the intended storage conditions.	n/a	Pass ^(b)

^a Representative testing performed on mRNA-1273

^b Representative testing performed on (b) (4)

For (b) (4), Memo PD-MEM-2459 in Module 3.2.R explains that (b) (4) 1mLL PFS and mRNA-1345 (b) (4) 1mLL PFS for design verification and shipping validation should come from the ^{(b) (4)} PPQ of each configuration. The UDP should be (b) (4) at (b) (4) (i.e., (b) (4)) then stored at (b) (4) (i.e., (b) (4)). UDP samples will be (b) (4) at the

time of label and pack operations. Upon completion of **label and pack** the product should be stored per the table below:

Product	Quantity	Storage	Shipping
(b) (4) 1mLL PFS	(b) (4)	(b) (4)	(b) (4)
(b) (4) 1mLL PFS	(b) (4)	(b) (4)	(b) (4)
mRNA-1345 (b) (4) 1mLL PFS	(b) (4)	(b) (4)	(b) (4)

LDP packaged into the blister pack configurations to be stored or shipped at (b) (4) (analogous to **long term storage**) should be (b) (4) at (b) (4) (i.e., (b) (4)) prior to storage. The n= (b) (4) 1mLL PFS should be stored at (b) (4) at (b) (4) until an appropriate test lab is identified and ready to receive the product.

Reviewer Comment: All the T=0 data above is leveraged from mRNA-1273, except for Product Label Visual Inspection which used (b) (4) .

As indicated in the bold text above, the processing of the (b) (4) and mRNA-1345 for design verification and shipping validation follows Process Flow 1. However, the duration of (b) (4) is not clear.

The mRNA-1273 (Spikevax) CoC PFS was reviewed in BLA 125752/74. In that supplement, verification data was gathered using (b) (4) Batch (b) (4) , which was (b) (4) after UDP manufacture (b) (4) , per Table 28 in Module 3.2.P.3.5 {(b) (4) – Variant 0.10 mg/mL PFS} of that supplement), (b) (4) , assembled, and packed, (b) (4) , and shipped (b) (4) for design verification testing. However, there is no additional information to determine if the data leveraged above is from that same lot.

Moderna should provide additional information on the mRNA-1273 and (b) (4) lots used to generate the data leveraged in Table 6 of Module 3.2.R “Regional Information – Prefilled Syringe” Section 1.12, including manufacturing process flow information and (b) (4) durations. See **IR#18.2** below.

Notably, Table 6 above cites (b) (4) , which are not currently FDA-recognized. However, the use of these non-recognized standards is acceptable as rationalized in the table below.

Cited Clauses in Standards Not Recognized by FDA	Reviewer Comment on Suitability of Standard

(b) (4)

Information Request #18.2

Date Sent: January 12, 2024

Date/Sequence Received: January 26, 2024/0025

IR Comment	Table 6 in Module 3.2.R “Regional Information – Prefilled Syringe” Section 3.2.R.1.12.1 contains design verification data leveraged from representative testing performed on mRNA-1273 PFS and (b) (4) PFS. Your rationale for the applicability of the data to mRNA-1345 PFS is reasonable. However, we could not find sufficient information about the mRNA-1273 PFS and (b) (4) PFS lots that were tested. Please identify and provide additional information on the mRNA-1273
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	<p>PFS and (b) (4) PFS lots used to generate the leveraged data in Table 6, including manufacturing process flow information and (b) (4) durations. This information is needed to further confirm the applicability of the leveraged data to the mRNA-1345 PFS manufactured using the manufacturing process flow described in Module 3.2.P.3.3 (particularly Process Flow 1).</p>
<p>Applicant Response (emphasis added by reviewer)</p>	<p>The mRNA-1273 design verification utilized Unlabeled Drug Product (UDP) Lot (b) (4) as referenced in QP-0022 (DHF-250 Design Verification Report for PFS). The Label and Packaging build for the batch is documented in PD-MEM-1574 (mRNA-1273 Drug Product in Pre-Filled Syringe Design Verification Build Configuration). The manufacturing process for this material followed the same process flow as the mRNA-1345 DP as shown in Table 1. The material underwent a (b) (4) at the UDP stage representative of Process Flow 1 for mRNA-1345 DP (Process Flow 2 for mRNA-1273 DP). The (b) (4) duration for the mRNA-1273 UDP was (b) (4) (Table 1).</p> <p>The (b) (4) design verification utilized Lot (b) (4) as documented in PD-MEM-2459 ((b) (4) and mRNA-1345 Drug Product in PFS for Design Verification and Shipping Validation Studies). The manufacturing process for this material followed the same process flow as the mRNA-1345 DP as shown in Table 1. The material underwent a (b) (4) at the UDP stage representative of Process Flow 1 for mRNA-1345. The (b) (4) duration was (b) (4) (Table 1).</p>

(b) (4)

Reviewer Comments	<p><i>There appears to be an error in the applicant's response regarding mRNA-1273: the lot number stated in QP-0022 is (b) (4) , not (b) (4) .</i></p> <p><i>Notably, PD-MEM-1574 states "UDP should be (b) (4) ... Upon completion of the labeling the drug product will undergo a (b) (4) at (b) (4) ... Upon (b) (4) LDP should be store at (b) (4) until time of shipping. Shipping will be under controlled temperature at (b) (4) . The (b) (4) products without labels will be shipped to (b) (4) for testing. The remaining (b) (4) product with labels will be shipped to Moderna (b) (4) for conditioning and testing." Based on the response, it appears that the mRNA-1273 used for device verification (which Moderna is leveraging for the majority of the mRNA-</i></p>
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	<p>1345 verification) is representative of the worst-case manufacturing process (i.e., (b) (4)). Additionally, the (b) (4) was (b) (4), which exceeds the (b) (4) duration limit for mRNA-1345 (i.e., (b) (4)).</p> <p>The duration of (b) (4) for (b) (4) Lot (b) (4) was (b) (4). Although far shorter than the maximum (b) (4) duration for mRNA-1345 (b) (4), (b) (4) may be more likely to impact the device performance metrics in question (particularly (b) (4)) than duration of (b) (4) storage.</p>
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Reviewer's Overall Assessment and Recommendations: Applicant provided adequate design verification information by leveraging data generated from other PFS products on the mRNA platform. Sufficient information was provided in the original submission and in response to IR#18 to support the applicability of this data to mRNA-1345.

V. Biocompatibility

Biocompatibility information is summarized in Module 3.2.R Regional Information – Pre-filled Syringe Section 3.2.R.1.11. The biocompatibility assessments are summarized in Table 4, recreated below.

Component	Material of Construction	Nature of Contact	Evaluation Performed	Results	Reference
Plunger Rod	Polypropylene (PP)	Surface device Intact skin A – Limited (≤ 24 hours)	Cytotoxicity	Acceptable	(b) (4) 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 (≤ 24 hours)	Cytotoxicity	Acceptable	(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	See 3.2.P.2.4 Suitability, with supporting stability data in 3.2.P.8 Stability
Plunger Stopper	Halobutyl rubber with fluoropolymer coating	Drug product contact	The product extractables and leachables profile shall indicate no chemicals exceeding levels of toxicological concern.	Acceptable	See 3.2.P.2.4 Suitability, with supporting stability data in 3.2.P.8 Stability
Tip Cap	Halobutyl rubber	Drug product contact	The product extractables and leachables profile shall indicate no chemicals exceeding levels of toxicological concern.	Acceptable	See 3.2.P.2.4 Suitability, with supporting stability data in 3.2.P.8 Stability

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
- DMF # (b) (4) (eCTD Document ID C_BIO) for the plunger
- DMF # (b) (4) (3.2.P.7) for the plunger elastomeric formulations, coatings, and films”

Reviewer’s Overall Assessment and Recommendations: *Biocompatibility information is sufficient. As discussed in [Section II Product Description](#) in this memo,*

the syringe components are identical to those used in mRNA-1273. Additionally, the drug products are manufactured on the same filling and packaging lines with the same critical fill parameters. 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) “Empty **syringe barrels**, ready-to-use (RU, RTU), are received sterile in plastic tubs with polypropylene nests and (b) (4) lids. (b) (4) **sterilization** of the syringe barrels in the tubs is performed according to (b) (4), to achieve the **sterility assurance level of (b) (4)**. The syringes are compliant with applicable (b) (4) requirements... The 1-mL long **fluoropolymer-coated plungers** are received RTU. The plungers are sterilized via (b) (4) following (b) (4), to achieve the **sterility assurance level of (b) (4)**.” Plunger rods are purchased non-sterile.

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

VII. Control Strategy

Essential Performance Requirement	Control Strategy Description (e.g., incoming acceptance, in-process control, and/or <u>release testing activities</u>):	Acceptable?
Dose Accuracy	In process control ((b) (4)), lot release testing (deliverable volume ≥0.5mL), design verification (see Section IV of this memo)	yes
(b) (4)	Purchasing controls, incoming controls, lot release testing ((b) (4)), design verification (see Section IV of this memo)	yes
(b) (4)	Purchasing controls, incoming controls, lot release testing ((b) (4)), design verification (see Section IV of this memo)	yes

Module 3.2.P.7 states “mRNA-1375 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. Representative certificates are provided as attachments. (b) (4) references for each component are summarized in Table 2.”

The compendial references in Table 2 are as follows:

- Syringe: (b) (4)

- Plunger: (b) (4)
- Plunger Rod: (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

Module 3.2.P.7.2 originally stated (in Sequence 0001) "The secondary packaging for LDP-100-AR02 is an assembled, labeled prefilled syringe (PFS); a total of two (2) PFS are contained within a sealed blister, with five (5) blisters total inside a secondary carton containing a total of ten (10) syringes in a 2-by-5 configuration. One (1) patient information leaflet (PIL) or prescribing information (PI) is also placed in the secondary carton. Each carton is then placed into a case containing a total of sixteen (16) cartons; total of 160 PFS per case. The case is then closed."

This section was updated in Module 3.2.P.7.2 of Amendment 39 (Sequence 0040) to the following: "The secondary packaging for LDP-100-AR02 is an assembled, labeled prefilled syringe (PFS), thermoformed tray and carton. Labeled syringes are placed into thermoformed trays and sealed. After sealing, the syringes are processed by a cutting station into blisters. The blisters are then packaged into secondary cartons, with prescribing information (PI) or a patient information leaflet (PIL). Cartons are placed into the shipping cases and the cases closed."

Reviewer Comment: The revised description is less specific about the secondary packaging configuration. Notably, shipping validation reports RPT-15162 (pallet) and RPT-15173 (small parcel) provided in the response to **IR#38** (Amendment 57, Sequence 0058) states “mRNA-1345 drug product (DP) at 0.1 mg/mL is filled in COC prefilled syringes during manufacturing and subsequently placed in secondary packaging (i.e., 5 blister packs, each containing 2 PFS each, with 10 total in a carton)” but describes the test samples as “10-pack blister packs, which were placed in cartons. Each carton contained 1 booklet and 10 blister packs with a single PFS in each blister pack.” During labeling review, regarding Section 16.1 “How Supplied” in the USPI, Moderna verified that in response to Labeling IR#43 (Sequence 0065) that the packaging configuration is indeed 5 blister packs, each containing 2 PFS each, with 10 total in a carton.

B. Stability

The proposed shelf-life is **18 months**, when stored at the long-term storage condition of **-40°C to -15°C including up to 30 days** of storage **at 2°C to 8°C** and up to **24 hours at room temperature (15°C to 25°C)** to support administration of the vaccine at the point-of-care site.

Some stability information for the mRNA-1345 PFS is provided in Module 3.2.R “Regional Information – Prefilled Syringe” Section 1.12. Table 5 (recreated below) includes the time points and temperatures for shelf-life testing.

Accelerated Aging	Real-Time Aging -20°C ^(a)	Real-Time Aging -20°C ^(a)	End to End Shelf-Life ^(b)
(b) (4)	T=10m @ -20°C T=(b) (4) @ 5°C	T=16m @ -20°C T=(b) (4) @ 5°C	T=(b) (4) @ -20°C ^(c) T=(b) (4) @ 5°C

^a Combination product shelf-life is the sum of storage time at -20°C and 5°C, i.e., 10m @ -20°C and (b) (4) at 5°C is representative of a -20°C 18-month shelf-life inclusive of (b) (4) @ 5°C. Combination product shelf-life needs to be at least equal if not greater than drug product shelf-life.

(b) (4)

Reviewer Comment: Moderna has not provided a basis for why the accelerated aging conditions are equivalent to the real-time frozen conditions and durations. See **IR#18.3** below. According to See **IR#18.2** in [Section III.B.iii Batch Analysis](#) in this memo, the (b) (4) lot used to generate data in Table 6 has an interim storage duration of 5 days.

Information Request #18.3 Date Sent: January 12, 2024 Date/Sequence Received: January 26, 2024/0025	
IR Comment	<p>In Module 3.2.R “Regional Information – Medical Device – Prefilled Syringe”, Section 3.2.R.1.12, you describe studies evaluating EPRs (i.e., (b) (4) Deliverable Volume), (b) (4), CCI, and label legibility after accelerated and real time aging. In the footnotes to Table 5, you state the accelerated aging conditions ((b) (4)) are equivalent to (b) (4).</p> <p>However, you did not sufficiently explain the basis of this claim. Please explain how you determined the equivalency between the accelerated and real-time aging conditions. Please also provide a brief comparison of the equivalent real time aging conditions to your proposed shelf life conditions (i.e., 18 months, when stored at the long-term storage condition of -40°C to -15°C including up to 30 days of storage at 2°C to 8°C and up to 24 hours at room temperature (15°C to 25°C) to support administration of the vaccine at the point-of-care site). This is being requested to understand how the data you provided demonstrate that device performance is maintained over the proposed shelf life.</p>
Applicant Response (emphasis added by reviewer)	<p>Accelerated aging conditions are based on standard medical device accelerated aging practices utilizing the Arrhenius equation to stress the PFS components, as described in (b) (4).</p> <p>Accelerated aging conditions covering the end-to-end storage of the PFS were determined by leveraging the Arrhenius equation and a Q10 factor of (b) (4). The accelerated aging condition ((b) (4)) was calculated based on worst case accelerated aging at (b) (4), intended to enable a range of potential commercial storage conditions.</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>The Accelerated aging duration for storage condition #1 and storage condition #2 are as shown in Table 2 and 3.</p>

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

	(b) (4)
Reviewer Comments	(b) (4) is an FDA recognized standard. It's not clear to this reviewer that Arrhenius equation is appropriate for (b) (4) conditions. However, real time aging studies and end-to-end studies (described in the remainder of this memo section) are ongoing to confirm these findings. See additional information below.

Moderna states “at the time of submission, accelerated aging data is available; real-time and end to end studies are ongoing.” The accelerated aging data leveraged from (b) (4) is excerpted below from Table 6 of Module 3.2.R “Regional Information – Prefilled Syringe” Section 1.12. Per the response to IR#18.2, the (b) (4) lot only has (b) (4).

Test Performed	Sample Size	Acceptance Criteria (95% Confidence / 95% Reliability)	Rationale & Test Method	(b) (4)
(b) (4)				
Deliverable Volume (EPR)	(b) (4)	Expelled fluid shall be ≥ 0.5 mL when tested at (b) (4)	(b) (4)	Pass ^(b) Mean: (b) (4) Min: (b) (4) Max: (b) (4)

Test Performed	Sample Size	Acceptance Criteria (95% Confidence / 95% Reliability)	Rationale & Test Method	T=34 Days at 40°C
(b) (4)				
Product Label Visual Inspection	n/a	Product labeling shall remain intact and legible when shipped and stored at the intended storage conditions.	After shipping and storage, samples were inspected to verify that labels were intact and legible.	Pass ^(b)

^b Representative testing performed on (b) (4)

Additionally, Moderna states “Ongoing stability studies that include test (b) (4) are described in 3.2.P.8.2.1 Stability Study.”

Module 3.2.P.8.1 states (b) (4) registration **UDP-100-AR02** lots manufactured at the commercial scale at (b) (4) and (b) (4) representative **LDP-100-AR02** lots made from those registration lots were placed on stability. “Additional end-to-end stability studies will be performed using both UDP-100-AR02 and LDP- 100-AR02 to demonstrate stability at 2°C to 8°C and 23°C to (b) (4) following initial (b) (4) storage.” The device-relevant metrics from the ongoing stability protocols (as described in Module 3.2.8.1 Stability Summary and Conclusion (Sequence 0001)) are listed below.

(b) (4)

2) LDP

- a) (b) (4)
 - i) -25°C to -15°C: 0, 3, 6, 12, (b) (4) months
 - ii) 2°C to 8°C: 0, (b) (4) months
 - iii) 23°C to (b) (4) °C: 24, (b) (4) hours
- b) Container Closure Integrity
 - i) -25°C to -15°C: 12, (b) (4) months
 - ii) 2°C to 8°C: (b) (4) months
 - iii) 23°C to (b) (4) °C: (b) (4) hours

(b) (4)

Available (b) (4) data is in Module 3.2.P.8.3 for the PPQ lots as listed below, reflecting the update submitted in the response to **CMC IR#23 Items 29 and 30** (Amendment 39, Sequence 0040). All applicable timepoints thus far have met acceptance criteria for (b) (4), and container closure integrity. The longest timepoints are indicated below (note: not all lots may have data up to the indicated timepoint).

(b) (4)

Reviewer Comment: Notably, the available stability data provided in Module 3.2.P.8.3 of Amendment 39 (sequence 40) does not completely align with the studies described in the original stability summary in Module 3.2.P.8.1 (sequence 0001). For example, the stability summary does not include measurement of (b) (4) at 6 months for the UDP-100-AR02 registration lots stored at (b) (4) °C to -30°C and -25°C to -15°C. Additionally, the stability summary did not include studies for UDP-100-AR02 stored at 23°C to (b) (4) °C for any length of time. However, this does not affect the ability to review the updated information in Module 3.2.P.8.3, and no further action is needed from the sponsor regarding this, from a device perspective.

In the response (Amendment 39, Sequence 0040) to **CMC IR#23 Item 29**, Moderna also:

- Committed to submitting final study reports for the end-to-end studies described in Section 3.2.P.8.1 {mRNA-1345 DP} with an estimated submission date of September 2025.
- Committed to submitting interim study reports for the end-to-end studies described in Section 3.2.P.8.1 {mRNA-1345 DP} with an estimated submission

date of June 2024 for the 12-month report and December 2024 for the 18-month report.

- Acknowledged Agency comment that these data may be submitted as a product correspondence or as part of a prior approval supplement if used to support implementation of a shelf-life extension of the DP.

CMC IR#23 Item 30 requested commitment to submit the final stability reports for the ongoing stability studies for PPQ DP lots (b) (4). In the response, Moderna stated that prior to finalizing the commitment to the Agency, they would like a short teleconference to “discuss the possibility of (b) (4) the allowed time at 2°C to 8°C [from 30 days to (b) (4)] while maintaining the overall shelf life of 18 months.” They state this (b) (4) duration was not proposed in the initial BLA due to limited data the time, but it is supported now by current data (“available stability data from clinical and development lots, the updated PPQ DP stability data, and comparability assessment of the DP PPQ stability data to the clinical and development stability data”). Based on the Agency feedback, Moderna proposed to either:

- will provide an updated Section 3.2.P.8.1 {mRNA-1345 DP} as soon as this is confirmed to be amenable to the Agency, or
- “submit the (b) (4) of the allowable storage duration at 2°C to 8°C to (b) (4) days as a CBE-30 immediately upon approval of the BLA. The Sponsor would commit to providing further updates to the stability data on the PPQ lots as part of the Annual Report throughout the duration of the studies and include studies performed to assess the cumulative storage conditions, as no further changes for shelf life are currently planned.”

In CMC IR#35 Item 4, the CMC review team communicated that “with respect to your response to item 30.a, pertaining to the updated stability data and commitment to submit final study reports for the (b) (4) DP PPQ lots, we are not able to undertake the review of the additional stability data to modify the storage recommendations to accommodate (b) (4) days at 2 °C to 8 °C at this point in the review cycle. Therefore, please submit a PAS/CBE-30 supplement to support the implementation of this change upon approval of the BLA.” Moderna acknowledged this in their response in Amendment 54 (Sequence 0055).

Reviewer Comment: Based on the CMC IR’s above, the final stability reports, along with a request to (b) (4) storage duration at 2-8°C will be submitted “immediately upon approval”. A combination of accelerated aging data, available real time data, and commitments regarding planned end-to-end and ongoing stability studies were deemed acceptable in the review Moderna BLA 125752/74 for mRNA-1273 and are also sufficient for licensure of the current product.

Module 3.2.P.8.2 states “Moderna TX, Inc commits to placing a minimum of (b) (4) mRNA-1345 DP lot on stability (b) (4).” The samples will be UDP.

- 1) Samples will be placed on stability at -25°C to -15°C for 17 months
 - a) (b) (4), Container Closure Integrity: 0, 12, 17 months
- 2) Samples will be transferred to 2°C to 8°C for 1 month

- a) (b) (4), Container Closure Integrity: 0, 1 month
- 3) Samples will be transferred to 23°C to (b) (4) °C for 24 hours
- a) (b) (4), Container Closure Integrity: 24 hours

C. Shipping

Module 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Validation states “Device functionality was conducted using a COC PFS containing a frozen (b) (4) DP (which uses the identical COC PFS as mRNA-1345 DP) in representative packaging.”

Based on PD-MEM-2459 (“(b) (4) and mRNA-1345 Drug Product in PFS for Design Verification and Shipping Validation Studies”), the (b) (4) and mRNA-1345 products utilize the same secondary packaging components.

Module 3.2.R “Regional Information – Prefilled Syringe” Section 1.12 states “EPRs (i.e., (b) (4), Deliverable Volume), (b) (4), CCI, and label legibility were tested after exposure of samples to simulated transit conditions (at 2°C to 8°C and -25°C to -15°C). Simulated transit conditioning was conducted in accordance with (b) (4), to verify that the shipper box and secondary packaging design protect the product. To simulate domestic or international transportation, the PFS samples were packaged in shipper boxes per the proposed commercial packaging configuration.”

According to Module 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Validation, (b) (4) includes the following test sequence: (b) (4)

The simulated transit conditioning data is excerpted below from Table 6 of this section.

Test Performed	Sample Size	Acceptance Criteria (95% Confidence / 95% Reliability)	Rationale & Test Method	T=0 Post Transit Conditioning at (b) (4)	T=0 Post Transit Conditioning at -20°C
(b) (4)					
Deliverable Volume (EPR)	(b) (4)	Expelled fluid shall be ≥ 0.5 mL when tested at ambient temperature	(b) (4)	Pass ^(b) Mean: (b) (4) Min: (b) (4) Max: (b) (4)	Pass ^(b) Mean: (b) (4) Min: (b) (4) Max: (b) (4)
(b) (4)					
Product Label Visual Inspection	n/a	Product labeling shall remain intact and legible when shipped and stored at the intended storage conditions.	After shipping and storage, samples were inspected to verify that labels were intact and legible.	Pass ^(b)	Pass ^(b)

^b Representative testing performed on (b) (4)

Reviewer Comment: According to Memo PD-MEM-2459 in Module 3.2.R and the response IR#18.2 documented in [Section IV Design Verification](#) in this memo, the

(b) (4) lot used to generate this data underwent (b) (4), assembly, label, pack, (b) (4), frozen shipping, thaw for testing. Although the (b) (4) was far shorter than the maximum (b) (4) duration for mRNA-1345 (b) (4), (b) (4) may be more likely to impact the device performance metrics in question (particularly (b) (4)) than duration of frozen storage. Therefore, (b) (4) is leverageable enough for purposes of licensure.

Module 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Validation states “Additional device functionality and product quality testing for mRNA-1345 DP in representative packaging using a small parcel and pallet shipper is ongoing. With the completion of these protocols and the approval of the reports that follow, the entire passive shipper family for shipping mRNA-1345 DP in a COC PFS blister pack at -25°C to -15°C will be bracketed.”

Reviewer Comment: Moderna should provide this additional data for the mRNA-1345 product if available. See **IR#38** below.

Information Request #38	
Date Sent: April 4, 2024	
Date/Sequence Received: April 15, 2024	
IR Comment	Module 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Validation states that “device functionality and product quality testing for mRNA-1345 DP in representative packaging using a small parcel and pallet shipper is ongoing.” Please submit the shipping validation data and final study report(s) by April 15th.
Applicant Response (emphasis added by reviewer)	<p>Both device functionality and product quality testing for mRNA-1345 DP in representative packaging for small parcel and pallet shippers were performed and met acceptance criteria post (b) (4), respectively) simulated shipping exposure. A summary of study results is provided below (Table 1–Table 2). The requested reports are included with this response. Section 3.2.P.3.5 Process Validation and/or Evaluation – Shipping Validation {mRNA-1345} has been updated to reflect that the small parcel and pallet shipping validation testing is complete.</p> <p>Attachments to this response.</p> <ol style="list-style-type: none">1. RPT-15163 mRNA-1345 COC PFS DP in Blister Pack Shipping Validation (-25°C to -15°C) Report – Small Parcel2. RPT-15173 mRNA-1345 COC PFS DP in Blister Pack Shipping Validation (-25°C to -15°C) ATO Report – Small Parcel

3. RPT-15164 mRNA-1345 COC PFS DP in Blister Pack Shipping Validation (-25°C to -15°C) Report - Pallet
4. RPT-15162 mRNA -1345 COC PFS DP in Blister Pack Shipping Validation (-25°C to -15°C) ATO Report – Pallet

Device functionality results excerpted from Table 1: Summary Test Result for mRNA-1345 DP Post **Small Parcel Shipper** (b) (4)

(b) (4) Simulated Shipping Exposure
(n=(b) (4) samples tested, mean result reported)

Attributes	Acceptance Criteria	Arm A Lot No: (b) (4)	Arm B Lot No: (b) (4)	Arm C Lot No: (b) (4)	Meets Study Acceptance Criteria
(b) (4)					

Device functionality results excerpted from Table 2: Summary Test Result for mRNA-1345 DP Post **Pallet Shipper** (b) (4)

(b) (4) Simulated Shipping Exposure (n=60 samples tested, mean result reported)

Attributes	Acceptance Criteria	Arm A Lot No: (b) (4)	Arm B Lot No: (b) (4)	Arm C Lot No: (b) (4)	Meets Study Acceptance Criteria
(b) (4)					

To support additional suppliers of “dimensionally equivalent (critical dimensions) component with the same product contact material of construction as the initial source”, Moderna proposes:

- “An assessment of stability profile impact, functionality, leachable and extractable profile, and a demonstration of container closure integrity.”
- “Updates to the combination product development package, assessed and implemented, as necessary.”
- “Data from at least one (1) PPQ lot per line / site.”
- “At least 1 month of stability data for PPQ lots at the accelerated storage temperature to support comparability and verify applicability of the stability model.”

“Comparability testing for each implemented post-approval change (or group of changes if deemed related) will be executed per the plan described in Table 2 and the outcomes will be documented in comparability report(s). Each report will contain a conclusion for the overall comparability of post-change materials and the corresponding reporting category, as well as additional information specified below:

1. Detailed description of and rationale for all changes implemented (process and analytical)
2. List of post-change batches included in comparability study, including lot number, date of manufacture, disposition, and justification for the number of lots included.
3. Data for post-change lots relative to comparability acceptance criteria and expected ranges
 - a. Release testing
 - b. Extended characterization testing (if included in the comparability protocol)
 - c. Stability (if included in the comparability protocol)
4. Discussion of deviations and investigations occurring during comparability demonstration of post-change batches
5. Conclusions for comparability demonstration
6. Reporting category”

The relevant portions of the referenced Table 2 related to changes to drug product container closure system are excerpted into the table below:

Potential Post-Approval Manufacturing Changes	Initial Reporting Category	Reduced Reporting Category	PPQ Required? (Yes/No)	# of PPQ Lots	Comparability Assessment
(b) (4)	PAS	CBE-30	Yes	3	Release Stability

System (CCS) used for storage and/or shipping of mRNA-1345 DP					
Adding or replacing a supplier for product-contact components of the CCS used for storage and/or shipping of mRNA-1345 DP that are supplied as ready-to-use or ready-to-sterilize without a change in the product-contact material of construction or dimensions	PAS	CBE-30	Yes	3	Release Stability

Reviewer's Overall Assessment and Recommendations: *The proposed comparability protocol is generally acceptable from a device perspective. Defer to CMC regarding the proposed reporting categories. Adequacy of the information provided will be a review issue at that time.*

X. Quality System

Module 3.2.R "Regional Information – Prefilled Syringe" Section 3.2.R.1.7 contains information regarding compliance with applicable current good manufacturing practices (CGMPs). Moderna states they "a streamlined approach based on drug cGMPs of 21 CFR Parts 210, 211, and 600-680 with the addition of" the 21 CFR 820 regulations called out in 21 CFR 4:

- 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

Moderna provides summaries of how they have met each called out required (including each subpart of design control requirements) in Section 3.2.R.1.7.2 through Section 3.2.R.1.7.5.

Moderna also provides several documents related to design controls in Module 3.2.R (e.g., documents from the design history file). Several of these documents are referenced throughout this review memo.

Reviewer's Overall Assessment and Recommendations: *Adequate information has been provided regarding design controls and purchasing controls. Review of*

management responsibility and corrective and preventative action (CAPA) is deferred to DMPQ.

XI. Appendices

A. Appendix 1 – Engineering Drawings

From document QER-12180 in Module 3.2.R:

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

**B. Appendix 2 – Relevant Comments and Responses: CMC IR#23
(Amendment 39, Sequent 0040); CMC IR#35 (Amendment 54, Sequence 0055)**

i. Comment 14

Information Request #23.14 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment (emphasis added by reviewer)	<p>With respect to the manufacture of the DP using Process Flow 1 that includes a (b) (4) for UDP-100-AR02 at (b) (4) for not less than (b) (4) followed by (b) (4) at (b) (4), the maximum duration of (b) (4) at each temperature has not been defined. Please describe the maximum duration for the (b) (4) at (b) (4) and for (b) (4) at (b) (4) and provide data to support these storage times.</p>
Applicant Response (emphasis added by reviewer)	<p>The Sponsor has set an internal operational upper limit of (b) (4) for the (b) (4) duration (at (b) (4)) of UDP-100-AR02 in Process Flow 1. A single-sided tolerance for this parameter has been established as there is negligible impact to product quality over the (b) (4) duration at (b) (4). Stability data to support (b) (4) duration in excess of this limit is provided in Section 3.2.P.8.1 {mRNA-1345 DP}. The limit has been selected as an internal operational limit, controlled by batch record, to ensure advancement of the process to (b) (4).</p> <p>A (b) (4) maximum duration of the (b) (4) duration at (b) (4) was proposed in a previous query response (IR #18), and Section 3.2.P.3.3 {mRNA-1345 DP} was updated accordingly. This duration is supported by LDP characterization and stability data wherein DP that had undergone (b) (4) of (b) (4) duration was labeled and packed. LDP characterization data of all lots after (b) (4) have been added to Section 3.2.P.2.3 Manufacturing Process Development – Process Characterization {mRNA-1345 DP} (“Characterization of UDP (b) (4) ” and “Characterization of Label and Pack Activities”). Negligible impact to product quality was observed when tested against relevant product quality attributes for either (b) (4) duration, thus supporting the proposed UDP (b) (4) duration of (b) (4).</p>
Reviewer Comments	<p>Incorporated into Section III.B.iii Batch Analysis and Section III.C.ii Process Validation – Process Flow 1 in this memo.</p>

ii. Comment 17

Information Request #23.17 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment	<p>Process 1 includes (b) (4)</p> <p>(b) (4) performs the (b) (4) for (b) (4)</p> <p>a. Please clarify if (b) (4) steps for labeled and unlabeled DP are performed at (b) (4) and specify where the (b) (4) and LDP long-term storage are located.</p> <p>b. Please update sections 3.2.P.3.1 Manufacturers and 3.2.P.3.3 Description of Manufacturing Process and Process Controls, as appropriate, to include the storage locations and description of shipment steps among the various DP manufacturing sites.</p>
Applicant Response (emphasis added by reviewer)	<p>The Sponsor would like to clarify that the (b) (4) step for both UDP (b) (4) and LDP long-term storage are performed at (b) (4). Section 3.2.P.3.1 {mRNA-1345 DP} and Section 3.2.P.3.3 {mRNA-1345 DP} have been updated to clarify the storage locations and the description of shipment steps among the various DP manufacturing sites.</p>
Reviewer Comments	<p>Incorporated in Section III.B Manufacturing Process of this memo.</p>

iii. Comment 19

Information Request #23.19 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment	<p>With respect to section 3.2.P.3.5 Process Validation and/or Evaluation {(b) (4)} and EXT-19309 Summary Report Process Validation UDP-100-AR02 RSV PFS {(b) (4)}, we note that these data validate only the (b) (4) steps.</p> <p>Nevertheless, we expect the entire UDP-100-AR02 process to be validated for Process Flow 1 including transport to (b) (4) for (b) (4) storage and then transport to (b) (4) for (b) (4), assembly, labelling, and packaging activities followed by transport back to (b) (4) for (b) (4) long term storage. Please submit validation reports for the remainder of the UDP-100-AR02 and LDP-100AR02 manufacturing activities, including the shipments between sites, labeling operations, and final freezing of LDP. If these data are not available, please provide a commitment to submit the final validation reports with these data post licensure and include the estimated submission date.</p>
Applicant Response (emphasis)	<p>The Sponsor confirms that the validation report has been updated to include qualification of Process Flow 1, inclusive of all activities through (b) (4) for long term storage. The UDP was sampled after shipment and (b) (4) at (b) (4), supporting the validation</p>

added by reviewer)	<p>of these manufacturing activities. LDP sampling, which occurs after shipment of the (b) (4) UDP (b) (4) and completion of the label and pack activities, supports the validation of the process through LDP manufacture. LDP samples were (b) (4) in a representative manner (b) (4) for testing. In addition, distribution stress studies demonstrate negligible product quality impact as a result of transport stress (Section 3.2.P.2.2 {mRNA-1345 DP}).</p> <p>A summary of information currently included in the validation report is presented in Table 2. Table 1 Version 1 of the validation report was provided with the initial file, and an updated validation report is provided with this response (version 2). The CPD and the release results for the remaining lots will be added to the validation report in a subsequent update, and the Sponsor submit to provide an updated validation report (version 3) by March 18, 2024).</p> <p>Table 2: Summary of Information Currently in PPQ Report</p> <table><tr><th rowspan="2">UDP Lot Number ModernaTX (b) (4)</th><th rowspan="2">LDP Lot Number</th><th colspan="3">Validation Report Availability Status</th></tr><tr><th>CPD</th><th>UDP Release Results</th><th>LDP Release Results^c</th></tr><tr><td rowspan="6">(b) (4)</td><td rowspan="6">(b) (4)</td><td>Version 1</td><td rowspan="6">Version 1</td><td>Version 2^a</td></tr><tr><td>N/A^b</td><td>N/A^b</td></tr><tr><td>Version 2^a</td><td>Version 2^a</td></tr><tr><td>N/A^b</td><td>N/A^b</td></tr><tr><td>Version 2^a</td><td>Version 2^a</td></tr><tr><td>N/A^b</td><td>N/A^b</td></tr></table> <p>^a Provided in the attached PPQ Report, Version 2</p> <p>^b Not available, will be provided in PPQ Report, Version 3.</p> <p>^c Purity results included in PPQ Report. Refer to Section 3.2.P.5.4 {mRNA-1345 DP} for complete LDP testing results</p>	UDP Lot Number ModernaTX (b) (4)	LDP Lot Number	Validation Report Availability Status			CPD	UDP Release Results	LDP Release Results ^c	(b) (4)	(b) (4)	Version 1	Version 1	Version 2 ^a	N/A ^b	N/A ^b	Version 2 ^a	Version 2 ^a	N/A ^b	N/A ^b	Version 2 ^a	Version 2 ^a	N/A ^b	N/A ^b
UDP Lot Number ModernaTX (b) (4)	LDP Lot Number			Validation Report Availability Status																				
		CPD	UDP Release Results	LDP Release Results ^c																				
(b) (4)	(b) (4)	Version 1	Version 1	Version 2 ^a																				
		N/A ^b		N/A ^b																				
		Version 2 ^a		Version 2 ^a																				
		N/A ^b		N/A ^b																				
		Version 2 ^a		Version 2 ^a																				
		N/A ^b		N/A ^b																				
Reviewer Comments	Incorporated into Section III.B.iii Batch Analysis and Section III.C.ii Process Validation – Process Flow 1 in this memo.																							

iv. Comment 23

Information Request #23.23 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment	<p>With respect to validation of the DP manufacturing process at (b) (4) we note that the qualification study did not report results for sterility, bacterial endotoxin, particulates, (b) (4), or deliverable volume, which are part of the DP release specifications in section 3.2.P.5 Control of DP. Please provide the results of the testing for the (b) (4) PPQ lots (b) (4) batches (b) (4) for these parameters in section 3.2.P.3.5.</p>
Applicant Response	<p>The Sponsor would like to clarify that the data summarized in Table 17 of Section 3.2.P.3.5 {mRNA-1345 DP} are related to cumulative</p>

(emphasis added by reviewer)	process duration samples , which were evaluated as a part of process qualification. Complete PPQ lot release data are available and provided in Section 3.2.P.5.4 {mRNA-1345 DP} , including sterility, bacterial endotoxin, (b) (4) and deliverable volume.
Reviewer Comments	Section Section III.B.iii Batch Analysis and Section III.C.ii Process Validation – Process Flow 1 in this memo.

v. Comment 26

Information Request #23.26 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment	Documents pertaining to the technical specifications for the plunger stopper (Document QER 122180) and plunger rod (Document QER 12167) were not available at the link provided in the BLA. Please provide the technical specification documents for these two items as intended.
Applicant Response (emphasis added by reviewer)	The Sponsor confirms the technical specification documentation (QER-12180 and QER- 12167) has been attached.
Reviewer Comments	<i>These documents were indeed already included in the original BLA. It appears the hyperlinks to these documents in the main BLA sections may have been broken. See Appendix 1 of this memo.</i>

vi. Comment 27

Information Request #23.27 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment	Please provide the CoA for the plunger rod and information pertaining to rod sterilization prior to insertion into the syringe. If rods are not sterilized prior to use, please update this section to note that this is the practice.
Applicant Response (emphasis added by reviewer)	An example Certificate of Conformance (CoC) for the plunger rod (EXT-13884) is provided as part of this response. Section 3.2.P.7 {mRNA-1345 DP} has been updated to clarify that the plunger rods are non-sterile.
Reviewer Comments	See Section VI Sterilization in this memo.

vii. Comment 28

Information Request #23.28 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment	In section 3.2.P.8.3 Stability Data, Table 49 shows the stability testing results for development lot (b) (4) at 2 °C to 8 °C; however, the results for appearance at 2 weeks, 1 month, (b) (4) were not provided. Please provide the results for appearance for these timepoints or update the table to include a footnote explaining the reason for the missing data.
Applicant Response (emphasis added by reviewer)	Section 3.2.P.8.3 {mRNA-1345 RNA} has been updated with all available mRNA-1345 DP stability data, including the appearance results for development lot (b) (4) at 2 °C to 8 °C. The Sponsor would like to note that Section 3.2.P.8.3 {mRNA-1345 DP} has been updated to separate the commercial and clinical scale lots (Section 3.2.P.8.3 {mRNA-1345 DP}) and development lots (Section 3.2.P.8.3 Addendum {mRNA-1345 DP}).
Reviewer Comments	See Section VIII.B Stability in this memo.

viii. Comment 29

Information Request #23.29 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment	With respect to the (b) (4) planned end-to-end stability studies described in section 3.2.P.8.1, a. Please provide a commitment to submit the final study reports and an estimated date for their submission. b. Please provide a commitment to submit the interim stability data from the end-to-end study that will include transfer of samples after 12 and 18 months of storage at -25°C to -15°C and an estimated date for their submission. c. The data in items “a” and “b” may be submitted as a product correspondence or as part of a prior approval supplement if used to support implementation of a shelf-life extension of the DP. Please acknowledge.
Applicant Response (emphasis added by reviewer)	a. The Sponsor commits to submit final study reports for the end-to-end studies described in Section 3.2.P.8.1 {mRNA-1345 DP} with an estimated submission date of September 2025. b. The Sponsor commits to submit interim study reports for the end-to-end studies described in Section 3.2.P.8.1 {mRNA-1345 DP} with an estimated submission date of June 2024 for the 12-month report and December 2024 for the 18-month report. c. The Sponsor acknowledges the Agency’s feedback.

Reviewer Comments	Incorporated into Section VIII.B Stability of this memo.
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ix. Comment 30

Information Request #23.30 Date Sent: February 15, 2024 Date/Sequence Received: February 28, 2024/0040	
IR Comment	<p>With respect to the ongoing stability studies for PPQ DP lots (b) (4) covered in section 3.2.P.8.3,</p> <p>a. Please provide currently available stability data.</p> <p>b. Please provide a commitment to submit the final stability report and an estimated date for submission. The report may be submitted as a product correspondence or as part of a prior approval supplement if used to support implementation of a shelf-life extension of the DP.</p>
Applicant Response (emphasis added by reviewer)	<p>Section 3.2.P.8.3 {mRNA-1345 DP} has been updated with all available mRNA-1345 DP stability data, including 9 months at (b) (4) °C to -30°C, -25°C to -15°C, and (b) (4) for all (b) (4) of the PPQ DP lots. The Sponsor respectfully requests a short teleconference in advance of the Late Cycle meeting to discuss shelf life prior to finalizing the commitment to the Agency. The current proposed shelf life of mRNA-1345 DP is 18 months at -25°C to -15°C inclusive of up to 30 days at 2°C to 8°C and up to 24 hours at room temperature (15°C to 25°C) to support administration of the vaccine at the point-of-care site. Based on the updated available data from the DP PPQ lots, the Sponsor would like to discuss the possibility of (b) (4) the allowed time at 2°C to 8°C while maintaining the overall shelf life of 18 months. The extended allowable time at 2°C to 8°C will make it easier for health care providers during high frequency vaccination months (September through November), particularly for providers that have limited freezer space due to COVID vaccination during this same time frame. In addition, this update is intended to reduce vaccine waste since the product cannot be refrozen once thawed. The proposed allowable duration at 2°C to 8°C of (b) (4) days was not included in the initial BLA as there was limited data available from PPQ lots at that time.</p> <p>This (b) (4) of the allowable 2°C to 8°C storage duration is supported by the available stability data from clinical and development lots, the updated PPQ DP stability data, and comparability assessment of the DP PPQ stability data to the clinical and development stability data.</p> <p>The Sponsor will provide an updated Section 3.2.P.8.1 {mRNA-1345 DP} as soon as this is confirmed to be amenable to the Agency. Alternatively, the Sponsor proposes to submit the (b) (4) of the</p>

	allowable storage duration at 2°C to 8°C to (b) (4) days as a CBE-30 immediately upon approval of the BLA. The Sponsor would commit to providing further updates to the stability data on the PPQ lots as part of the Annual Report throughout the duration of the studies and include studies performed to assess the cumulative storage conditions, as no further changes for shelf life are currently planned.
Reviewer Comments	Incorporated into Section VIII.B Stability in this memo. Also see follow-on IR#35.4 below.

Follow-On Information Request #35.4 Date Sent: March 22, 2024 Date/Sequence Received: April 5, 2024 / 0055	
IR Comment	<p>With respect to your response to item 30.a, pertaining to the updated stability data and commitment to submit final study reports for the three DP PPQ lots, we are not able to undertake the review of the additional stability data to modify the storage recommendations to accommodate (b) (4) days at 2 °C to 8 °C at this point in the review cycle. Therefore, please submit a PAS/CBE-30 supplement to support the implementation of this change upon approval of the BLA.</p>
Applicant Response (emphasis added by reviewer)	<p>The Sponsor acknowledges the feedback that the Agency cannot undertake the review of the package to modify the storage recommendation to accommodate (b) (4) days at 2°C to 8°C at this point in the review cycle.</p> <p>Given that this change would require an update to the USPI, the Sponsor would like to obtain clarity on the reporting category (PAS or CBE-30) to appropriately plan for implementation. The Sponsor sent an email on April 2, 2024, to propose a short teleconference with CBER to obtain this clarification.</p> <ul style="list-style-type: none"> • The Sponsor considers that a CBE-30 is appropriate, based on the following: • the data that support the new storage claim were already submitted to the BLA (with IR#23) • the package to support the modification to the USPI would be limited to: <ul style="list-style-type: none"> ○ Update to USPI ○ Section 3.2.P.8.1: Modified storage claim supported by an updated analysis of the data*. ○ Section 3.2.P.8.2: Post-approval stability protocol will be updated to reflect the new storage claim. ○ Optionally, updated stability data in Section 3.2.P.8.3 may be provided, if available at the time of submission. <p>*Note: The original analysis submitted to the BLA supported a (b) (4) -day storage at 2°C to 8°C, but the Sponsor conservatively set a 30-day</p>

	storage at 2°C to 8°C based on limited data from the PPQ lots at that time. The analysis will be refreshed based on the currently available data.
Reviewer Comments	<i>Sponsor acknowledged Agency feedback. and changes to shelf life will be submitted post-approval. Defer to CMC on the proper reporting category. Incorporated into Section VIII.B Stability in this memo.</i>