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CBER/(b) (6) CMC/Facility BLA Review Memorandum

BLA STN 125835/0

COVID-19 Vaccine

[MNEXSPIKE]

(b) (6)

Reviewer

1. BLA#: STN 125835/0

2. APPLICANT NAME AND LICENSE NUMBER

Name: ModernaTx, Inc.

US License #: 2256

3. PRODUCT NAME/PRODUCT TYPE

Proper name: COVID-19 Vaccine

Proprietary name: MNEXSPIKE

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: mRNA vaccine
- b. Dosage form: suspension
- c. Strength/Potency: 10 µg
- d. Route of administration: intramuscular injection
- e. Indication(s): active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older

5. MAJOR MILESTONES

- Application Receipt Date: September 30, 2024
- First Committee Meeting: October 21, 2024
- Filing Action: November 29, 2024
- Internal Mid-Cycle Meeting: January 14, 2025
- Mid-Cycle Communication: January 30, 2025
- Late-Cycle Meeting with Applicant: March 16, 2025
- PDUFA Action Due Date: May 31, 2025

6. (b) (6) CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Sequence #	Comments/ Status
Sep 30, 2024	125835/0.0	0001	Original application
Nov 27, 2024	125835/0.5	0006	Response to (b) (6) IR#1, confirming no significant changes for the facilities

Date Received	Submission	Sequence #	Comments/ Status
Mar 13, 2025	125835/0.31	0032	Response to (b) (6) IR#2, regarding media fill run, visual inspection, CCIT, equipment cleaning and sterilization, and utilities.
Apr 30, 2025	125835/0.50	0051	Response to (b) (6) IR#3, regarding AVI and AQL

8. REFERENCED REGULATORY SUBMISSIONS (e.g., IND, BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BL 125752	ModernaTx, Inc	Entire BLA	Provided	Spikevax (Moderna COVID-19 Vaccine)
BL 125796	ModernaTx, Inc	Entire BLA	Provided	MRESVIA (Moderna RSV Vaccine)
MF (b) (4)	ModernaTx, Inc	(b) (4) (formerly known as (b) (4))	Provided	
DMF (b) (4)	(b) (4)	(b) (4) Glass Prefillable Syringe (PFS)	Provided	
DMF (b) (4)	(b) (4)	(b) (4) syringes manufactured in (b) (4)	Provided	
DMF (b) (4)	(b) (4)	Piston (Plunger), Elastomeric Formulations, Coatings and Films	Provided	

9. REVIEWER SUMMARY AND RECOMMENDATION

1) EXECUTIVE SUMMARY

ModernaTx, Inc. (hereafter Moderna) submitted documentation to BLA STN 125835/0 to support licensure of mRNA-1283 or MNEXSPIKE, an mRNA vaccine indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

CBER/(b) (6) reviewed and evaluated the drug substance (DS) and drug product (DP) manufacturing processes, and the facilities proposed for use for the manufacture of DS and DP. Information reviewed, evaluated, and documented in this memo includes data to validate and support the consistency of the manufacturing process and product quality; facility information which includes utilities, contamination prevention measures, and maintenance of controlled environments; and equipment for use during the manufacturing process.

Facility inspections for all DS and DP manufacturing and testing facilities were waived based on the evaluations of the facilities' inspection compliance histories along with consideration of manufacturing experience. The decision evaluation for the inspection consideration are documented in a separate inspection waiver memo which is part of the BLA file in CBER Connect.

This submission was granted priority review with 8-month review cycle.

2) RECOMMENDATION

Approval of the BLA is recommended from (b) (6) perspective with the following inspectional consideration.

CBER understands that the recommendations below may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

- The out of specification test results from WFI monitoring in 2024 appear to be mostly attributable to sampling errors.

SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
(b) (6)	Concur	
(b) (6)	Concur	
(b) (6)	Concur	

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List of Acronyms

3PL	Third-Party Logistics
AHU	Air Handling Units
AQL	Acceptable Quality Limit
AVI	Automatic Visual Inspection
(b) (4)	
BCT	Bacterial Challenge Test
CFU	Colony Forming Units
CHT	Clean Hold Time
CIP	Clean In Place
CMO	Contract Manufacturing Organizations
CMS	Continuous Monitoring System
COC	Cyclic Olefin Copolymer
CPD	Cumulative Process Duration
CPP	Critical Process Parameter
CQA	Critical Quality Attributes
DHT	Dirty Hold Time
DP	Drug Product
DS	Drug Substance
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
EIR	Establishment Inspection Report
EM	Environmental Monitoring
EPR	Essential Performance Requirements
EU	Endotoxin Units
(b) (4)	
HVAC	Heating, Ventilation and Air Conditioning
(b) (4)	
ISO	International Organization For Standardization
(b) (4)	
JP	Japanese Pharmacopoeia
LDP	Labeled Drug Product
LNP	Lipid Nanoparticles
(b) (4)	
(b) (4)	
(b) (4)	
MCB	Master Cell Bank
NF	National Formulary
NTD	N-Terminal Domain

OOS	Out Of Specification
OQ	Operational Qualification
PAI	Pre-Approval Inspection
PCM	Phase Changing Material
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PES	Polyethersulfone
PETG	Polyethylene Terephthalate Glycol
PFS	Pre-Filled Syringes
Ph. Eur	European Pharmacopoeia
POU	Point of Use
PPQ	Process Performance Qualification
PQ	Performance Qualification
psi	Pounds Per Square Inch (Unit For Pressure Measurement)
PW	Purified Water
q.s.	Quantum Sufficit
(b) (4)	
RBD	Receptor-Binding Domain
(b) (4)	
RSV	Respiratory Syncytial Virus
RTU	Ready to Use
SAL	Sterility Assurance Level
(b) (4)	
SM-102	(b) (4)
SUM	Sing-Use Mixture
(b) (4)	
TCV	Temperature-Controlled Vehicles
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
UDP	Unlabeled Drug Product
(b) (4)	
USP	US Pharmacopeia
UTR	Untranslated Region
WCB	Working Cell Bank
WFI	Water for Injection

BACKGROUND of SUBMISSION

mRNA-1283 is a lipid-encapsulated mRNA-based vaccine encoding the receptor-binding domain (RBD) and N-terminal domain (NTD) of the Spike glycoprotein of SARS-CoV-2 virus (b) (4) 4 lipids: SM-102 (a custom-manufactured ionizable lipid); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG) to form RNA LNPs.

Compared with the approved Moderna COVID-19 Vaccine Spikevax (mRNA-1273, BL 125752) which encodes the full-length Spike protein, mRNA-1283 lacks the furin cleavage site present in the full-length Spike protein which facilitates cleavage of the protein into S1 and S2 regions by host furin proteases. The furin cleavage site mediates the release of the soluble S1 domain into the circulation and the circulating S1 immunogen is indicated to be associated with the rare risk of myocarditis and pericarditis.

Like the mRNA-1273 COVID-19 vaccines, mRNA-1283 is also able to encode Spike protein sequences from different SARS-CoV-2 strains by using strain-specific (b) (4) . Moderna's nomenclature for a strain-specific mRNA-1283 is designated by adding the strain code affix, for example, mRNA-1283.815, mRNA-1283.116, etc.

Moderna's (b) (4) manufacturing processes undergo ongoing evaluation and development. The manufacturing process versions used for the production of mRNA-1283 vaccines are the (b) (4) , respectively.

Spike protein sequences from several SARS-CoV-2 strains have been used during the development of mRNA-1283. The strains and corresponding mRNA-1283 components are summarized in Table 1.

Table 1. SARS-CoV-2 Strains Used in mRNA-1283 Process and Clinical Development

Strain	mRNA ID
Wuhan-Hu-1 (D614G)	(b) (4)
Omicron B.1.1.529	
Omicron BA.4/BA.5	
Beta B.1.351	
Omicron XBB.1.16	
Omicron XBB.1.5	

mRNA-1283.815 is the vaccine intended for commercial supply under this BLA; mRNA-1283.815 encodes the Spike protein RBD and NTD domains for the Omicron XBB.1.5 strain.

Reviewer's Comment: *In addition to Spikevax, another commercial mRNA vaccine that utilizes Moderna's (b) (4) manufacturing platform technology is the Respiratory Syncytial Virus (RSV) Vaccine, mRESVIA.*

Review of the current BLA references the review of the following BLAs and/or supplements. (Please note that the summary below, following each STN number, only includes the contents or changes referenced during the review of the current BLA. It may not encompass all contents of the referenced submission.)

- BLA 125752/0 – Moderna COVID-19 vaccine (Spikevax) application, approved January 31, 2022.
- BLA 125752/74 – Introducing pre-filled syringe (PFS) presentation for Spikevax, approved September 11, 2023.
- BLA 125752/90 – Introducing (b) (4) filling line at (b) (4) for PFS manufacturing, approved September 28, 2023. A pre-approval inspection (PAI) was conducted (b) (4) in support of STN 125752/90.
- BLA 125796/0 – Moderna RSV vaccine (mRESVIA) application, approved May 31, 2024.
- BLA 125752/208 – Introducing (b) (4) filling line at (b) (4) for PFS manufacturing, approved August 9, 2024.
- BLA 125752/224 – Introducing mRNA 1273 DP thawing and secondary shipping at 5°C.

3.2.S DRUG SUBSTANCE - mRNA-1283.815 (b) (4)

(b) (4)

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

(b) (4)

3.2.P DRUG PRODUCT – mRNA-1283 DP**3.2.P.1 Description and Composition of the Drug Product**

The DP is an RNA-lipid complex dispersion that contains RNA and four lipids that act as protectants and carrier of the RNA. DP is supplied as a sterile, single-dose, ready-to-use liquid solution at 10 µg/0.2 mL for intramuscular administration in a 1-mL PFS. Each PFS delivers 10 µg of RNA and 200 µg of total lipids as a white to off-white dispersion in preservative-free buffer. Composition of the DP is summarized in Table 16. For long-term storage, DP is stored at -40°C to -15°C.

Table 16. Composition of mRNA-1283.815 DP

Component	Grade	Function	Unit Formula (mg/mL)	Unit Formula (in 0.2 mL dose)
mRNA-1283.815 RNA	(b) (4)	mRNA encoding the linked NTD and RBD of the spike glycoprotein of the SARS-CoV-2 virus	0.05	10 µg
SM-102		Lipid component	(b) (4)	(b) (4)
Cholesterol		Lipid component	(b) (4)	(b) (4)
DSPC		Lipid component	(b) (4)	(b) (4)
PEG2000-DMG		Lipid component	(b) (4)	(b) (4)
Tris		Buffer	0.45	90 µg
Tris-HCL		Buffer	2.6	510 µg
Sucrose		Cryoprotection	(b) (4)	17 mg
WFI		Diluent	q.s. to 1.0 mL	q.s. to 0.2 mL

^a Total lipids: 1.0 mg/mL

^b Total lipids per dose: 200 µg/dose

NF = National Formulary; USP = US Pharmacopeia

3.2.P.2.4 Container Closure System

Refer to section 3.2.P.7 Container Closure System for the primary container closure system description, specifications, and qualification under (b) (6) purview.

3.2.P.2.5 Microbiological Attributes

Microbiological attributes of the DP are maintained via multiple levels of control, including the manufacturing process, release and stability testing, container closure suitability, and environmental controls.

DP is sterilized by filtration [REDACTED]. [REDACTED] is monitored as part of the manufacturing process and sterilizing filter integrity is tested [REDACTED] (refer to section 3.2.P.3.4 and 3.2.P.3.5). The microbiological quality attributes are assessed by testing for sterility and bacterial endotoxins at release (refer to section 3.2.P.5.1). The microbiological suitability of the selected primary container closure system has been demonstrated through container closure integrity characterization and plunger movement testing (refer to section 3.2.7). CCI is also monitored as part of the manufacturing process and [REDACTED] as part of the stability testing program. Maintenance of an aseptic manufacturing environment is assured through facility controls at [REDACTED] (refer to section 3.2.A.1).

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

See section 3.2.A.1 for a complete list of facilities involved in the manufacture of mRNA-1283.815 UDP and mRNA-1283.815 LDP.

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

(b) (4)



3.2.P.3.4 Controls of Critical Steps and Intermediates

The in-process controls under (b) (6) purview are summarized in Table 17:

(b) (4)

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

(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

Process Performance Qualification (PPQ)

(b) (4)

(b) (4)

13 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)

The mRNA-1283 DP release specifications under (b) (6) purview are summarized in Table 28.

Table 28. mRNA-1283 DP release specifications

Attribute (UDP or LDP)	Analytical Procedure	Release Specification	Shelf-Life Acceptance Criteria
Bacterial Endotoxin (b) (4)	(b) (4)	(b) (4)	(b) (4)
Sterility (b) (4)		No Growth	No Growth
Particulate Matter (b) (4)		(b) (4)	(b) (4)
Deliverable Volume (b) (4)		For each of the (b) (4) syringes: (b) (4) 0.2 mL	For each of the (b) (4) syringes: (b) (4) 0.2 mL
(b) (4)		(b) (4)	(b) (4)
(b) (4)		(b) (4)	(b) (4)
Container Closure Integrity (b) (4)		N/A	Pass

Container closure integrity testing is performed on stability in lieu of sterility.

Reviewer's Comment: The DP release specifications associated with microbial quality attributes and the acceptance criteria appear acceptable. Assessment of the other release tests is deferred to OVRP reviewers.

3.2.P.5.4 Batch Analyses

Batch analysis data from the (b) (4) mRNA-1283 UDP PPQ lots and the corresponding (b) (4) mRNA-1283 LDP lots are provided. Additionally, batch analysis data from (b) (4) clinical batches produced between July 2020 and October 2023 are provided. The clinical lots are mRNA-1283 DPs of SARS-CoV-2 strain variant as described in Table 1. All results met the bacterial endotoxins, sterility, particulate matter, deliverable volume, (b) (4) specifications as in Table 28.

Reviewer's Comments: Batch release testing results under (b) (6) purview appear acceptable.

3.2.P.7 Container Closure System

Components of the Container Closure System

The primary container closure system of the DP PFS consists of a syringe, a plunger, and a plunger rod. Empty syringe barrels are received sterile ((b) (4) sterilization) and ready-to-use (RTU) in plastic tubs with polypropylene nests and (b) (4) lids. The plunger stoppers are received sterile ((b) (4)) and RTU. The plunger rods are received non-sterile.

Table 29. mRNA-1283 DP Primary Packaging Components

Component	Description	Manufacturer	Sterility Control	Standards
Syringe	1-mL long COC syringe with halobutyl rubber tip cap in rigid plastic cover	(b) (4)	(b) (4) sterilization per (b) (4), SAL (b) (4)	(b) (4)
Plunger Stopper	1-mL long halobutyl rubber plunger with (b) (4) coating on product contact surface	(b) (4)	(b) (4) sterilization per (b) (4), SAL (b) (4)	(b) (4)
Plunger Rod	Polypropylene long plunger rod, non-sterile (non-product contact)	(b) (4)	N/A	N/A

COC = cyclic olefin copolymer

SAL = sterility assurance level

DP container closure components are received, inspected, and released for use according to established procedures, which include review of the manufacturer's Certificate of Analysis, Certificate of Compliance, etc., and testing per component-specific quality control test plan. Sterility and bacterial endotoxins results are documented by supplier quality certificates, as applicable.

During secondary packaging, an assembled and labeled PFS is packed into a carton. One patient information leaflet or prescribing information is also placed in the secondary carton. Cartons are then placed into a case and the cases are closed.

Reviewer's Assessment: *The description of the container closure system appears acceptable. The same syringe components are used for Spikevax (BL 125752) and mRESVIA (BL 125792) vaccines.*

Container Closure Integrity Test (CCIT)

CCIT using (b) (4) test is performed at the (b) (4) facility. For CCIT, (b) (4)

The test was initially established for Spikevax PFS and the same test method was subsequently verified for mRNA-1283 DP PFS to detect (b) (4) defect on mRNA-1283 DP PFS.

CCI of mRNA-1283 UDP is verified as part of the PPQ runs. PFS were manufactured at the target plunger insertion parameters, and a total of (b) (4) samples (b) (4) each from (b) (4) were subject to CCIT from each lot. All samples passed the CCIT.

CCI of mRNA-1283 DP through end of shelf life at intended storage conditions, after accelerated aging, and after transit simulation is verified as part of stability testing. (b) (4) mRNA-1283 LDP PFS are subject to (b) (4) testing at T=0, after transit simulation at (b) (4) °C or at 5 °C, and after accelerated aging of (b) (4). All samples passed the CCIT.

Reviewer's Comment: *CCI verification of mRNA-1283 DP PFS appears acceptable.*

Data to support suitable functionality of the selected container closure system for ensuring PFS integrity was first provided for mRNA-1273 PFS in STN 125752/74. Briefly, (b) (4) analysis methods were used. CCI was demonstrated for intended storage and use conditions including frozen at (b) (4), refrigerated at 4°C ± 2°C, room temperature at 2°C to 25°C, and after (b) (4). Refer to the (b) (6) review memo for STN 125752/74 for details.

Plunger Stopper Placement

The suitability of the container closure system with respect to plunger placement has been demonstrated through plunger movement studies.

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

3.2.P.8 Stability

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

To support shelf-life assessment, stability studies for the three mRNA-1283.815 LDP PPQ lots (Lot (b) (4)), are performed. All stability lots have the same RNA concentration (0.05 mg/mL) and container closure system (1 mL COC PFS). The storage conditions include -25°C to -15°C for 12 months or at 2°C to 8°C for (b) (4) or at 23°C to (b) (4) °C for (b) (4). The PPQ lots are also placed on end-to-end stability study, in which samples are stored at -25°C to -15°C for 9 months, followed by 2°C to 8°C storage for 3 months, and followed by 23°C to (b) (4) °C storage for 24 hours.

The CQAs assessed for stability study include particulate matter, container closure integrity, (b) (4), deliverable volume, bacterial endotoxins under (b) (6) purview. For the PPQ lots, these attributes are tested at 0-, 1-, 6-, 9- and 12-months for storage at -25°C to -15°C, at 0-, 1-, 3-, (b) (4) for storage at 2°C to 8°C, and at 0-day, 1-day, and (b) (4) for storage at 23°C to (b) (4) °C (additional (b) (4) and deliverable volume testing is performed at (b) (4) for storage at 23°C to (b) (4) °C).

Stability study data through August 2024 are available, including data for up to 12 months of storage at (b) (4), at (b) (4) °C, and at -25°C to -15°C; up to (b) (4) of storage at 2°C to 8°C; and up to (b) (4) of storage at 23°C to (b) (4) °C for development lots. CQA testing under (b) (6) purview as described above for all batches met the acceptance criteria.

A shelf life of 12 months is proposed for mRNA-1283 DP in the PFS, when stored at the long-term storage condition of -40°C to -15°C including up to 90 days of storage at 2°C to 8°C and up to 24 hours at room temperature (up to 25°C) to support administration of the vaccine at the point-of-care site.

Reviewer's Comment: *From microbial quality aspects, a 12-month shelf-life claim for the mRNA-1283 DPs in PFS appears acceptable based on stability data. Review of other quality aspects of the stability study is deferred to OVRP reviewers.*

3.2.A APPENDICES

Facilities Table

Manufacturing / Testing Activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	CMO?	Comments
Facility: ModernaTX, Inc. One Moderna Way Norwood, MA 02062 FEI#: 3014937058 DS manufacturing; DS release, stability, in-process testing; DS lot release; DS storage	Waiver	Yes	Yes	No	(b) (6) Surveillance Inspection, NAI, Apr 16-19, 2024
Facility: (b) (4) (b) (4) FEI#: (b) (4) Manufacture and release testing of (b) (4)	Waiver	Yes	Yes	Yes	CBER (b) (6) PLI NAI, (b) (4) (b) (6) surveillance inspection, NAI, (b) (4)
Facility: (b) (4) (b) (4) FEI#: (b) (4) UDP Manufacturing; DP in-process testing	Waiver	Yes	Yes	Yes	CBER (b) (6) PAI NAI, (b) (4) (b) (6) surveillance inspection, VAI, (b) (4)

Manufacturing / Testing Activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	CMO?	Comments
Facility: (b) (3), (b) (4) FEI#: (b) (3), (b) (4) UDP and LDP (b) (4) ; DP frozen storage ((b) (4) long-term)	Waiver	Yes	Yes	Yes	Records Request review performed in (b) (3), (b) (4) and found acceptable.
Facility: (b) (4) FEI#: (b) (4) UDP (b) (4), primary labeling and secondary packaging; DP in-process, release and stability testing	Waiver	Yes	Yes	Yes	(b) (6) PAI VAI, (b) (4)
Facility: (b) (3), (b) (4) FEI#: (b) (3), (b) (4) DP release and stability testing	Waiver	Yes	Yes	Yes	MRA Surveillance inspection by (b) (3), (b) (4) VAI, (b) (3), (b) (4)

Manufacturing / Testing Activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	CMO?	Comments
Facility: Moderna Biotech Spain S.L. Calle Julian Camarillo 31 28037 Madrid, Spain FEI#: 3030155316 DP batch release; DP release and stability testing	Waiver	Yes	Yes	Yes	MRA Surveillance Inspection by Spain AEMPS, VAI, (b) (3)
Facility: (b) (4) (b) (4) FEI#: (b) (4) DS release and stability testing (endotoxin)	Not Required	No	Yes	Yes	
Facility: (b) (4) (b) (4) FEI#: (b) (4) DS storage	Not Required	No	Yes	Yes	
Facility: (b) (4) (b) (4) FEI#: (b) (4) DS storage	Not Required	No	Yes	Yes	

DS = Drug Substance;

DP = Drug Product;

UDP = Unlabeled Drug Product;

LDP = Labeled Drug Product;

PLI = Pre-license Inspection;

PAI = Pre-Approval Inspection;

VAI = Voluntary Action Indicated;

NAI = No Action Indicated;

CBER = Center for Biologics Evaluation and Research;

(b) (6) ;

(b) (6)

(b) (6)

AEMPS = Spanish Agency of Medicines and Medical Products

ModernaTX Norwood Facility

The ModernaTX Norwood Facility manufactures (b) (4) for commercial products and mRNA-based clinical products. The manufacturing activities for (b) (4) take place in the (b) (4) building and involve the rooms in Table 31.

Table 31. Commercial Manufacturing Areas at ModernaTX Norwood (b) (4)

(b) (4)

Reviewer's Comment: The Moderna Norwood facility is also used for production of (b) (4) for Spikevax under BL 125752 and for mRESVIA (mRNA-1345 DP) under BL 125796. Moderna stated in IR response STN 125835/0.5 (eCTD# 006) that the facility areas and equipment used for the production of mRNA-1283 (b) (4)

Please note that (b) (4) manufacturing rooms (b) (4) manufacturing rooms (b) (4) which are used for mRNA-1345 are not used for mRNA-1283 mRNA and (b) (4) production in the current submission.

It is also indicated in the above-mentioned IR response that since the approval of BL 125796, the only change made to the facility and equipment is (b) (4). There is no other change to the controlled environments, material/product/waste flows, utilities, equipment, facility and equipment cleaning, contamination and cross-contamination procedures, or computer systems.

Therefore, review of the facilities and equipment of the ModernaTX Norwood facility leverages the review of BL 125796 for the following aspects:

- *Material/product/personnel/waste flows*
- *Contamination and cross-contamination procedures including line clearance procedures*
- *Facility cleaning*
- *Utilities (water systems, gas, and HVAC) qualification*
- *Environmental monitoring program*
- *Equipment qualification*
- *Computer systems*

Utilities

The utilities used at the facility include water for injection (WFI), process gases (compressed air, process air, and (b) (4)) and HVAC. All utilities are qualified and monitored.

For WFI system, the (b) (4) loop undergoes a regular (b) (4) cycle. The loops are monitored via the Continuous Monitoring System (CMS) for (b) (4). All manufacturing points of use (POUs) are sampled (b) (4) for (b) (4). The WFI specifications are summarized in Table 32.

(b) (4)

Compressed air is used to support automation of equipment; process air, which is compressed air (b) (4), is used where process contact is required. The (b) (4) process air is continuously monitored via the

CMS for (b) (4). Testing for process air is performed (b) (4) for (b) (4).

(b) (4) is used for (b) (4). It is supplied to the manufacturing areas via a (b) (4) gas header. (b) (4) is continuously monitored via the CMS for (b) (4). Testing for (b) (4) is performed (b) (4) for (b) (4).

Acceptance criteria for process air and gases monitoring are as in Table 33.

(b) (4)

The mRNA-1283 (b) (4) production areas are under the control of the following air handling units (AHUs) as in Table 34.

(b) (4)

Cleanrooms are certified for use for non-viable particulates, HEPA filter leak and integrity, airflow volume, room pressure differential, temperature, and relative humidity

requirements as per relevant ISO standards. HVAC operation and controls are also verified through the EM program.

Reviewer's Comment: *Utilities monitoring procedure and acceptance criteria appear acceptable to support the bioburden-controlled processes at ModernaTX Norwood. Refer to the review memo for BLA 125796/0 for detailed description of the utilities and their qualifications.*

Equipment Cleaning

The product-contact equipment used in the (b) (4) manufacturing processes are listed in Table 35, Table 36 and Table 37.

(b) (4)

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

(b) (4)

(b) (4) **Facility**

(b) (4) manufactures the DP PFS for mRNA-1283 vaccine. The process steps that take place at this facility are from (b) (4) until visual inspection of the UDP PFS. Facility areas involved in the manufacturing process are summarized in Table 41.

(b) (4)

Reviewer's Comment: The (b) (4) facility and the (b) (4) filling line are approved to manufacture mRNA-1273 DP PFS under STN 125752/90 and a PAI was conducted (b) (4) in support of this supplement. This PAI evaluated the manufacturing areas associated with the DP production and related systems including facilities and equipment systems and production systems, etc.

Moderna stated in IR response STN 125835/0.5 (eCTD# 006) that there have been no major changes for the facility and equipment in Building (b) (4) at (b) (4) since the approval of BL 125752/90. Therefore, review of the (b) (4) facilities and equipment in support of the production of mRNA-1283 DP PFS leverages the review in STN 125752/90 for the following aspects:

- Material/product/waste flows

- *Contamination and cross-contamination procedures including line clearance procedures*
- *Facility cleaning*
- *Utilities (water systems, gas, and HVAC) qualification*
- *Environmental monitoring program*
- *Equipment qualification*
- *Computer systems*

Utilities

All utilities at [REDACTED] have been qualified and monitored.

Water Systems

Purified Water (PW) is used to produce WFI and clean steam. WFI is used for [REDACTED]

[REDACTED] The production and distribution systems for water are designed and monitored to meet the [REDACTED] specifications and the guideline on the quality of water for pharmaceutical use.

Clean steam is used in [REDACTED]

[REDACTED] Clean Steam comply with the requirements of the [REDACTED].

WFI and clean steam is routinely monitored with the following monitoring specifications:

(b) (4)

Monitoring data since the beginning of 2024 are provided. Out-of-specification (OOS) results are as follows:

(b) (4)

[REDACTED]

(b) (4)



Reviewer's Comment: *The initial qualification of water systems was reviewed in STN 125752/90 and found acceptable. Routine monitoring data are provided in IR response STN 125835/0.31 (eCTD #0032). The monitoring specifications appear acceptable and deviations that occurred since January 2024 appear to be investigated and resolved.*

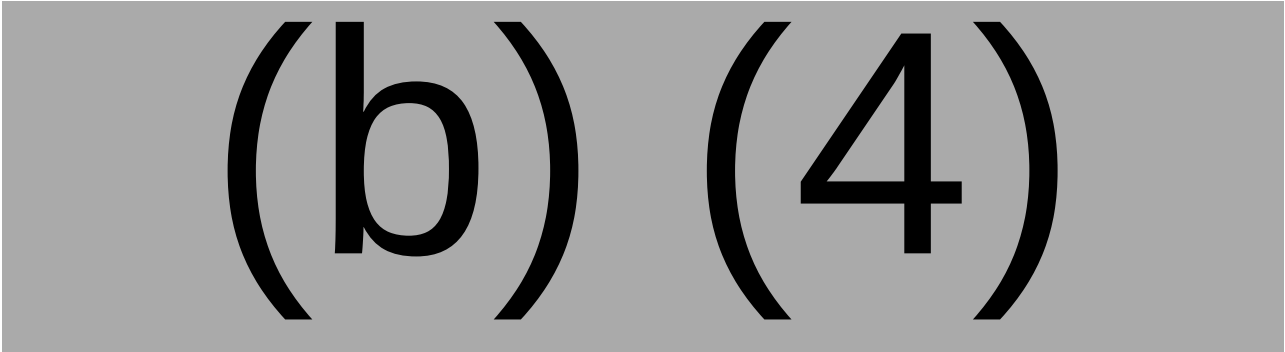
As WFI monitoring OOS results in 2024 appear to be mostly attributed to sampling errors, (b) (4), (b) (5), (b) (7)(E)



Process Gases

Clean compressed air (CCA) is used in (b) (4)
CCA does not have direct product contact. (b) (4) gas, obtained from (b) (4), is used to (b) (4). (b) (4) that contacts the product is (b) (4).

Compressed air and (b) (4) gas has the following monitoring specifications:



(b) (4)

Monitoring of compressed air and (b) (4) gas occurs (b) (4). Monitoring test results since January 2024 all conform to specifications except one deviation (S0004/25) on December 31, 2024 in which the sampling/results was missing for (b) (4). The root cause was determined to be that SOP did not account for missing QC shifts on certain days.

Reviewer's Comment: *The initial qualification of process gas was reviewed in STN 125752/90 and found acceptable. Routine monitoring data are provided in IR response STN 125835/0.31 (eCTD #0032). The monitoring specifications appear acceptable and deviations that occurred since January 2024 appear investigated and resolved.*

Equipment

Major equipment used in the manufacture of DP are summarized in Table 44.

(b) (4)

(b) (4)

Reviewer's Comment: All equipment used for the production of mRNA-1283 DP is the same as used for mRNA-1273 DP. Equipment qualification was assessed in STN 125752/90 and during the September 12-18, 2023 PAI and found acceptable.

Equipment Cleaning Validation

Cleaning procedures for filling needles and vessels have been validated. Equipment cleaning validation was performed for mRNA-1273 DP (Spikevax) and is considered applicable to mRNA-1283 DP.

mRNA-1273 DP and mRNA-1283 DP are produced using the (b) (4)

Acceptance criteria for cleaning validation performed with mRNA-1273 DP are summarized in Table 45.

Table 45. Cleaning Validation Acceptance Criteria

(b) (4)

These acceptance criteria were re-assessed against the mRNA-1283 batch size range and dose volume, and cleaning validation results were confirmed to be applicable.

Reviewer's Comment: In the IR response STN 125835/0.31 (eCTD #0032), it was clarified that equipment cleaning revalidation including dirty hold time and clean hold time study is performed every (b) (4) at (b) (4). The most recent cleaning validation for the (b) (4) filling line is the original cleaning validation provided and found acceptable for mRNA-1273 DP under STN 125752/90, in which cleaning validation for the (b) (4) were performed and the results met the cleaning acceptance criteria.

All cleaning procedures are (b) (4)

Sterilization

Validation

(b) (4)

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

(b) (4)

3.2.R REGIONAL INFORMATION (USA) – COMBINATION PRODUCT

Moderna intends to market the product 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, which is a biologic/vaccine drug product under 21 CFR Part 210-211/600-680.

The device components of the combination product are summarized in Table 47.

Table 47. mRNA-1283 DP PFS Device Components

Component	Description	Function	DMF #
Syringe Barrel	1-mL long COC (cyclic olefin copolymer) syringe	To contain and provide a sterile barrier for the drug product.	(b) (4)
Rigid Tip Cap	Halobutyl rubber tip cap in rigid plastic cover. The rigid tip cap is pre- assembled with the syringe barrel.	To provide a sterile barrier between the drug content in the syringe barrel and the outside environment.	(b) (4)
Plunger	1-mL long halobutyl rubber plunger with (b) (4) coating on product contact surface	To contain and provide a sterile barrier for the drug product. When depressed, the plunger pushes the drug product through the syringe tip and through attached needle.	Plunger: (b) (4); Formulation, Coatings, Films: (b) (4)
Plunger Rod	Polypropylene (PP) plunger rod	To transfer axial force from the user to the plunger to push the drug product through the syringe tip and attached needle.	(b) (4)

Reviewer's Comment: The syringe components are the same as approved for the Moderna Spikevax (STN 125752/74) and mRESVIA (STN 125796) vaccines, and (b) (4) facility has been approved to manufacture Spikevax PFS (STN 125752/74). Therefore, review of the following provisions of the QS regulation for the combination product leverages the review in STN 125752/74 and STN 125796/0:

- § 820.20 - Management responsibility
- § 820.50 - Purchasing controls
- § 820.100 - Corrective and preventive actions

Design Controls, § 820.30

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 ISO 13485:2016 Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes.

Moderna established Essential Performance Requirements (EPRs) for the PFS, which includes (b) (4), and deliverable volume, by evaluating the user need to assure the combination product's safe and effective clinical performance at the point of use. The specifications for the EPRs are as follows: (b) (4)

The EPR control strategy includes purchasing controls, incoming controls, in-process controls, and release testing. Incoming controls associated with (b) (4)

. In-process controls for deliverable volume include testing the fill (b) (4) during the drug product filling process.

Studies were conducted to verify the design of the PFS and ensure that design outputs meet the design input requirements. For design verification, CCI, EPRs and other syringe functionality aspects were tested at t=0, after shipping simulation (at 5°C (b) (4)), after aging studies, or after a combination of shipping simulation and aging studies. Shipping simulation was performed per (b) (4). The simulation conditions selected are considered to be worst-case compared to routine shipping stresses encountered on (b) (4) transport. Accelerated and real-time aging conditions simulated the mRNA-1283 DP PFS shelf-life time points.

Table 48. Design Verification Results Summary

(b) (4)

(b) (4)

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, appear acceptable.

It was indicated that design verification data for the mRNA-1283 0.2 mL vaccine PFS includes data generated during the development of the mRNA-1273 0.5 mL PFS, as mRNA-1273 DP and mRNA-1283 DP have (b) (4). From PFS design verification perspective, the difference between the mRNA-1283 DP and mRNA-1273 DP is the fill volume and RNA/LNP concentration (mRNA-1283 DP: 0.2 mL of 0.05 mg/mL vs. mRNA-1273 DP: 0.5 mL of 0.1 mg/mL). Therefore, it appears acceptable to include testing of the mRNA-1273 PFS for the mRNA-1283 PFS design verification.