

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125796

Respiratory Syncytial Virus Vaccine (MRESVIA)

Erin Hill, Reviewer, MRB-2/DMPQ

1. **BLA#:** STN 125796

2. **APPLICANT NAME AND LICENSE NUMBER:** ModernaTx, Inc., US License Number: 2256

3. **PRODUCT NAME/PRODUCT TYPE**

Respiratory Syncytial Virus Vaccine (MRESVIA)

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

- a. Pharmacological category: mRNA vaccine
- b. Dosage form: Suspension
- c. Strength/Potency: 50 µg
- d. Route of administration: Intramuscular injection
- e. Indication(s): Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older.

5. **MAJOR MILESTONES**

First Committee Meeting: September 26, 2023

Filing Meeting: October 26, 2023

Filing Action: November 9, 2023

Inspection: January 24, 2024

PDUFA ADD: May 31, 2024

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Erin Hill, OCBQ/DMPQ/MRB2	2.3 Quality Overall Summary 3.2.S Drug Substance 3.2.P Drug Product 3.2.A.1 Facilities and Equipment 3.2.R Regional Information

7. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
June 29, 2023	STN 125796/0	Original submission (Part 1)
September 12, 2023	STN 125796/0	Original submission (Part 2)
December 22, 2023	Amendment STN 125796/0.18	Response to IR on December 15, 2023
February 21, 2024	Amendment STN 125796/0.33	Response to IR on December 15, 2023
February 21, 2024	Amendment STN 125796/0.34	Response to IR on December 15, 2023

Date Received	Submission	Comments/ Status
April 5, 2024	Amendment STN 125796/0.55	Response to IR on March 25, 2024
April 19, 2024	Amendment STN 125796/0.58	Response to IR on April 15, 2024
May 3, 2024	Amendment STN 125796/0.63	Response to IR on May 1, 2024

8. ACRONYM KEY

List of key abbreviations and acronyms

Abbreviations/Acronyms	Description
RNA-100-AR02 (b) (4)	(b) (4)
RNA-100	Platform process used to manufacture RNA-100-AR02
DSPC	Lipid component (1,2-distearoyl-sn-glycero-3-phosphocholine)
PEG2000-DMG	Lipid component (1,2,-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000)
SM-102	A custom-manufactured ionizable lipid (Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate)
(b) (4) DS intermediate	(b) (4)
LNP-100-AR02 DS	LNP-100-AR02 is the lipid nanoparticle (LNP) used in the mRNA-1345 vaccine. LNP-100-AR02 is the mRNA-1345 LNP containing RNA-100-AR02 that encodes for the RSV F glycoprotein stabilized in the prefusion conformation.
LNP-100	Platform process used to manufacture LNP-100-AR02
UDP-100-AR02	mRNA-1345 Unlabeled Drug Product (UDP)
LDP-100-AR02	mRNA-1345 Labeled DP

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Moderna Tx, Inc. submitted Biologics License Application (BLA) 125796 for Respiratory Syncytial Virus Vaccine (MRESIVIA), a mRNA vaccine intended for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older. The BLA was submitted in two

parts for rolling review: rolling submission Part 1, submitted on June 29, 2023, and Part 2 submitted on September 12, 2023.

This DMPQ review memo includes summaries and assessments of the DS and DP manufacturing processes, microbial quality attributes, facility information including utilities, cross-contamination controls, qualification and maintenance of classified environments and manufacturing equipment, and cleaning and sterilization processes.

The pre-license inspection (PLI) for the DS manufacturer, (b) (4), was conducted from (b) (4), and is documented in an Establishment Inspection Report (EIR). No Form FDA 483 was issued at the conclusion of the inspection and the outcome of the inspection is the classification, No Action Indicated (NAI). The PLIs for the DS and DP facilities ((b) (4), ModernaTX (b) (4), (b) (4)) are waived based on their inspection histories and compliance status. The basis for waiving the inspection of these facilities is documented in a separate inspection waiver memo uploaded under BLA STN 125796.

B. RECOMMENDATION

I. APPROVAL

Based on the review of the information submitted to the original BLA 125796/0 and corresponding amendments, and in conjunction with the outcome of the PLI and inspectional compliance history evaluations, the production process, facilities, equipment, and controls appear acceptable for the licensure of MRESVIA, approval is recommended.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Erin Hill, Consumer Safety Officer (CSO), CBER/OCBQ/DMPQ/MRB2	Concur	
Anthony Lorenzo, Branch Chief, CBER/OCBQ/DMPQ/MRB2	Concur	
Carolyn Renshaw, Director, CBER/OCBQ/DMPQ	Concur	

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Module 3

3.2.S DRUG SUBSTANCE

LNP-100-AR02 is a LNP consisting of RNA-100-AR02 encapsulated in a lipid mixture, specifically (b) (4). LNP-100-AR02 is the mRNA-1345 LNP containing RNA-100-AR02 that encodes for the RSV F glycoprotein stabilized in the prefusion conformation. The LNP is an RNA-lipid complex dispersion composed of the following lipid components: SM-102, cholesterol, DSPC, and PEG2000-DMG. The LNP-100-AR02 DS manufacturing process is (b) (4) controlled. The DS is stored (b) (4) in (b) (4) as low-bioburden material. The (b) (4) are stored at (b) (4).

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

See section 3.2.A.1 for a complete list of drug substance manufacturers.

3.2.S.2.2 Description of Manufacturing Process

□ Manufacturing process steps

(b) (4)

[REDACTED]

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

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The mRNA-1345 DP (encompassing UDP-100-AR02 and LDP-100-AR02) is an RNA-lipid complex suspension that contains RNA, that encodes for the RSV F glycoprotein stabilized in the prefusion conformation, and four lipids that act as protectants and carriers of the RNA. The buffer components are preservative free. The DP is supplied as a sterile, single-dose, ready-to-use liquid solution at 0.10 mg/mL for intramuscular administration in a 1mL prefilled syringe (PFS). Each PFS is intended to deliver 50 micrograms (mcg) of RNA in a dose volume of 0.5 mL.

The container closure consists of a 1mL long syringe, 1mL long plunger rod, and 1mL long plunger. The DP is manufactured at (b) (4) formulation, filling), (b) (4), and (b) (4) CMOs.

3.2.P.2.5 Microbiological Attributes

The mRNA-1345 DP is manufactured using an aseptic process. The DP is sterile filtered, and the filter is (b) (4). (b) (4) bioburden is monitored during the manufacturing process, and microbiological quality attributes are controlled by testing for sterility and bacterial endotoxins at release. Sterility is also monitored (b) (4) as part of the stability testing program. The microbiological suitability of the primary container closure system was demonstrated through container closure integrity testing (CCI) studies.

Growth Promotion Study

A microbial growth promotion study, also called a microbial challenge hold time study, was conducted on the COVID mRNA-1273 DP to evaluate the product's ability to hinder growth of the microorganisms over a timeframe corresponding to the proposed "in-use time" of at least (b) (4). mRNA-1345 DP has identical lipid composition and buffer matrix as mRNA-1273 DP and therefore is fully validated based on mRNA-1273 DP results. The study was performed on 0.10 mg/mL and 0.50 mg/mL mRNA-1273 DP and involved inoculating low levels ((b) (4)) of selected (b) (4) microorganisms as specified in (b) (4), including (b) (4) as well as an additional typical skin flora, (b) (4). (b) (4)

(b) (4). The results demonstrated that growth was hindered for up to (b) (4) at (b) (4). Based on the similarity of the two DP's, it was concluded that mRNA-1345 DP solution hinders growth of common microorganisms for at least (b) (4) at (b) (4).

DP release testing consists of sterility, bacterial endotoxin, and (b) (4) testing for the PFS. The specifications under DMPQ purview are summarized in the table below.

mRNA-1345 UDP Release and Shelf-life Specifications

Batch Analysis Testing Parameter	Analytical Method	Acceptance Criteria
Sterility	(b) (4)	No growth
Bacterial endotoxin	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Container closure integrity	(b) (4)	Pass ¹

1. Release acceptance criteria for container closure integrity is N/A. Shelf-life acceptance criteria is 'pass.' (b) (4)

Reviewer's comment for 3.2.P.2.5: The results from the growth promotion study and the release test specifications were reviewed and appears acceptable. The established process controls were applied during the manufacturing process validation and were reviewed and appear adequate.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

The sterile filtered solution is filled into ready-to-use syringes (RTU) on Grade (b) (4) filling line within a Grade (b) (4) area. Pre-sterilized, RTU plungers are placed in the syringes after filling within the Grade (b) (4) area. The PFS then undergo 100% manual or automated visual inspection. After visual inspection, an acceptable quality limit (AQL) sample set is

manually inspected for the lot. The nominal batch size for mRNA-1345 DP is (b) (4) (nominal bulk formulated volume). There are two manufacturing process flows for UDP-100-AR02 DP. In the primary process flow, Process Flow 1, the (b) (4) prefilled, inspected syringes undergo an (b) (4) prior to assembly (plunger rod insertion), label, and packaging activities. The (b) (4) step is included to allow flexibility in the scale of label and packaging operations. Process Flow 2 is forward processed without the (b) (4) operations. A (b) (4) is performed after Process Flow 1 and Process Flow 2, and the (b) (4) syringes are transferred to long-term storage.

All syringes are 100% inspected. The acceptance criteria for critical, major, and minor defects during AQL, including both the percentage and limit of accepted defective units based on the (b) (4)-unit sample size used for mRNA-1345 are listed in the table below. A level III tightened inspection criteria is applied.

AQL Acceptance Criteria During Automatic visual inspection (AVI)

Defect Severity	AQL Acceptance Criteria	Limits of Accepted Units
Critical	(b) (4)	(b) (4)
Major		
Minor		

The acceptance criteria for rejections, indicating the criteria for AQL, critical, major, and minor defects was provided in amendment STN 125796/0.55 (eCTD 0056).

After visual inspection, accepted units are collected for UDP product quality and release testing. For assembly, a plunger rod is inserted into the syringes, and the syringes are labeled using an automatic labeler. The 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 cartons (multi-syringe pack) with variable data printed on the package. After assembly, labeling and packaging, units are collected for LDP product quality release testing. The packaged syringes in cases are transferred at (b) (4) to (b) (4), in (b) (4) and then moved to freezing units. Reprocessing is not performed for any DP process step.

The PPQ process parameters and target ranges are listed in the table below.

mRNA-1345 DP PPQ Process Parameters

Operation	Process Parameter	Target/Range
(b) (4)	(b)	(4)
(b) (4)		
Sterile filtration		
Sterile filtration		
Sterile filtration		
Sterile Filtration		
(b) (4)		
(b) (4)		

Reviewer's comment for 3.2.P.3.5: The description of the manufacturing process including PPs with DMPQ purview was reviewed and appears acceptable. The IR response is adequate.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The (b) (4) steps are carried out in a Grade (b) (4) manufacturing area. Filling and plunger placement are performed in Grade (b) (4) within a Grade (b) (4) area. Dilution buffer is (b) (4) prior to use. Manufacturing operations utilize dedicated multi-use or single-use sterile materials for product-contact equipment. Tanks and filling equipment are product dedicated and (b) (4) between batches. Manufacturing controls for microbial control of the DP manufacturing process, including IPC and CIPC testing are listed in the table below.

(b) (4) DP Manufacturing Process Microbial Controls

Process Step	Test	Acceptance Criteria	Criticality
(b) (4)			
Sterile Filtration	(b) (4)	(b) (4)	(b) (4)
Sterile Filtration	(b) (4)	(b) (4)	(b) (4)
Sterile Filtration	(b) (4)	(b) (4)	(b) (4)
Sterile Filtration	(b) (4)	(b) (4)	(b) (4)
Filling	(b) (4)	(b) (4)	(b) (4)
Filling	Container closure integrity (b) (4)	(b) (4)	(b) (4)
Filling	(b) (4)	(b) (4)	(b) (4)

A (b) (4) test may be used as an alternative; (b) (4); WFI: water for injection

The (b) (4) test method includes a (b) (4)

Subsequently, the test is conducted with (b) (4), and the vendor qualified (b) (4) test limit for (b) (4) is applied.

A description of the (b) (4) test method was provided in amendment STN 125796/0.55 (eCTD 0056).

The CPPs and the associated PAR are listed below. The cumulative process duration begins at the (b) (4) and ends when the last pallet is moved into long term storage after assembly, label, and pack operations.

- Cumulative process duration (b) (4)
- Cumulative process duration (b) (4)

Reviewer's Comment for 3.2.P.3.4: Steps that are critical to microbial quality, including sterile filtration, filling, and plunger placement steps are included in the process. The PFS fill and finish manufacturing process appears to have appropriate control strategy to assure product quality and process consistency. The (b) (4) hold time was the only hold time identified for DP manufacturing process. The review of the (b) (4) hold time and associated qualification is deferred to the OVRP reviewers. The IR response appears adequate.

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4) consecutive UDP-100-AR02 PPQ lots were executed on the (b) (4) Filling Line using the single dose 1mL long cyclic olefin copolymer (COC) PFS at a fill volume of (b) (4) mL and concentration of 0.10mg/mL. The batches were manufactured at batch scales ranges from the minimum and maximum batch sizes ((b) (4)).

UDP-100-AR02 PPQ Batches Filled on (b) (4) Filling Line

PPQ Lot Number ModernaTX (b) (4))	Batch Size / # of Syringes	Filled Syringes	Compliant Units ¹	Manufacturing Date
(b) (4)				

1. After visual inspection

The hold times were challenged during the PPQ batches. Buffer Holding Time of (b) (4) is covered by the validation for the mRNA-1273 variants (same Buffer).

Automatic visual inspection was performed according to internal procedures. The AQL of the (b) (4) .

All PPs, CPPs, IPCs, CIPCs, and final release under DMPQ purview including sterility, endotoxin, (b) (4) met the pre-defined acceptance criteria. Microbial control and control of container closure integrity were carried out during the manufacturing of all PPQ batches. All filter (b) (4) test results were within specification and the total product contact time during sterile filtration was (b) (4) .

Two deviations were noted during the PPQ relating to data integrity and sampling. There was no impact to the study and both deviations are closed.

- During PPQ validation of batch (b) (4) , samples from the (b) (4) phase (b) (4) hold bioburden) could not be collected since there was no remaining product in the (b) (4) . There is no impact to the validation, since the samples were collected in subsequent validation batches. Additionally, the filling hold time is already considered validated for previous Moderna platform products.
- Inadequate documentation practices during AQL inspection of batch (b) (4) was not compliant with data integrity practices. CAPAs have been established to avoid reoccurrence, including changes in the document template to facilitate documentation and training.




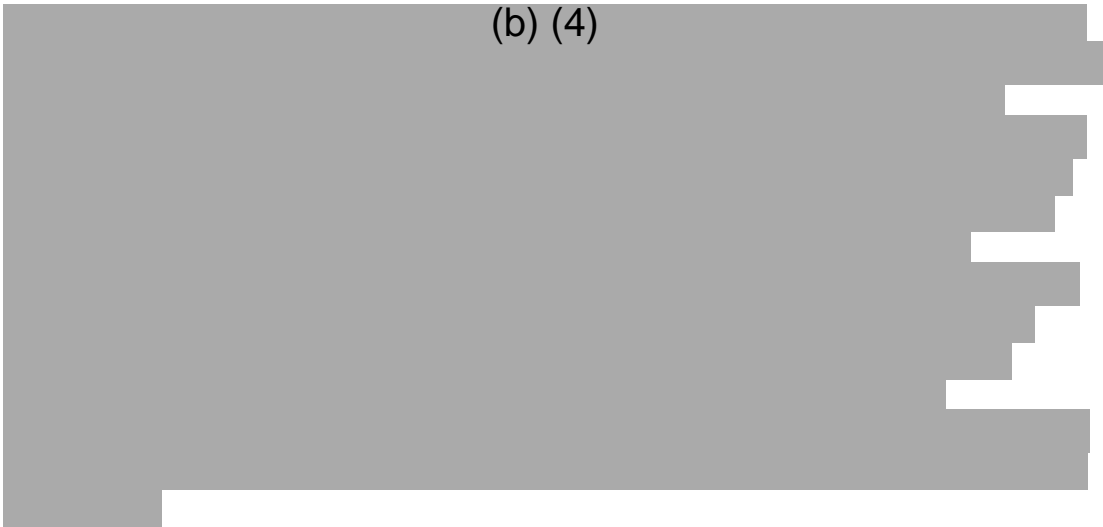
Reviewer's Comment: All PPs, CPPs, IPCs, CIPCs, and final release under DMPQ purview for all PPQ lots met the predefined acceptance criteria demonstrating consistent, robust, and well-controlled process performance and product quality. The deviation events, root cause analyses, and applicable CAPAs were reviewed and appear acceptable.

Media Fill

(b) (4)

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

(b) (4)



3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Refer to section 3.2.P.2.5 Microbiological Attributes.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Refer to section 3.2.P.7 Container Closure System for assessment of CCIT.

3.2.P.5.4 Batch Analyses

The PPQ lots produced for PPQ-comparability and stability studies are listed below. The acceptance criteria for the PPQ lots are listed in section 3.2.P.2.5, *Table: mRNA-1345 UDP Release Specifications*.

(b) (4) PPQ Batches		
PPQ Lot Number ModernaTX ((b) (4))	Batch Size / Syringes	Manufacturing Date
(b) (4)		

The ModernaTX lot numbers are sequential however, the (b) (4) lot number for the first PPQ lot is not. The date of manufacturing presented is for the UDP. All (b) (4), bacterial endotoxin, and sterility results are within the release acceptance criteria.

Reviewer comment for section 3.2.P.5.4: The CoAs for the PPQ lots were reviewed and appear acceptable. The PPQ-commercial lots appear to be (b) (4) filled between (b) (4). The ModernaTX lot numbers are (b) (4). The (b) (4) lot numbers are (b) (4) except for the first UDP batch produced ((b) (4)). The PPQ lots were placed on stability studies. All available data was reviewed and discussed in section “3.2.P.8 Stability”.

3.2.P.7 Container Closure System

The mRNA-1345 DP PFS primary CCS, including syringe, plunger, and plunger rod, is summarized in the table below.

PFS Primary CCS

Container Closure Component	Manufacturer	Description/Materials of Construction	Standards
Syringe	(b) (4)	1 mL long, halobutyl rubber tip-cap in rigid plastic cover	(b) (4)
Plunger	(b) (4)	1 mL long halobutyl rubber plunger with fluoropolymer coating on product contact surface	(b) (4)
Plunger rod	(b) (4)	1 mL long polypropylene plunger rod (non-product contact)	(b) (4)

COC: cyclo olefin copolymer; ISO: The International Organization for Standardization

The CCS components are received RTU. Empty syringe barrels are received sterile via (b) (4) in plastic tubs with polypropylene nests and (b) (4) lids. The plungers are sterilized via (b) (4), to achieve the sterility assurance level of (b) (4). The syringe and plunger are tested for (b) (4). The plunger rod is tested for (b) (4). The (b) (4) specification for the syringe

(barrel and closure) is (b) (4) per syringe, and the specification for the plunger is (b) (4)/plunger stopper. The sterility specification for both components is 'sterile.' Functionality tests were conducted and included (b) (4)

. Design verification demonstrated the suitable functionality of the plunger as a closure for the syringe in conjunction with the plunger rod. Refer to section 3.2.R *Regional Information - Combination Products – Design Verification* of this review memo.

Reviewer's Comment: *The descriptions, microbial specifications, technical specifications including drawings and dimensions, and the CoA and certificates of conformance (CoC) were reviewed for the PFS components and appear acceptable.*

Container Closure Integrity Testing (CCIT)

The suitability of the container closure was demonstrated through CCIT of representative PFS at the intended storage conditions and of PFS filled on the (b) (4) Filling Line. CCIT was performed using the (b) (4) method (b) (4), and by (b) (4) analysis.

The following test methods were developed to test CCI at the intended PFS storage and usage temperatures:

(b) (4)

PFS CCIT at Intended Storage Conditions

The intended manufacturing and storage conditions for the 0.10 mg/mL DP include both frozen (b) (4) °C to -15°C) and non-frozen (2°C to 25°C) temperatures, in both the LDP, (plunger rod assembled) and UDP (no plunger rod) configurations. CCIT was performed

with representative DP at the worst-case low temperature, at refrigerated temperature, at room temperature, and at room temperature after (b) (4) freeze-thaw cycles between worst-case low temperature and room temperature. The CCI study conditions, testing method, acceptance criteria, number of units tested are summarized in the table below. All results met the acceptance criteria.

CCIT Studies for PFS

Condition	Test Subject	Test Method	Acceptance Criteria	Number of Units Tested
(b) (4)	1 mL Long COC PFS with plunger rod inserted	(b) (4)	(b) (4)	(4)
(b) (4)	1 mL Long COC PFS without Plunger rod inserted			
(b) (4)	1 mL long COC PFS without plunger rod inserted			
4°C	1 mL long COC PFS with plunger rod inserted			
4°C	1 mL long COC PFS without plunger rod inserted			
20°C - 25°C	1 mL long COC PFS with plunger rod inserted			
20°C - 25°C	1 mL long COC PFS without plunger rod inserted			
After Freeze-Thaw Cycles	1 mL long COC PFS with plunger rod inserted			
After Freeze-Thaw Cycles	1 mL long COC PFS without plunger rod inserted			

Reviewer's Comment: CCIT methods (b) (4) testing) were established at temperatures pertinent to mRNA-1345 DP PFS storage conditions. Test method detection limits were defined. PFS container closure integrity appears appropriately verified.

CCI Verification of UDP

CCI of UDP was also verified as part of PPQ activities. The PFSs were manufactured at the target plunger insertion parameters and sampled from (b) (4) of

fill. CCI was tested on the samples per the validated (b) (4) method. A total of (b) (4) UDP samples were collected from (b) (4) PPQ batches each (b) (4) (b) (4) (b) (4) PFS were subjected to (b) (4) testing at (b) (4). The remaining samples were used as a negative control, positive control, and back-up. The sensitivity of the positive control is (b) (4). All samples tested met the acceptance criteria of “(b) (4).”

The quantity of UDP samples tested for (b) (4), the sensitivity of the positive control used in the testing, and the storage conditions were provided in amendment STN 125796/0.58 (eCTD 0059).

CCI of the LDP through the end of shelf life at intended storage conditions, during accelerated aging, and after shipping simulation are also verified as part of Design Verification testing. Refer to section 3.2.R *Regional Information - Combination Products – Design Verification*.

Reviewer’s Comment: PFS CCI was further verified by the (b) (4) test on the PPQ UDP PFSs. The results demonstrate that the facility is capable of consistently manufacturing integral PFS. The IR response is acceptable.

Plunger Placement

After filling, the plunger is positioned within the syringe at an insertion depth of (b) (4). The plunger insertion depth measurement is a CIPC for the manufacture of mRNA-1345 DP. The suitability of the container closure with respect to plunger placement has been demonstrated through plunger movement studies. The criticality of insertion depth is based on potential for plunger movement directly related to the size of PFS headspace.

Plunger movement studies simulated expected worst-case storage and transportation conditions for (b) (4) transportation of UDP, frozen transportation of LDP, and (b) (4) transportation of LDP. Frozen transportation was simulated by (b) (4)

The length of the sterile barrier for the 1 mL long COC PFS was assessed to be no less than (b) (4) based on analysis of measured samples. During simulation of (b) (4) transportation of UDP, frozen transportation of LDP, and (b) (4) transportation of LDP, syringes prepared with up to (b) (4) showed plunger movement of no more than (b) (4). The plunger movement is therefore smaller than the sterile barrier length for all conditions and configurations tested.

Reviewer's Comment: Plunger position control of (b) (4) is determined based on the (b) (4) of (b) (4) and plunger movement studies. The studies demonstrated that the migration of the plunger does not exceed the sterile barrier length in the syringe barrel during the intended PFS storage and transportation conditions when the plunger position control of (b) (4) is implemented. This appears acceptable.

Shipping Validation

(b) (4)

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

(b) (4)

Reviewer's Comment: *The information provided for device functionality was reviewed and appears acceptable. Stability during transport is deferred to the OVRP reviewers.*

Reviewer's Comment for Section 3.2.P.7: *The information provided for the CCS, CCIT, and shipping validation appears acceptable.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

An initial shelf life of 18 months is proposed for mRNA-1345 DP material stored in the commercial CCS 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. The studies include long-term ((b) (4) °C to -30°C) and accelerated (2°C to 8°C and 23°C to (b) (4) °C) storage conditions.

((b) (4) registration UDP-100-AR02 lots manufactured at the commercial scale were placed on stability at ((b) (4) °C to -30°C and -25°C to -15°C. ((b) (4) and container closure integrity testing will occur at months 0, 12, and ((b) (4). Endotoxin testing will occur at months 0, 3, 12, and ((b) (4). Sterility testing will occur at month 0.

The UDP-100-AR02 lots were also placed on stability at 2°C - 8°C. ((b) (4), endotoxin, and container closure integrity testing will occur at months 0, ((b) (4). Endotoxin testing will occur at months 0, ((b) (4). Sterility testing will occur at months 0 and ((b) (4).

((b) (4) registration LDP-100-AR02 lots manufactured at the commercial scale at ((b) (4) were placed on stability at -25°C to -15°C. ((b) (4) testing will occur at months 0, 3, 6, 12, and ((b) (4). Bacterial endotoxin testing will occur at months 0, 3, 12, and ((b) (4). Container closure integrity testing will occur at months 12 ((b) (4).

The LDP-100-AR02 lots were also placed on stability at 2°C - 8°C. ((b) (4), testing will occur at months 0, ((b) (4). Bacterial endotoxin testing will occur at months 0, ((b) (4). Container closure integrity testing will occur at month ((b) (4).

The LDP-100-AR02 lots were also placed on stability at 23°C to ((b) (4) °C. ((b) (4), testing will occur at 24, ((b) (4) hours. Bacterial endotoxin testing will occur at ((b) (4) hours. Container closure integrity testing and sterility testing will occur at ((b) (4) hours.

A total of ((b) (4) clinical lots of mRNA-1345 DP ((b) (4))

manufactured using (b) (4) processes were placed on stability at -25°C to -15°C and 2°C to 8°C. The firm provided a complete listing of time intervals for bacterial endotoxin, container closure integrity, and sterility testing in the submission.

All available results met the release and stability acceptance criteria.

Moderna TX, Inc commits to placing a minimum of (b) (4) mRNA-1345 DP (UDP or LDP) lot on stability (b) (4). (b) (4) bacterial endotoxin, and CCIT will be assessed at time intervals specified in the submission.

Reviewer's comment for section 3.2.P.8.1: (b) (4), bacterial endotoxin, and CCIT stability test results were reviewed and appear acceptable.

3.2.A APPENDICES

DS and DP Manufacturing Facilities

Manufacturing Facility	Manufacturing/Testing Activity
<p>(b) (4)</p> <p>FEI#: (b) (4)</p>	<p>Manufacture of (b) (4) for mRNA;</p> <p>Release testing of (b) (4)</p>
<p>ModernaTX, Inc. (ModernaTX (b) (4)) (b) (4) FEI#: (b) (4)</p>	<p>Manufacturing of:</p> <ol style="list-style-type: none"> mRNA-1345 RNA (DS intermediate) (b) (4) (b) (4) mRNA-1345 LNP (DS) (b) (4) <p>in-process, final release, and (b) (4) testing of mRNA-1345 RNA (DS intermediate), (b) (4) (DS intermediate), and mRNA-1345 LNP (DS);</p> <p>storage of mRNA-1345 RNA (DS intermediate) and (b) (4) (DS intermediate);</p> <p>DP batch release and combination product development and lifecycle</p>
<p>(b) (4)</p> <p>FEI#: (b) (4)</p>	<p>Manufacturing of:</p> <ol style="list-style-type: none"> (b) (4) (DS intermediate) (b) (4) mRNA-1345 LNP (DS) (b) (4)); <p>in-process, release, and (b) (4) testing of (b) (4) (DS intermediate);</p> <p>final release and (b) (4) testing of DS;</p> <p>storage</p>
<p>ModernaTX, Inc. (ModernaTX (b) (4)) (b) (4) FEI#: (b) (4)</p>	<p>Final release and (b) (4) testing of mRNA-1345 RNA (DS intermediate) and mRNA-1345 LNP (DS);</p> <p>in-process, release, and (b) (4) testing of (b) (4) (DS intermediate)</p>

Manufacturing Facility	Manufacturing/Testing Activity
(b) (4) FEI#: (b) (4)	Final release and (b) (4) testing of (b) (4) (DS intermediate) and mRNA-1345 LNP (DS)
(b) (4) FEI#: (b) (4)	DP manufacturing (formulation, sterile filtration, filling, storage); in-process, final release, and stability testing of DP
(b) (4) FEI#: (b) (4)	Release testing for (b) (4) (DS intermediate)
(b) (4) FEI#: (b) (4)	Final release testing for mRNA-1345 LNP (DS) Primary labeling, and packaging; DP release and stability testing
(b) (4) FEI#: (b) (4)	(b) (4) ; storage

(b) (4)

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

(b) (4)

ModernaTX (b) (4), **MA (mRNA-1345 RNA and mRNA-1345 LNP)****Facility Design**

ModernaTX, Inc.'s (b) (4) is a multi-product manufacturing and testing site for mRNA-based products including mRNA-1345 RNA and mRNA-1345 LNP that are the subject of this review memo. Moderna also manufactures mRNA-1273 (out of scope) and mRNA based clinical products that are not yet approved including (b) (4). The facility consists of (b) (4) levels that are approximately (b) (4) square feet. The (b) (4) building is adjacent to (b) (4) and consists of a warehouse, storage, shipping, and receiving supply chain area.

The manufacturing area is located on the (b) (4) floor and is adjacent to the quality control (QC) laboratories ((b) (4)). The laboratories consist of microbiology, raw materials, bioassay, chemistry, sample management, and stability departments. The QC microbiology laboratory testing facilities are segregated from the chemistry laboratories. The QC sterility testing area has a separate AHU from that supplying the QC chemistry laboratory. The HVAC systems servicing the QC microbiology laboratory area have been qualified. To increase analytical testing capacity, an additional ModernaTX, Inc. QC Laboratory was established, located at (b) (4). In-process, release, and stability testing are conducted at this laboratory.

Grade C Manufacturing Areas at ModernaTX (b) (4)

mRNA-1345 Process	Room	Process Train
RNA-100	(b) (4)	(4)
RNA-100		
RNA-100		
RNA-100		
RNA-100		
(b) (4)		
(b) (4)		
LNP-100		
LNP-100		
LNP-100		
LNP-100		
LNP-100		
Buffer Preparation		

Contamination and Cross-Contamination Controls

The manufacturing process for RNA-100, (b) (4), LNP-100, and buffer preparations for production of mRNA-1345 occurs in Grade (b) (4) rooms. Manufacturing is campaign-based. The clean rooms are designed to provide a controlled environment for production. The surface finishes in the production areas are designed for durability and easy cleaning. The production processes primarily use single-use systems. Product changeover and equipment cleaning criteria were established to prevent product cross contamination in the multi-product manufacturing rooms. Changeover begins at the

(b) (4)

The primary steps for room changeover include (b) (4)

Room pressurization, airlocks, and gowning rooms facilitate product/process separation and containment. Controlled written procedures define gowning, material, equipment, waste, and personnel flows and flows are also illustrated in facility diagrams.

Materials and equipment flow: Materials and equipment are transferred from uncontrolled areas to controlled not classified (CNC) areas through designated airlocks, placed on dedicated carts, and cleaned with appropriate sanitizers or disinfectants. Gowned personnel retrieve the equipment from the airlock from the CNC corridor. All buffer prep, mRNA, and LNP process materials are transferred from the CNC (b) (4) area and dedicated Grade (b) (4) transfer airlocks to the cleanroom suites.

Waste flow: Waste is labeled prior to transport. Waste from the mRNA manufacturing process is transferred from the cleanrooms through designated CNC exit and uncontrolled corridors. Chemicals are disposed of according to local, state, and federal regulations.

Personnel flow and gowning: Badge access is granted to qualified personnel in the manufacturing areas. All cleanroom suites have separate airlocks for gowning and de-gowning. Personnel must exit from one production area and don fresh gowning prior to entering other cleanroom suites. Flow within the CNC areas may be either (b) (4). Movement within the Grade (b) (4) areas is unidirectional.

Reviewer comment: Flow diagrams covering the movements of waste, product, personnel, and materials were provided under 3.2.A.1 in the submission for each building and appears acceptable. The flows for equipment and materials, product, wastes and personnel in the production areas appear acceptable using defined flows and directions. Waste and incoming materials appear to take separate paths. Most flows appear to be unidirectional for Grade (b) (4) and above except for some areas where (b) (4) flow is permitted. Movements appear controlled and use personnel and material and equipment airlocks for entry and exit to the controlled areas.

Facility Cleaning

Facility cleaning is governed by site procedures that describe frequency, methods, equipment, and materials required to clean controlled areas and cleanrooms. Cleaning agents include (b) (4). (b) (4) is used as the rinse agent. Surface cleaning (b) (4). Regular cleaning is performed on a (b) (4) basis. Non-routine cleaning, also called response cleaning, is conducted (b) (4) or as needed such as for an unplanned AHU shutdown or in response to negative EM trends. (b) (4) is applied for a minimum (b) (4) contact time. Following (b) (4) cleaning, (b) (4) surfaces are wiped down with (b) (4).

Disinfectant Efficacy Studies

The disinfectant efficacy coupon studies challenged the effectiveness of (b) (4) against a combination of in house-isolates and (b) (4) organisms including (b) (4). The study used the (b) (4). All results of the disinfectant validation met the acceptance criteria.

Reviewer comment: *The cleaning and disinfectant efficacy studies were reviewed and appear acceptable.*

Utilities

Critical utilities used for the mRNA-1345 RNA manufacturing process include WFI, process gases, and HVAC. The utilities are periodically evaluated per procedure.

HVAC Systems

The HVAC system controls the temperature and humidity of the air using preheat coils, chilled water-cooling coils, and a steam humidification system. (b) (4)

(b) (4)

The HVAC system is controlled by the BMS. Area classification requirements are established and maintained through HEPA filtration and constant air changes. Space pressurization is controlled via a static air balance. Differential pressures are monitored via the Continuous Monitoring System (CMS) and alarms are displayed when the differential pressure is out of range for more than fifteen minutes. The CMS also monitors the temperature and humidity in the classified areas.

As part of OQ, cleanrooms are certified for (b) (4)

requirements as per the (b) (4) standard. Re-qualification frequency for cleanrooms is (b) (4) for Grade (b) (4) (ISO (b) (4)) and Grade (b) (4) (ISO (b) (4)).

(b) (4)

(b) (4)

The latest requalification's from 2023-2024 met the acceptance criteria.

The description of the most recent HVAC qualification with details of the testing performed including (b) (4), and acceptance criteria was provided in amendment STN 125796/0.55 (eCTD 0056).

Reviewer's comment: *Diagrams of room classifications, pressure differentials, air supply and air return locations in the areas used for manufacturing were reviewed appears acceptable. HVAC parameters for process and logistics rooms*

including room classifications, minimum air changes per hour and differential pressure appear adequate. The IR response is acceptable.

EMPQ

EM for the manufacturing areas is performed per the site procedure. All new areas undergo, at minimum, (b) (4). For existing areas that have been previously qualified, a reduced EMPQ (i.e., (b) (4)) are used to requalify the space. (b) (4) sites are selected based on a risk-based sampling plan. Each area is evaluated under (b) (4) conditions with the maximum occupancy. Representative (b) (4) collected during each sample session were identified.

A description of the EMPQ study duration was provided in amendment STN 125796/0.55 (eCTD 0056).

(b) (4)

(b) (4)

(b) (4)

All other EMPQ results met the acceptance criteria.

A description of the deviations and excursions that occurred during EMPQ were provided in amendment STN 125796/0.55 (eCTD 0056).

Routine EM consists of (b) (4)

monitoring. The Grade (b) (4), Grade (b) (4) and Grade (b) (4) areas are sampled (b) (4). CNC areas are sampled (b) (4). Surface and personnel are monitored using surface (b) (4) testing. (b) (4)

(b) (4) EM trend reports are generated (b) (4). The alert level and action level excursions are escalated based on the severity of the event. All excursions are reviewed on a (b) (4) basis.

(b) (4)

Reviewer's comment: *The EMPQ appears acceptable. The EM excursion was reviewed, and the corrective action appears adequate. The IR response appears acceptable.*

WFI

The ModernaTX (b) (4) facility uses (b) (4) different sources of water for manufacturing including WFI, (b) (4). In-house WFI is used at the point of fill and is tested to meet (b) (4)

The use of WFI (b) (4) in the manufacture of (b) (4) was provided in amendment STN 125796/0.55 (eCTD 0056).

(b) (4)

(b) (4)

IOQ and Performance Qualification (PQ)

IOQ was successfully completed for the WFI generation system and the WFI storage and distribution system. During PQ, the systems were tested for (b) (4) per the (b) (4).

(b) (4)

All results met the acceptance criteria.

The WFI generation, storage, and distribution systems are routinely monitored and trended. (b) (4)

A summary detailing the frequency of monitoring for WFI was provided in amendment STN 125796/0.55 (eCTD 0056).

(b) (4)

(b) (4)

Reviewer's comment: *The WFI PQ was evaluated in detail during the PLI (NAI) in October 2021. Additionally, a surveillance inspection was performed in September 2023 and classified Voluntary Action Indicated (VAI). No objectionable findings were noted. The IR response appears acceptable.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Computer Systems

All computerized systems used in manufacturing are installed, validated, maintained, and supported in accordance with the appropriate regulations and guidance, including 21 CFR Part 11. Systems are tracked as either supporting systems or manufacturing process control systems and related changes are periodically reviewed. The computer systems that are used for the mRNA manufacturing process are noted in the table below.

Manufacturing Process Control Computer Systems

Computer System	Description	Manufacturing Step Used
	(b) (4)	

(b) (4) : data historian system; PCS: process control system

The (b) (4) records and historizes event and time series data from Moderna manufacturing PCS components into a data archive. (b) (4) is a validated (b) (4) platform used in the automation of manufacturing process systems and the digital integration of connected process equipment for manufacturing. (b) (4) is the manufacturing execution system (MES) used in product manufacture and includes production orders, equipment, and materials management.

IOQ for the computer system validations were conducted. The validations generally included (b) (4)

(b) (4)

All results met the acceptance criteria.

Reviewer's comment: *A general description of the computer systems controlling the manufacturing processes was provided and reviewed. The computer systems are validated and appear acceptable.*

Equipment

The manufacturing processes for RNA-100, (b) (4) , and LNP-100 use a combination of reusable non-product contact equipment, single-use disposable product-contact equipment, and reusable product-contact equipment. The mRNA-1345 manufacturing processes use mostly single-use equipment and materials. All single-use equipment is disposable and is (b) (4) prior to receipt. The reusable equipment may be used for multi-product manufacturing after changeover. (b) (4)

(b) (4) are shared across mRNA-based commercial products and clinical products under development: mRNA-1273, (b) (4) . (b) (4) are dedicated to mRNA-1345 RNA.

The firm identified the major reusable product-contact equipment that is dedicated or shared, and listed the other products that share the equipment in amendment STN 125796/0.55 (eCTD 0056).

The reusable and disposable product-contact equipment for the RNA-100, (b) (4) , and LNP-100 manufacturing processes are listed in the tables below.

(b) (4)

(b) (4)

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

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Reviewer's comment: *The equipment descriptions and qualification results were reviewed and appear acceptable. The IR response is acceptable.*

Cleaning of Major Equipment

The (b) (4) reusable equipment used in the manufacturing processes includes the
(b) (4)

(b) (4)

Cleaning validation of reusable equipment for mRNA-1345 is currently in progress and will be executed concurrently with the next scheduled manufacturing batches of mRNA-1345. Moderna states cleaning verification will be performed for all reusable equipment at the predefined steps until PQ is completed. Cleaning verification acceptance criteria are identical to PQ requirements.

(b) (4)

(b) (4)

The acceptance criteria ((b) (4)) and results from the cleaning verification for all major reusable product-contact equipment was provided in amendment STN 125796/0.55 (eCTD 0056).

Reviewer's comment: *The cleaning verification acceptance criteria and results for the reusable equipment was reviewed and appears acceptable. The IR response is acceptable.*

(b) (4)

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

(b) (4)

(b) (4)

(mRNA-1345 DP)

(b) (4) (hereafter referred to as (b) (4)) is a CMO that performs UDP (b) (4) and LDP (b) (4) and storage for mRNA-1345 DP.

(b) (4) states in amendment STN 125796/0.55 (eCTD 0056) that no relevant changes with respect to facility descriptions, facility flows, contamination/cross-contamination procedures, computer systems, facility/equipment cleaning, equipment descriptions, and equipment validations have occurred since the approval of SPIKEVAX. The same equipment and areas are used for mRNA-1273 DP (SPIKEVAX) and mRNA-1345 DP. No major deviations occurred during validation studies.

Reviewer's Comment: An IR was sent to confirm whether there have been any changes to the facility and equipment since the approval of SPIKEVAX and to indicate if any major deviations occurred during validation studies. Additionally, (b) (4) was asked to indicate if the equipment and manufacturing areas that are used for mRNA-1273 DP are the same equipment and areas used for mRNA-1345 DP. The same equipment and manufacturing areas are used for mRNA-1273 DP (SPIKEVAX) and mRNA-1345 DP. The response was provided in amendment STN 125796/0.55 (eCTD 0056) and appears acceptable. The facility description and flows, utilities, contamination/cross-contamination controls, equipment, facility and equipment cleaning, and computer systems were previously reviewed in PAS STN 125752/74. A 704(a)(4) Records Request and Review was performed to support the review of PAS STN 125752/74 and was found acceptable.

3.2.R Regional Information (USA)

□ **Combination Products**

ModernaTX is intending to market mRNA-1345 vaccine PFS as a single-dose, single-entity, drug/device combination product as per the definition established in FDA 21 CFR 3.2(e)(1). The drug constituent is the primary mode of action. The mRNA-1345 vaccine PFS does not have a previous generation in the US however, the vaccine uses the same syringe components as the mRNA-1273 PFS (Spikevax) for COVID-19. The PFS is composed of the following components: syringe barrel, plunger, plunger rod, and rigid tip cap. The components are described in the section 3.2.P.7 *Container Closure System*.

Design Controls

Moderna has established a design control process that complies with 21 CFR 820.30. This process was applied to the design and development activities of the mRNA-1345 vaccine PFS.

Product Design and Development

The PFS was developed in accordance with design controls as per FDA's Quality System Regulation at 21 CFR Part 820.30 and requirements for Design & Development specified in (b) (4)

The mRNA-1345 vaccine PFS was developed using the same process and components as the mRNA-1273 (COVID-19) PFS.

Risk management activities were an integrated part of the development process and were completed according to (b) (4)

as well as human factors engineering activities according to *FDA Guidance Applying Human Factors and Usability Engineering to Medical Devices (February 2016)*.

Design Change and Design History

ModernaTX has established a change control procedure for managing design changes in accordance with the design control procedure. Design changes are evaluated for impact to risks, project deliverables, and any design verification and design validation. Quality Agreements are established with suppliers to define the collaboration process for design changes to individual components manufactured by ModernaTX suppliers.

ModernaTX procedures require the establishment of a design history file (DHF) that contains all records related to the design history. A DHF has been established for the PFS. The DHF is stored and controlled electronically in Moderna's electronic document management system. The DHF is updated throughout product development and commercialization as required.

Design Inputs and Design Outputs

A User Needs and Product Requirements document has been created to define the use specification (i.e., user needs, intended use, intended users) and design input requirements for the PFS. The requirements identified were established per the intended use of the combination product, including the needs of the patient and user.

Design outputs have been created to satisfy the product requirements identified in the User Needs and Product Requirements document. This included labeling, drawings, component, and drug product specifications, testing requirements, or similar documents deemed necessary to document the translation of design input requirements. Documents supplied by contract manufacturers were leveraged to fulfill design outputs as appropriate.

Design Verification

Studies were conducted to verify the design of the PFS and ensure that design outputs meet the design input requirements. Design verification evidence supporting the mRNA-1345 vaccine PFS includes data and reports that were generated during the development of the mRNA-1273 PFS. The syringe components are identical, and both DP's are manufactured on the same filling and packaging lines with the same critical fill parameters. Therefore, based on these similarities, the results of design verification testing and reports of the mRNA-1273 PFS is suitable to use for the design verification of the mRNA-1345 vaccine PFS.

(b) (4) testing were conducted to verify container closure integrity to ensure that the sterile barrier remains intact throughout manufacturing, freezing, transit, storage, thawing, and intended use. In addition to design verification testing at t=0, (b) (4), deliverable volume, (b) (4), CCI, and label legibility were tested after exposure of samples to simulated transit conditions (at (b) (4) and -25°C to -15°C) and accelerated aging preconditioning.

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.

Accelerated, real-time aging, and end-to-end studies were conducted. At the time of submission, accelerated aging data is available, and real-time and end-to-end studies are ongoing. Accelerated aging was performed for (b) (4) at (b) (4). Real-time aging was conducted for storage at -20°C for 10 and 16 months, and at 5°C for (b) (4) months. End-to-end studies were performed at -20°C for (b) (4) months and at 5°C for (b) (4) months.

Design verification testing was conducted on samples that were representative of the commercial product manufactured at (b) (4). Evaluation of results was based on 95% reliability at a confidence interval of 95%; therefore, a sample size of (b) (4) was used for each verification test. There were no unexpected results or significant deviations that impacted the study results.

PFS Design Verification Testing Summary

Test	Acceptance Criteria	Standard	Sample Conditions
(b) (4)			
Deliverable volume	Expelled fluid shall be \geq 0.5 mL when tested at ambient temperature	(b) (4)	T=0; T=0 post transit conditioning at (b) (4) °C; T=0 post transit conditioning at -20°C T= (b) (4) days at (b) (4) °C
(b) (4)			
CCI – dye ingress	CCI testing shall indicate that the primary container is maintained under the intended storage and use conditions.	(b) (4)	T=0 T=0 post transit conditioning at (b) (4) °C; T=0 post transit conditioning at -20°C T= (b) (4) days at (b) (4) °C
(b) (4)			

Test	Acceptance Criteria	Standard	Sample Conditions
<div style="display: flex; justify-content: space-around; font-size: 48pt; font-weight: bold;"> (b) (4) </div>			
Product label visual inspection	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.	T=0 T=0 post transit conditioning at (b) (4) °C; T=0 post transit conditioning at -20°C T=(b) (4) days at (b) (4) °C

Reviewer's Comment: The design verification studies, including testing for CCI, (b) (4) and deliverable volume of the DP PFS with end-of-shelf-life storage and shipping simulations, were reviewed and appear acceptable. Study results support that the design outputs fulfill the design input requirements and that the performance of the mRNA-1345 DP PFS is sufficient for the intended use.

Design Validation

Design validation activities were conducted in accordance with FDA guidance Applying Human Factors and Usability Engineering to Medical Devices (February 2016). Design validation activities included:

- Establishing plans for design validation and human factors.
- Defining the use specification (i.e., user needs, intended use, intended users).
- Conducting a human factors validation study with the mRNA-1345 vaccine PFS that validated the labeling and packaging.
- Leveraging the human factors validation study that was conducted for the mRNA-1273 PFS to validate the PFS design and user interface associated with administration and storage.
- Summarizing human factors activities and design validation results in a Human Factors Usability Engineering Summary Report.

Reviewer's Comment: *The mRNA-1345 DP PFS design validation is in place and appears acceptable. Review of the human factors validation study is deferred to OVRR reviewers.*

Management Responsibility

Senior management has appointed a management representative and has established a quality policy and quality objectives per 21 CFR Part 820.20. Quality objectives are established and approved at relevant functions and levels in the organization and reviewed by quality management. Senior management has the ultimate responsibility to review the QMS at defined intervals and frequency to ensure that an effective QMS is implemented.

Purchasing Controls

The supplier management program is implemented per 21 CFR 820.50 *Purchasing Controls*. Processes are in place to approve and select materials, services, and contract organizations including risk-based auditing and monitoring of initial selection and ongoing performance. The supplier management program is used to track vendor performance; categorize vendors based upon risk, quality, and business attributes; and determine appropriate action when warranted. The supplier management program manages quality agreements, supplier corrective action reporting, and supplier change notifications.

The materials management process includes purchasing activities associated with incoming raw materials and supplies, manufactured and/or purchased products, inventory management/controls, and vendor/supplier surveillance requirements. The process also includes defining specified requirements including quality, part/lot numbering, shipping, transporting, and receiving of cGMP materials. Product and material management and handling systems are designed to protect product and material integrity and to avoid deterioration.

Corrective and Preventive Action

Moderna has implemented a system for CAPAs that complies with 21 CFR 820.100. Discrepancy events include events that are not performed or documented as required in an approved cGMP record. The discrepancy process includes but is not limited to deviations, internal or external audit observations, regulatory observations, trend analyses, product complaints, gap analyses, supplier/material quality defects, validation departures, etc. Discrepancies must be clearly identified, documented, investigated, patient and/or product impact, determined, and any necessary corrective action taken. Any nonconforming product must be appropriately dispositioned.

CAPAs may result from the investigation of a discrepancy or other sources. CAPA responsibilities are divided between Moderna and suppliers in accordance with established quality agreements.

Risk Analysis

Moderna has applied a risk management process to the PFS in accordance with (b) (4). Risk

management activities were conducted to ensure the safety and performance of the combination product in connection with all aspects of development, design, manufacturing, use, and product lifecycle management.

The Risk Management Plan (RMP) defines the process and documentation used to identify, evaluate, and control risks throughout the product lifecycle. Measures taken to control or mitigate risks associated with product design, process, use, and materials have been recorded in the risk management file. The Risk Management Report (RMR) documents that the RMP has been appropriately implemented, summarizes the results of risk management activities, and concludes that all residual risk levels have been effectively reduced as far as possible, the benefits of the PFS outweigh the individual and overall risk, and that the resulting overall residual risk is acceptable.

Reviewer's Comment: Management responsibility, purchasing controls, risk analysis and CAPAs for the mRNA-1345 DP PFS combination product were reviewed and appear acceptable.

Reviewer's Comment for 3.2.R Combination Products Section: The information as it relates to design controls for the PFS was reviewed and appears acceptable.

❑ **Post-Approval Change Management Protocol**

The firm indicated that a post-approval change management protocol (PACMP) is planned to be submitted post-approval. A listing of the potential changes to the manufacturing processes of the (b) (4) mRNA-1345 DP including the proposed number of PPQ lots to be performed in support of these changes were provided and are detailed in the table below.

(b) (4)

(b) (4)

The firm indicated that the initial reporting category for the PACMP will be a PAS followed by a reduced reporting category of a CBE-30 except for adding a new manufacturing site for mRNA-1345 DP. A reduced reporting category is not proposed. A comparability assessment will be provided with release and stability data.

Reviewer's Comment: *The acceptability of the planned PACMP proposal for the potential post-approval changes to the BLA will be determined when the Prior Approval Supplement for the PACMP is submitted to the Agency.*