



U.S. FOOD & DRUG
ADMINISTRATION

CMC Review Memorandum

Date: January 28, 2022

To: The Biological License Application (BLA) File STN 125752

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CMC Product Reviewer

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Applicant: ModernaTX, Inc.

Product: COVID-19 Vaccine, mRNA (SPIKEVAX™)
Human Coronavirus mRNA Vaccine for the Prevention of Coronavirus
Disease 2019 (COVID-19)

Subject: CMC Review of Original BLA STN 125752.0

Abbreviations Used in the Memorandum

(b) (4)

CCS Container Closure System
CIPC Critical In-process Control
CoA Certificate of Analysis
CPD Cumulative Process Duration
CPP Critical Process Parameter
CPV Continuous Process Verification
CQA Critical Quality Attribute
CRT Controlled Room Temperature

(b) (4)

DS Drug Substance
DP Drug Product

(b) (4)

EUA Emergency Use Authorization
GMP Good Manufacturing Practice

(b) (4)

IPC In-process Control

(b) (4)

LNP Lipid Nanoparticle

(b) (4)

(b) (4)

(b) (4)

PAR Proven Acceptable Ranges

(b) (4)

(b) (4)

PPQ Process Performance Qualification

PVU Personal Vaccine Unit

RSD Relative Standard Deviation

TAR Target Acceptable Range

(b) (4)

TOR Time Out of Refrigeration

(b) (4)

(b) (4)

WFI Water for Injection

Abbreviations not included in the above list are provided in figure legends and table footnotes.

1. Product Name/Product Type

Non-proprietary name: Moderna COVID-19 Vaccine

Proprietary name: Spikevax™

Generic name: (b) (4)

Product Type: Human Coronavirus mRNA vaccine expressing SARS-CoV-2 Spike glycoprotein (Moderna UNII code number EPK39PL4R4) formulated with lipids SM-102, PEG2000-DMG, DSPC, and cholesterol to form RNA-encapsulating lipid nanoparticles (LNPs).

2. Applicant Name and License Number: ModernaTX, Inc. (# 2256)

3. General Description of the Final Product

The mRNA-1273, COVID-19 Vaccine (SPIKEVAX™) is an mRNA-based vaccine indicated for active immunization for prevention of coronavirus disease 2019 (COVID-19). The mRNA encodes a full-length spike (S) glycoprotein of SARS-CoV-2, modified to introduce two proline residues that stabilize the S glycoprotein into the prefusion conformation. In addition, the mRNA is transcribed using N1-methyl-pseudouridine instead of uridine nucleoside. The *in vitro* transcribed single-stranded RNA is encapsulated in a lipid nanoparticle (LNP) composed of four lipids: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC).

mRNA-1273 vaccine is provided as a sterile, clear, colorless suspension for intramuscular injection. Each 0.5 mL vaccine dose is targeted to contain 0.1 mg mRNA in 20 mM trometamol (Tris) buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate. The vaccine does not contain preservatives, antibiotics, adjuvants, and human- or animal-derived materials.

The date of manufacture the final drug product will be the date of the final sterile filtration at the time of filling.

The vaccine is supplied as a multiple-dose ready-to-use solution for intramuscular administration in 10-mL (10R) vials that are closed with a rubber stopper and aluminum crimp flip-off seal. The mRNA-1273 DP is provided in two fill presentations: the (b) (4) mL target fill volume, which allows removal of a maximum of 11 doses per vial and the (b) (4) mL, which allows removal of a maximum of 15 doses per vial.

The vaccine is stored frozen between -50° to -15°C but can be stored refrigerated between 2° to 8°C for up to 30 days prior to first use.

mRNA-1273 vaccine is administered intramuscularly as a series of two doses (0.5 mL each). The second dose is administered 28 days after the first dose. Prior to administration, the vaccine should be thawed in refrigerated conditions between 2° to 8°C for 2.5 hours and kept at room temperature for 15 minutes before administering. Alternatively, it can be thawed at room temperature between 15° to 25°C for 1 hour. The vaccine is authorized for use in individuals of 18 years of age and older.

4. Major Milestones

Regulatory Events / Milestones	Date
1. Pre-IND meeting	February 19, 2020
2. IND submission	IND 19635 for Phase 1 Study: February 20, 2020. IND 19745 for Phase 2 Study: April 27, 2020.
3. Fast Track designation granted (if applicable)	May 11, 2020
4. Pre-BLA meeting	April 28, 2021, Clinical July 1, 2021, CMC/Regulatory
5. BLA 125752/0 submission	August 24, 2021
6. BLA filed & Priority Review Granted	October 14, 2021
7. Mid-Cycle communication	The Applicant cancelled
8. Late-Cycle meeting	The Applicant cancelled
9. Action Due Date	April 24, 2022

5. CMC/Quality Review Team

Reviewer/Affiliation	Section/Subject Matter
Alena Dabrazhynetskaya, OVRD/DVP	Primary product reviewer
Sara Gagneten, OVRD/DVP	
Keith Peden, OVRD/DVP	
Robin Levis, OVRD/DVP	
Jerry Weir, OVRD/DVP	

6. Submissions Reviewed

Date Received	Submission	Comments/ Status
May 28, 2021	STN 125752/0	BLA Roll 1 submission for non-clinical studies including pharmacology, pharmacokinetics, and toxicology studies reports.
August 16, 2021	STN 125752/1	BLA Roll 2 submission containing all quality-related information included in Module 3.

Date Received	Submission	Comments/ Status
August 24, 2021	STN 125752/2	BLA final roll submission containing common technical documents including quality overall summary, non-clinical overview and tabulated summaries.
September 30, 2021	STN 125752/7	Response to DVP IR regarding the live VN assay (b) (4), pseudovirus VNA (Duke), anti-S IgG ELISA (b) (4) and anti-S IgG (b) (4)
October 12, 2021	STN 125752/10	<ul style="list-style-type: none"> Response to DVP/DBSQC IR regarding the SOP-1142 status. Response to DVP IR related to multiple CMC issues for CX-024414 mRNA manufacturing process and controls.
October 18, 2021	STN 125752/12	<p>Submission of additional CMC information:</p> <ul style="list-style-type: none"> Justification of using (b) (4) as container closure system for storage of mRNA-1273 LNP DS. PPQ summary report for (b) (4) Lonza process. Response to DBSQC IR regarding compendial testing for bacterial endotoxin, bioburden, and sterility testing.
October 26, 2021	STN 125752/15	Response to OCBQ IR regarding the for CX-04414 mRNA test samples.
November 5, 2021	STN 125752/17	Submission of the results of a (b) (4) stability study for (b) (4) lot (b) (4) manufactured at Moderna.
November 8, 2021	STN 125752/18	Response to DBSQC IR regarding the method validation reports and method transfer report.
November 22, 2021	STN 125752/24	Response to DVP IR regarding the change of PARs for CPD and TORs proposed for the DP.
November 23, 2021	STN 125752/25	Response to discussion points regarding Moderna Norwood, MA site FDA inspection.
November 30, 2021	STN 125752/26	Response to DVP/DBSQC IR regarding the SOP-1142 for mRNA purity and product-related impurities and results of bridging study.
December 6, 2021	STN 125752/29	Response to DVP IR#25 regarding multiple CMC issues, involving information for manufacturers, batch analyses for mPEG2000-DMG (b) (4), (b) (4) (b) (4) step, and stability data for CX-024414 mRNA, (b) (4) intermediates, DS and DP.
December 8, 2021	STN 125752/30	Response to DBCQC IR#26 regarding the compendial analytical procedure for bacterial endotoxin testing.

Date Received	Submission	Comments/ Status
December 12, 2021	STN 125752/35	Submission of the revised and updated Package Insert and the artwork for the vial labels and cartons.
December 12, 2021	STN 125752/36	Response to OCBQ IR#28 regarding the LRP template.
December 22, 2021	STN 125752/41	Response to DVP IR#29 regarding the mRNA-1273 DP specifications.
December 22, 2021	STN 125752/42	Response to DVP IR#38 regarding multiple CMC issues on intermediates and the DS.
December 28, 2021	STN 125752/43	<ul style="list-style-type: none"> Response to DVP IR#40 regarding multiple CMC issues on the DP. Response to DBSQC IR#42 regarding the endotoxin testing of DP by (b) (4) procedure.

7. Referenced Regulatory Submissions (e.g., IND BLA, 510K, Master File, etc.)

Right of reference letters were provided for previously submitted CMC information from Moderna (IND 19365, IND 19745 and EUA 27073) and for the following manufacturers and quality testing sites: Endotoxin testing (b) (4)

(b) (4) (Adevron, LLC), DSPC lipid (b) (4) container-closure system (b) (4)

Drug Substance (Lonza), Drug Product (Baxter Pharmaceutical Solutions, LLC and Catalent Indiana, LLC). However, all the relevant supportive CMC information was included in the BLA.

8. Reviewer Summary and Recommendation

A. Executive Summary

This review encompasses all CMC-related information in Module 3 of BLA 125752 and additional information submitted in multiple BLA amendments. The results of nonclinical studies relevant to evaluating effectiveness and risk for enhanced respiratory disease (Module 4) and validation of clinical diagnostic assays supporting clinical efficacy endpoints (Module 5) are provided in separate memorandums.

Chemistry, Manufacturing, and Controls

The Moderna COVID-19 vaccine (Code number mRNA-1273) is a nucleoside-modified messenger RNA (mRNA)-based vaccine indicated for active immunization for the prevention of coronavirus disease 2019.

The manufacturing process for the drug substance (DS) consists of (b) (4)

. The mRNA-1273 drug product (DP) is manufactured by (b) (4)

filling of final containers, and labeling/packaging. To support the BLA, process performance qualification (PPQ) data and in-process, release,

characterization, and stability results for (b) (4) mRNA and (b) (4), DS, and DP lots were provided for each manufacturing facility.

The mRNA-1273 manufacturing process underwent scale-related changes during vaccine development to increase production capacity. Scale A process (b) (4), while Scale B process (b) (4). A comprehensive analytical comparability assessment was performed based on a minimum of (b) (4) Scale A and Scale B. The submitted data show that the intermediates, DS, and DP lots manufactured at Scale A and Scale B are highly comparable, and the lots manufactured at Scale B in different facilities are also comparable. The manufacturing process and controls have been well characterized and qualified. The generated data demonstrate that the manufacturing process at all facilities is under control and capable of consistently producing DP that complies with the established specifications and quality attributes.

The analytical procedures developed and used for the release and stability monitoring of intermediates, DS, and DP include tests to ensure vaccine safety, identity, purity, quality, and potency. The appropriate assay methods were established and performed in accordance with the standard operating procedures (SOPs). Each analytical procedure has been adequately validated at all sites proposed for the release and stability testing through analytical method validation protocol or by method-transfer protocol. The validation results demonstrate acceptable precision, accuracy, sensitivity, specificity, and reproducibility of the analytical assays, indicating that they are suitable for the product-quality control.

Stability studies have been conducted for the CX-0244114 mRNA (b) (4) (b) (4), DS, and DP lots to support the licensure of the mRNA-1273 vaccine. All available stability data generated to date support the initial commercial shelf-life of 9 months for the mRNA-1273 DP lots stored in the commercial container-closure system at the recommended long-term storage condition of -25°C to -15°C (-20°C). The proposed shelf life includes up to 1 month (30 days) of storage at 2 – 8°C (5°C) and up to 24 hours at room temperature (25°C) to support administration of the vaccine at the point of care site. The final commercial shelf life of mRNA-1273 vaccine is intended to be (b) (4) months when stored at -25°C to -15°C (-20°C). Stability studies are ongoing.

The on-site pre-licensure inspections of ModernaTX, Inc. (Norwood, MA), Lonza Biologics, Inc. (Portsmouth, NH), and Aldevron (Fargo, ND) manufacturing facilities that are involved in the manufacture, controls, and storage of CX-024414 mRNA, (b) (4), and mRNA-1273 LNP DS were accomplished by the FDA inspection team with participation of Anissa Cheung (Consumer Safety Officer, OVRD/DVP, CBER). The results of inspections and FDA recommendations were documented in the Establishment Inspection Report for each facility. For the subject BLA, inspections for Catalent Biologics, LLC (Bloomington, IN) and Baxter Pharmaceutical Solutions, LLC (Bloomington, IN) facilities used for the fill/finish, in-process testing, release testing (sterility), and storage of mRNA-1273 DP were waived as these facilities were determined to have an acceptable compliance history for manufacturing of previously approved FDA licensed products that include parental drugs and DP formulations.

B. Recommendation**I. Approval**

I recommend approval of this BLA.

II. Signature Block

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Alena Dabrazhynetskaya, OVRD/DVP		
Sara Gagneten, OVRD/DVP		
Keith Peden, OVRD/DVP		
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MODULE 3 - Reviewer's note:

The BLA eCTD includes six Drug Substance (DS) sections:

- CX-024414 mRNA DS intermediate, the Drug Product (DP) active component (b) (4) (b) (4) (b) (4)
- mPEG2000-DMG (b) (4), the starting material for (b) (4) manufacture
- mPEG2000- DMG (b) (4) the starting material for (b) (4) manufacture
- SM-102 (b) (4) the starting material for (b) (4) manufacture
- mRNA-1273 LNP DS, the LNP-encapsulated mRNA.

Since mPEG2000-DMG and SM-102 custom lipids are classified as starting materials for the (b) (4) manufacture, the related CMC information is discussed in section 3.2.S.2.3 *Control of Materials* (b) (4) of the current review memo.

3.2.S DRUG SUBSTANCE INTERMEDIATE {CX-024414 mRNA}

3.2.S.1 Nomenclature, Structure and General Properties

The CX-024414 mRNA Drug Substance (DS) intermediate (b) (4)

3.2.S.2 Manufacture {CX-024414 mRNA}

3.2.S.2.1 Manufacturers

The facilities for manufacture and testing of CX-024414 mRNA are listed in [Table 1](#). All sites are cGMP compliant and have US FDA establishment licenses.

Table 1. Facilities and responsibilities for manufacture, release, and stability testing of CX-024414 mRNA

Facility	Responsibility
Aldevron 4055 41 st Avenue South Fargo, ND 58104 USA DUNS 048764943	<ul style="list-style-type: none"> • Manufacture of (b) (4) (b) (4) • Release testing of (b) (4) (b) (4)
ModernaTX, Inc. One Moderna Way Norwood, MA 02062 USA FEI3014937058 DUNS 116912313	<ul style="list-style-type: none"> • Manufacturing of CX-024414 mRNA • In-process, release, and stability testing (excluding (b) (4) for material manufactured at Lonza Biologics, Inc.) • Storage
ModernaTX, Inc. (b) (4) (b) (4) USA (b) (4) (b) (4)	<ul style="list-style-type: none"> • Release, stability, in-process testing (excluding (b) (4) for material manufactured at Lonza Biologics, Inc.)
Lonza Biologics, Inc. 101 International Drive Portsmouth, NH 03801 USA FEI3001451441 DUNS 093149750	<ul style="list-style-type: none"> • Manufacturing of CX-024414 mRNA • Release and stability testing ((b) (4) for material manufactured at site) • Storage


3.2.S.2.2 Description of Manufacturing Process

The CX-024414 mRNA manufacturing process consists of (b) (4)

(b) (4)

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

(b) (4)



3.2.S.2.3 Control of Materials {CX-024414 mRNA}

3.2.S.2.3.1 Raw Materials

All raw materials used in the CX-024414 mRNA manufacturing process are obtained from qualified accredited suppliers and quality tested prior to release to assure that the

supplied raw materials meet the minimum quality requirements. No human- or animal-derived materials are used in the preparation of the CX-024414 mRNA. All non-compendial materials are supported with representative Certificates of Analysis (CoAs) or Certificates of Compliance. All non-compendial raw materials used for CX-024414 mRNA manufacture and their specifications are listed in [Table 2](#).

(b) (4)

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

(b) (4)

Reviewer's comment:

Since all non-compendial raw materials used in the DS intermediates and the DS manufacturing processes across multiple suppliers comply with their corresponding master specifications established at Moderna, re-testing of these attributes is not performed at the ModernaTX or Lonza sites. However, as part of incoming raw material quality inspection, at a minimum, the identity of each raw material is tested at each manufacturing site.



There are no custom raw materials used in the CX-024414 mRNA manufacture. Notably, all materials of biological origin, (b) (4)

3.2.S.2.3.2 Starting Materials

(b) (4)

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

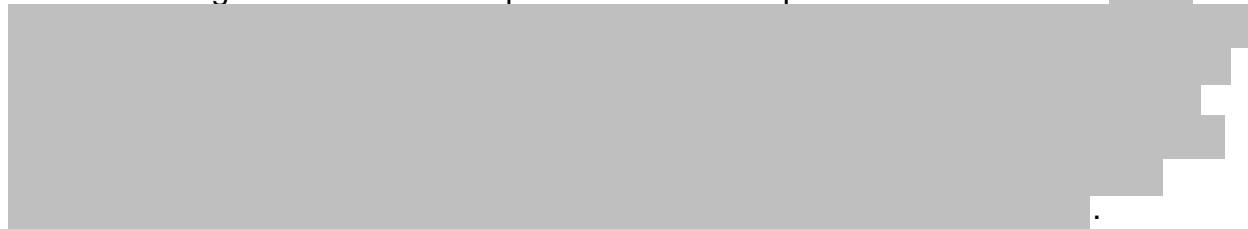
(b) (4)



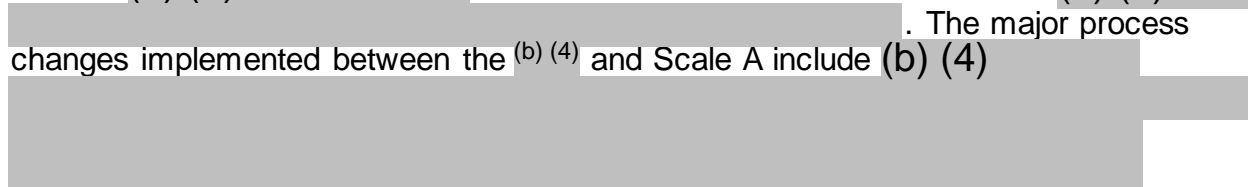
Reviewer's conclusion: The overall PPQ activities were successfully completed demonstrating that the commercial-scale manufacturing process is capable of consistently producing CX-024414 mRNA that complies with the established quality attributes.

3.2.S.2.6 Manufacturing Process Development {CX-024414 mRNA}


The manufacturing process for CX-024414 mRNA was developed progressively to support clinical development, emergency use authorization (EUA) supplies, and commercial registration. The initial process was developed in the ModernaTX (b) (4)



To support increases in manufacturing capacity, the process underwent scale-related changes denoted as Scale A (b) (4) initial Scale B (b) (4) and commercial Scale B (b) (4). The defined increases in scale included (b) (4)



. The major process changes implemented between the (b) (4) and Scale A include (b) (4)



. Subsequent unit operations remained consistent from Scale A through commercial Scale B. A summary of changes implemented into the (b) (4), Scale A, initial Scale B, and commercial Scale B manufacturing processes is provided in [Table 9](#).

(b) (4)

(b) (4)

3.2.S.2.6.3 Comparability Assessment

Process comparability was demonstrated through a) analytical comparability assessment by release, extended characterization, and stability testing and b) process performance comparability assessment by IPCs and CPPs evaluated against expected ranges or PARs. The comparability strategy for CX-024414 mRNA involved (b) (4)

performed using (b) (4) batches as shown in [Table 10](#).

Table 10. Comparability strategy for assessment of CX-024414 mRNA process

(b) (4)

The information for Phase 1/2 comparative batch analysis is provided in Master Comparability Report DPAD-PRO-0431 and demonstrated that the changes implemented during the manufacturing process development do not impact the CX-024414 mRNA quality attributes, and the products are comparable across (b) (4), Scale A, and initial Scale B.

Analytical comparability of PPQ batches manufactured at the commercial Scale B (b) (4) process was demonstrated through (b) (4). As presented in [Table 11](#), all release results conformed to both the specification and comparability acceptance criteria across all lots manufactured with (b) (4) ModernaTX and Lonza sites.

(b) (4)


(b) (4)

(b) (4)

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

3.2.S DRUG SUBSTANCE {mRNA-1273 LNP}**3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties**

(b) (4)



(b) (4)

3.2.S.2 Manufacture {mRNA-1273 LNP}**3.2.S.2.1 Manufacturer(s)**

The mRNA-1273 LNP manufacturing and testing sites are listed in [Table 43](#).

Table 43. mRNA-1273 LNP DS manufacturing and testing facilities

Facility	Responsibility
ModernaTX, Inc. One Moderna Way Norwood, MA 02062 FEI3014937058 DUNS 116912313	<ul style="list-style-type: none">• Manufacturing of mRNA-1273 LNP• In-process, release, and stability testing (excluding (b) (4) testing for mRNA-1273 LNP manufactured at Lonza Biologics, Inc.)• Storage

Facility	Responsibility
ModernaTX, Inc. (b) (4)	<ul style="list-style-type: none">• In-process, release, and stability testing (excluding (b) (4) testing for mRNA-1273 LNP manufactured at ModernaTX and Lonza; excluding (b) (4) testing for mRNA-1273 LNP manufactured at Lonza Biologics, Inc.)
Lonza Biologics, Inc. 101 International Drive Portsmouth, NH 03801 FEI3001451441 DUNS 093149750	<ul style="list-style-type: none">• Manufacturing of mRNA-1273 LNP• Release testing (b) (4) of mRNA-1273 LNP manufactured at site)• Storage
(b) (4)	(b) (4)

3.2.S.2.2 Description of Manufacturing Process {mRNA-1273 LNP}

The mRNA-1273 LNP DS manufacturing process consists of (b) (4)

The flow diagram is shown in [Figure 4](#). Each unit operation is described below.

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

(b) (4)

(b) (4)

Reviewer's comment:


The following FDA discussion points were issued with regard to ModernaTX Norwood site inspection (October 25-29, 2021):

3 (a): Stability testing has not been completed as per the approved stability protocol in that there are missed stability time points. It is critical that Moderna adheres to its approved stability protocol requirements.

In their response submitted in Amendment 125752.25 (November 23, 2021), the sponsor notified that the stability time points included in the agreed stability protocol for mRNA-1273 will be adhered to for the upcoming time points, in accordance with internal SOP's and policies. Moderna will complete a retrospective analysis of the stability program and implement additional actions, where necessary, on or before February 1, 2022.

An additional stability study was conducted to investigate compatibility of mRNA-1273 LNP bulk DS stored for (b) (4) months at the intended (b) (4) storage condition in

(b) (4)



3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

The sponsor commits to placing a minimum of (b) (4) on stability (b) (4) and testing according to the protocol QC-STAB-PTL-0133 as summarized in [Table 55](#).

Table 55. mRNA-1273 LNP (b) (4) stability protocol

(b) (4)

Reviewer's conclusion: Overall, data provided for the mRNA-1273 LNP manufacture and controls support validation of this process step and qualify the use of the Drug Substance for the mRNA-1273 Drug Product manufacture.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product {mRNA-1273}

The mRNA-1273 Drug Product (DP) is an mRNA-lipid complex suspension composed of an mRNA encapsulated in lipid nanoparticles. The mRNA-1273 DP is a sterile, preservative-free solution that contains 0.20 mg/mL CX-024414 mRNA and 3.87 mg/mL SM-102 LNPs in a buffer containing 20 mM Tris, 87 g/L sucrose, and (b) (4) mM acetate, pH 7.5. DP is supplied as a multiple-dose ready-to-use solution for intramuscular administration in 10-mL (10R) vials that are closed with a rubber stopper and aluminum crimp flip-off seal. The mRNA-1273 DP is provided in two presentations containing the same formulation per 0.5 mL dose:

- Maximum 11-dose (0.5 mL per dose) vial: The target fill volume is (b) (4) mL, which allows removal of a maximum of 11 doses (0.5 mL per dose) per vial. The label fill volume is 5.5 mL.
- Maximum 15-dose (0.5 mL per dose) vial: The target fill volume is (b) (4) mL, which allows removal of a maximum of 15 doses (0.5 mL per dose) per vial. The label fill volume is 7.5 mL.

The proprietary formulation was developed to ensure the DP stability and compatibility with the container-closure system. [Table 56](#) provides the DP composition per each vial fill volume and per dose.

Table 56. mRNA-1273 Drug Product composition

Component		Function	Unit Formula (mg/mL)	Unit Formula (mg/vial) (6.3 mL fill)	Unit Formula (mg/vial) (8.0 mL fill)	Unit Formula (mg/dose) (0.5 mL dose)
CX-024414 mRNA		mRNA that encodes for the pre-fusion stabilized Spike glycoprotein of 2019-novel Coronavirus (SARS-CoV-2)	0.20	(b) (4)		0.10
SM-102 LNP	SM-102	Lipid Nanoparticles (The individual lipids make up the Lipid Components of the SM-102 LNP)	3.87	(b) (4)		
	Cholesterol					
	DSPC					
	PEG2000-DMG					
Tromethamine (Tris)		Components in Tris buffer	0.61	(b) (4)		0.31
Tromethamine HCl (Tris-HCl)			2.35	(b) (4)		1.18
Acetic acid (b) (4)		Buffer components for Sodium Acetate buffer in LNP	0.085	(b) (4)		0.043
Sodium acetate trihydrate			0.39	(b) (4)		0.20
Sucrose		Cryoprotection	87	(b) (4)		43.5
Water for injection		Diluent	q.s. 1.0 mL	(b) (4)		q.s. 0.5 mL

DSPC - 1,2-distearoyl-sn-glycero-3-phosphocholine; q.s. - quantum sufficit; w/w - weight/weight.

3.2.P.2 Pharmaceutical Development {mRNA-1273}

3.2.P.2.3 Manufacturing Process Development

Manufacturing process development for mRNA-1273 DP (b) (4)

(b) (4) Scale A process, (b) (4)

(b) (4) ModernaTX and then scaled (b) (4) at Catalent

(Bloomington, IN). To support emergency use authorization supplies and commercial registration, the commercial Scale B process at Catalent (b) (4)

(b) (4)

3.2.P.2.3.2 Summary of Manufacturing Process Changes

Major process changes implemented between the (b) (4) Scale A relate to (b) (4)

The most significant process and presentation changes introduced from Scale A to commercial Scale B are summarized in [Table 58](#).

Table 58. Comparison of mRNA-1273 DP process and presentation changes from Scale A to Scale B process

(b) (4)

(b) (4)

The analytical methods were developed concurrently with process development. Importantly, no changes have been implemented that impact the comparison of data generated from the tests for the purpose of comparability assessment and comparison between the clinical development and registration lots. The mRNA DP analytical procedures changes are described below:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

All DP release specification changes implemented through the mRNA-1273 DP process development are summarized below:

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)





(b) (4)



3.2.P.2.3.2 Comparability Assessment {Catalent and Baxter}

For each comparison of scales, the mRNA-1273 DP analytical comparability was assessed using relevant release, stability, and extended characterization testing against pre-defined acceptance criteria. Critical process parameter (CPP) and in-process control (IPC) results were also evaluated against expected ranges for demonstration of the process performance comparability.

(b) (4)



manufacturing sites as shown in [Table 59](#). The table contains summary information for each filling line validated at Catalent and Baxter for (b) (4) mL and (b) (4) mL fill presentations and provides the associated lot nomenclature for the (b) (4) lots used in comparability studies.

(b) (4)

Scale B process comparability {Catalent and Baxter}

Process performance

(b) (4)

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(b) (4)

Reviewer's comment:

In Amendment 24 submitted on November 22, 2021, in response to FDA Information Request issued on October 12, 2021, Moderna provided release-testing results for (b) (4) DP lots manufactured at Catalent up to July 2021. All lots met the specification

(b) (4)

The following comments on (b) (4) were issued on December 21, 2021, and the sponsor response (shown in *Italic*) was received In Amendment 43 on December 28, 2021:

1. Regarding the revised proven acceptable ranges (PARs) proposed for (b) (4)

The sponsor notified that the applicable eCTD sections of the BLA have been revised as indicated in Section 2 of this submission.

2. In section 3.2.P.2.3.1.2.3 *Characterization of* (b) (4), please include:

- a. Available information to support the revised (b) (4)

- b. Available information on (b) (4)

Section 3.2.P.2.3.1.2.3 {Process Characterization} has been revised to include available information up to Mid November 2021 to support the revised

(b) (4) [REDACTED] for mRNA-1273 DP lots manufactured at Catalent and Baxter.

All CIPCs and IPCs established for the Catalent commercial process met the expected ranges provided in [Table 70](#) of the memo. IPC charts were reviewed for consistency as part of the comparability demonstration, and all results were within the control limits.

Analytical comparability

Release testing of PPQ lots was performed in accordance with the specifications established for the (b) (4) mL and (b) (4) mL fill presentations. Analytical comparability was assessed by determining the percentage of post-change values that fall in the comparability range, and comparability was demonstrated if at least 99% of the new-scale results fall within the comparability range. In addition to the lots identified in [Table 59](#), a statistical analysis included all representative lots manufactured to date to establish the expected analytical ranges, including stability and extended characterization lots.

(b) (4) **mL fill presentation {Catalent}**

(b) (4) [REDACTED]

(b) (4)

(b) (4)

(b) (4)

(b) (4) ***mL fill presentation {Catalent and Baxter}***

(b) (4)

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

All results conformed to both the specification and comparability acceptance criteria for all PPQ lots. Cumulative control charts are compiled from all historical comparability lots manufactured at Catalent and Baxter.

(b) (4)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The DP manufacturing and testing operations are performed at the sites listed in [Table 64](#).

Table 64. mRNA-1273 Drug Product manufacturers

Facility	Responsibility
Catalent Indiana, LLC 1300 S Patterson Drive Bloomington, IN 47403 FEI 3005949964 DUNS 172209277	<ul style="list-style-type: none"> • Manufacturing of drug product • In-process testing • Release testing (sterility) • Storage
Baxter Pharmaceutical Solutions, LLC 927 S. Curry Pike Bloomington, IN 47403 FEI 1000115571 DUNS 604719430	<ul style="list-style-type: none"> • Manufacturing of drug product • In-process testing • Release testing (sterility) • Storage
(b) (4)	<ul style="list-style-type: none"> • Distribution
(b) (4)	<ul style="list-style-type: none"> • Release and stability testing of drug product (bacterial endotoxin)
ModernaTX, Inc. One Moderna Way Norwood, MA 02062 FEI 3014937058 DUNS 116912313	<ul style="list-style-type: none"> • Release and stability testing (excluding bacterial endotoxin and sterility testing) • Lot Release
ModernaTX, Inc. (b) (4)	<ul style="list-style-type: none"> • Release and stability testing (excluding bacterial endotoxin and sterility testing)

Facility	Responsibility
(b) (4)	<ul style="list-style-type: none"> Stability testing of drug product (Container Closure Integrity Testing)

3.2.P.3.2 Batch Formula

Representative batch size, composition, and formula for the DP manufacture are provided in [Table 65](#) and [Table 66](#), respectively.

Table 65. Target batch size for the DP manufactured at Baxter and Catalent

Product (Strength)	Site
0.20 mg/mL mRNA	Baxter
0.20 mg/mL mRNA	Catalent

(b) (4)

Table 66. Batch composition for DP batches manufactured at Baxter and Catalent

Component
CX-024414 (mRNA)
SM-102 Lipid Nanoparticle
Tromethamine (Tris)
(b) (4)
Tromethamine (Tris-HCl) (non-compendial)
(b) (4)
Acetic Acid
(b) (4)
Sodium Acetate Trihydrate
(b) (4)
Sucrose (b) (4)
Water for Injection (b) (4)

(b) (4)

3.2.P.3.3 Description of Manufacturing Process

The DP manufacturing processes at Catalent and Baxter are very similar and consist of the same unit operations, (b) (4)

(b) (4) sterile filtration, filling, stoppering, and capping, visual inspection, labeling and packing, freezing and storage. A flow diagram for the DP manufacturing process and in-process controls performed at Catalent is shown in [Figure 5](#). Each unit operation is described below. The DP process parameters and in-process controls are detailed in section 3.2.P.3.4 *Controls of Critical Steps and Intermediates* and reflect parameters differences for the maximum 11-dose presentation and the maximum 15-dose presentation, and differences in the IPC tests performed to control the DP manufacture at Catalent and Baxter.

(b) (4)

Figure 5. DP process flow diagram {Catalent}



The unit operations and in-process controls (IPC) are defined for Catalent. For the Baxter process,

(b) (4)

. The details of IPCs performed for the Catalent and Baxter processes are provided in sections 3.2.P.3.4 *Controls of Critical Steps and Intermediates* for {Catalent} and {Baxter}.


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(b) (4)



Sterile filtration

Sterile filtration is performed (b) (4)



Filling, stoppering, and capping

The sterile filtered (b) (4) DP (b) (4)



Visual inspection, label, and pack

All vials undergo 100% visual inspection by qualified operators for container defects, closure defects and product defects. At Catalent, vial inspection is performed either through a manual, semi-automated, or fully automated process. The automated visual inspection process can be combined with the manual or semi-automated visual inspection process. At Baxter, visual inspection is (b) (4) Vials that fail visual inspection are segregated from the batch as labeled visual inspection rejects.

Vial labels are printed, or laser coded in-line with lot number and expiry dates and are applied to the inspected vials. Inspected and labeled vials are then packaged 10 per carton along with a package insert. The carton is sealed with glue or a tamper evident

seal and is then printed, or laser coded in-line with: Global Trade Identification Number (GTIN), Lot, Expiry Date, Serial Number and 2D GS1 DataMatrix. Twelve cartons are then placed into a shipping case.

Vial conditioning freeze and storage

The packaged DP vials are (b) (4)

freezer at the final storage at -20 °C.

Reprocessing

Reprocessing is not performed for any DP process step. However, validation of a (b) (4) step will be completed under Process Validation Protocol VPPQ-256-100-00011-P. Upon the study completion, the final (b) (4) Validation Report VPPQ-256-100-00011-S will be submitted as a post-approval supplement.

(b) (4) step is not to be implemented at Baxter.

Reviewer's comment:

The following comment on description of manufacturing process was issued on December 21, 2021, and Moderna's response (shown in *Italic*) was received in Amendment 43 on December 28, 2021:

- In section 3.2.P.3.3 *Description of Manufacturing Process and Process Controls {Baxter}*, you indicated that mRNA-1273 DP is manufactured in two presentations, (b) (4) mL and (b) (4) mL fill volume, which contradicts the information provided for Baxter manufacturing process across the BLA submission. Please clarify.

In their response, Moderna stated that the mRNA-1273 DP 7.5 mL presentation with an (b) (4) mL fill volume is the only presentation currently qualified for manufacture at Baxter. The eCTD section 3.2.P.3.3 {Baxter} has been revised to reference only the mRNA-1273 DP (b) (4) mL presentation.

3.2.P.3.4 Controls of Critical Steps and Intermediates

All CQAs defined for the manufacture of commercial mRNA-1273 DP are the same as the release specifications (provided in [Table 73](#) below).

Critical Process Parameters {Catalent and Baxter}

The CPPs and their PARs established for the commercial Scale B manufacturing process at Catalent and Baxter are summarized in [Table 67](#).

Table 67. Critical process parameters for the Scale B manufacturing process at Catalent and Baxter

(b) (4)

CPPs characterization studies

Proven acceptable ranges for CPPs were characterized using a science- and risk-based approach that leveraged current process understanding and historical knowledge from platform unit operations for similar products.


(b) (4)

The integrity of the vials was maintained for all (b) (4) tested at -20°C storage conditions. Based on crimp setting and container-closure integrity studies conducted for each site/fill line, the PARs for the stoppering and capping operations were defined as shown in [Table 67](#).


Characterization of Cumulative Process Duration

Cumulative Process Duration (CPD) and Time Out of Refrigeration (TOR) are defined as CPPs for the manufacture of mRNA-1273 DP. CPD is the total time in refrigeration (2 to 8°C) and TOR (20 to 25°C) required for the process. The limits for cumulative TOR (20 to 25°C) are established to control out of refrigeration unit operations and to mitigate the risk of failing the DP specifications. The classification of these process parameters as critical is based on development hold-time studies and manufacturing experience with GMP batches at Moderna's Norwood facility and at the Catalent facilities. The biophysical and chemical quality attributes of mRNA-1273 DP, particularly mRNA purity (b) (4), are potentially impacted by processing duration and temperature.


(b) (4)




(b) (4)



(b) (4)



(b) (4)



Process Parameters {Catalent and Baxter}

The Scale B process parameters (PP) and their acceptable ranges/acceptance criteria are summarized for each unit operation and operation variables performed at Catalent and Baxter and provided in [Table 69](#).

Table 69. Summary of process parameters for Scale B manufacturing process at

(b) (4)

(b) (4)

In-process Controls {Catalent and Baxter}

The in-process controls, their acceptance criteria and criticality are presented in [Table 70](#) for Catalent and Baxter.

Table 70. In-process controls for Scale B DP manufacturing process at Catalent and Baxter

(b) (4)


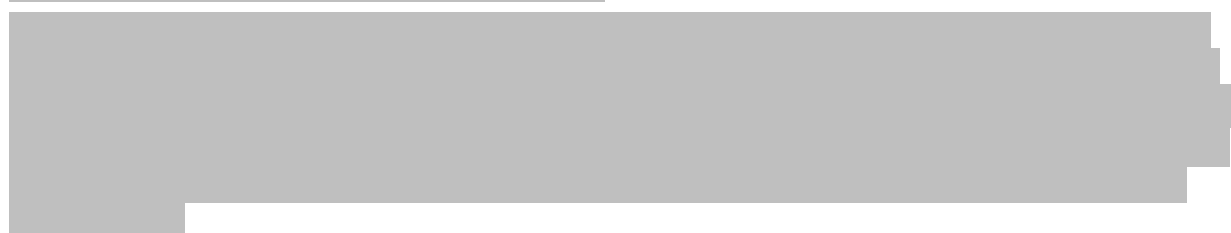
(b) (4)

(b) (4)

3.2.P.3.5 Scale B Process Validation and/or Evaluation {Catalent}


(b) (4)

(b) (4)

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Scale B Process Validation and/or Evaluation {Baxter}

(b) (4)

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3.2.P.4 Control of Excipients

All excipients used for the mRNA-1273 DP formulation are the (b) (4). The full list of excipients, including their function and grade, are provided in [Table 71](#).

Table 71. mRNA-1273 DP excipients

Excipient	Function	Grade
Sucrose	Cryoprotectant	(b) (4)
Tris(hydroxymethyl)aminomethane (Tris)	Buffering agent	
Tris(hydroxymethyl)aminomethane hydrochloride (Tris-HCl)	Buffering agent	
Water for injection	Diluent	

All excipients are received from qualified vendors. The compendial excipients are tested and released in compliance with current compendia and supported with the CoAs and/or release testing. Of note, additional release testing is performed for (b) (4)

The (b) (4) non-compendial excipient used in the manufacture of the DP (b) (4)

(b) (4)

There are no novel excipients or excipients of human or animal origin in mRNA-1273 DP.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

The specifications for mRNA-1273 DP at release and throughout its shelf life are provided in [Table 73](#).

Table 73. Specifications for mRNA-1273 DP

Test	Method	Acceptance Criteria
Appearance	Visual	White to off-white dispersion. May contain visible, white or translucent product-related particulates
Identity	(b) (4)	(b) (4)
Total RNA Content	(b) (4)	(b) (4)
Purity Product-Related Impurities	(b) (4)	(b) (4)
Purity Product-Related Impurities	(b) (4)	(b) (4)
%RNA (b) (4)	(b) (4)	(b) (4)
Particle Size	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
SM-102	(b) (4)	(b) (4)
Cholesterol	(b) (4)	(b) (4)
DSPC	(b) (4)	(b) (4)
PEG2000-DMG	(b) (4)	(b) (4)
SM-102	(b) (4)	(b) (4)
Cholesterol	(b) (4)	(b) (4)
DSPC	(b) (4)	(b) (4)
PEG2000-DMG	(b) (4)	(b) (4)
Lipid Impurity	(b) (4)	Individual Impurities: (b) (4) Total impurities: (b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
pH	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Container Content ^a	(b) (4)	Maximum 11 Dose (0.5 mL per dose) Presentation Syringe/Needle: Option A: 11 doses of 0.5 mL from 1 vial Option B: 10 doses of 0.5 mL from 1 vial
Container Content ^a	(b) (4)	Maximum 15 Dose (0.5 mL per dose) Presentation Syringe/Needle: Option A: 15 doses of 0.5 mL from 1 vial Option B: 13 doses of 0.5 mL from 1 vial
Bacterial Endotoxins	(b) (4)	(b) (4)
Sterility	(b) (4)	Release No growth

Test	Method	Acceptance Criteria
Container-Closure Integrity (Stability only)	(b) (4)	End of Shelf Life Pass

^a Container content is measured based on SOP-1229

Option A: (b) (4)

(b) (4)

Option B: (b) (4)

3.2.P.5.2 Justification of Specification(s)

All specifications needed for the assessment of CQAs of commercial mRNA-1273 DP were justified based on product manufacturing history and scientific understanding. Product attribute results were gathered for more than (b) (4) manufacturing lots used to supply clinical trial Phases 1, 2, and 3 and additional development, PPQ, and EUA lots. Statistical analysis for the setting of specifications for each quality attribute (with numerical results) includes the following elements:

(b) (4)

The specifications have been revised during the DP manufacturing process development as described in section 3.2.P.2.3.2 *Summary of Manufacturing Process Changes* of this memo. A summary of the justification of specifications related to the purpose of each test is provided in [Table 74](#). As explained above, the proposed acceptance limit for each release and stability test in [Table 74](#) is based on analysis of results from clinical lots (manufactured at various scales) and EUA lots (manufactured at commercial scale) and as such are reflective of process capability (i.e., statistical analysis of CQA results provided in the BLA) and clinical experience (i.e., effectiveness and safety data from clinical lots).

Table 74. Justification of specifications for mRNA-1273 DP

Test	Acceptance Criteria	Justification ^(a)
Appearance – Visual	White to off-white dispersion. May contain visible white or translucent product-related particulates	Based on the currently available release and stability data.

Test	Acceptance Criteria	Justification ^(a)
Identity – (b) (4)	(b) (4)	To specifically confirm the identity of mRNA-1273 DP ^{(b) (4)}
Total RNA Content – (b) (4)	(b) (4)	(b) (4)
Purity Product Related Impurities – (b) (4)	(b) (4)	(b) (4)
	(b) (4)	
%RNA (b) (4)	(b) (4)	(b) (4)
Particle Size – (b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Lipid identification		
SM-102 – (b) (4)	(b) (4)	To specifically confirm the identity of mRNA-1273 DP. The presence of 4 components which compose the LNP are confirmed to establish identity. The method specifically identifies the expected LNP lipids and potential impurities.
Cholesterol (b) (4)	(b) (4)	
DSPC – (b) (4)	(b) (4)	
PEG2000-DMG – (b) (4)	(b) (4)	
Lipid Content (mg/mL)		
SM102 – (b) (4)	(b) (4)	The acceptance criteria have been defined based on the ability of the method to accurately quantify each Lipid independently.
Cholesterol – (b) (4)	(b) (4)	
DSPC – (b) (4)	(b) (4)	
PEG2000-DMG – (b) (4)	(b) (4)	
Lipid Impurity – (b) (4)	Individual Impurities: (b) (4) (b) (4) Total impurities: (b) (4)	The acceptance criteria have been defined based on current process and method capabilities and (b) (4) guidelines.
(b) (4)		
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
pH (b) (4)	(b) (4)	The pH range has been defined as (b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Test	Acceptance Criteria	Justification ^(a)
Container Content SOP-1229	Container Content ensures that each container of the product contains sufficient volume of solution to allow successful withdrawal of the labeled quantity / number of doses	Based on current fill volume process capabilities to allow for delivery of the target volume.
Bacterial Endotoxins – (b) (4)	(b) (4)	Based on patient safety and the requirements (b) (4)
Sterility – (b) (4) Container Closure Integrity – (b) (4)	No growth	According to (b) (4) to ensure a sterile final product. mRNA-1273 DP is expected to be free of microbial and fungal contamination based on the manufacturing process and controls in place.

EOSL - end of shelf life; (b) (4)

^a Acceptance criteria are based on process capability (i.e., statistical analysis of CQA results) and effectiveness and safety data from clinical lots.

Reviewer's comments:

The following comments were issued on December 9, 2021, with regard to the justification of specifications for the mRNA-1273 DP. Each comment is followed by a summary of Moderna's responses (*in Italics*) submitted in the SNT 125752/41 on December 22, 2021.

To support the DP release and stability acceptance limits, please include the following information in section 3.2.P.5.6 *Justification of Specifications*:

- In several IND communications including the CBER pre-BLA written responses from July 7, 2021, we had requested that a (b) (4) be performed for DP release and stability monitoring. In the absence of such a (b) (4) please provide available (b) (4) results performed on DS or DP lots as a characterization test using your qualified (b) (4). Please provide (b) (4) results for all DS or DP lots for which (b) (4) data are available at release or as part of stability studies together with data for RNA content (by (b) (4)), and RNA purity and product-related impurities (by (b) (4)) from corresponding lots and time points.
The combined release and extended characterization results (including (b) (4) RNA content, RNA purity and product-related impurities data) are provided for a total of (b) (4) development, clinical, and Scale B mRNA-1273 DP lots. The (b) (4) assay will continue to be included in the demonstration of analytical comparability when new scales, sites and process improvements are introduced for mRNA-1273 LNP to provide additional assurance of product consistency as part of post approval comparability.
- Please include a description of the (b) (4) method (or any other (b) (4) test method used) and a summary of results for the DS in section 3.2.S.2.6 *Manufacturing Process Development {Comparability Scale A to Scale B}*

and/or the DP in section 3.2.P.2 *Pharmaceutical Development {Comparability}*, as applicable.

A description of the (b) (4) method and a summary of results for the mRNA-1273 LNP lots has been added in CTD Section 3.2.S.2.6.3.3.6 {mRNA-1273 LNP, Comparability}. In the current memo, the (b) (4) method description is added into section 3.2.S.3 Characterization {mRNA-1273 LNP}.

- Please provide a justification for not performing a (b) (4) test as a quality release and stability test in section 3.2.P.5.6 *Justification of Specifications*.

CTD Section 3.2.P.5.6 has been revised to include the justification for not performing a (b) (4) test based on the rationale below:

- (b) (4)

- Regarding the release and stability acceptance limit justifications and supportive data for RNA content (release and end of shelf life: (b) (4) and RNA purity (release: (b) (4) we acknowledge the analytical data provided for (b) (4) DP lots. In addition, please include:

- The clinical data from dose-ranging studies and effective delivery dose (EDD) ranges in Phase 3 studies, which support the proposed lower and upper limits for RNA content and lower limit for RNA purity.

*(b) (4) DP lots, (b) (4) with average (b) (4) purity for the (b) (4) lots combined, were administered in two nominal doses of 50 µg and 100 µg in Phase 2 clinical trial. The immunogenicity results obtained in the studies support consistency of immune response for an effective dose of (b) (4) (= (b) (4) purity * 50 µg nominal dose) compared with (b) (4) (100 µg nominal dose). In Phase 3 clinical trial, median purity of DP lots has been (b) (4), ranging from (b) (4) which translates to an Effective Delivered Dose range of (b) (4) for the nominal dose level 100 µg. The purity of commercial DP doses will be consistent with the Phase 3 trial doses.*

- The data and statistical analyses used to derive the (b) (4) end of shelf-life limit for RNA purity.

To ensure a minimum Purity of (b) (4) through shelf life, a Minimum Release Limit for Purity will be set at (b) (4). This internal limit allows for up to 8 months of storage at -20°C, plus up to 1 month of storage at (b) (4) plus up to 24 hours of use

at 25°C. The median purity estimated from simulation study for (b) (4) commercial doses is projected at (b) (4) with lower quartile (b) (4) and upper quartile (b) (4)

- Please provide information on the calculations used to estimate RNA purity release limits based on DP degradation curves, estimated degradation during storage and handling, and known assay variability. In addition, please provide report DPAD-00881 *Justification of Specifications for mRNA-1273 Purity Minimum Release Limit* submitted to EUA 27073 and updated degradation curve data for DP lots stored at the intended storage conditions.


Missing report DPAD-00881 is included as an attachment to Section 3.2.P.5.6. This report provides the calculations used to derive the RNA minimum purity release limit based on the minimum purity requirement throughout shelf life, the estimated degradation rates during storage and handling, and the estimated assay variability.

Reviewer's conclusion: The acceptance limits proposed for the release and stability testing of the registered DP lots are acceptable. All sponsor's responses are adequate.

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

All analytical procedures employed for release and stability testing of mRNA-1273 LNP DS lots are applicable to the mRNA-1273 DP testing. An additional (b) (4) is performed to confirm the functional activity of the mRNA-1273 extracted from the DP sample. The analytical procedure description and method validation results are detailed below.

(b) (4)



(b) (4)

3.2.P.5.4 Batch Analysis

Batch analysis data generated for the mRNA-1273 DP include results from a total of (b) (4) development lots used for Phase 1 and Phase 2 studies, (b) (4) clinical lots used for Phase 3 studies, and (b) (4) commercial Scale B lots. Comparative analyses were performed for the (b) (4) mL and (b) (4) mL fill presentations PPQ lots manufactured at Catalent and Baxter as detailed in section 3.2.P.2.3.2 *Comparability assessment* of this memo. The CoAs for all (b) (4) lots were included in the BLA. The release results for all lots met the specifications at the time of release, demonstrating the capabilities of the manufacturing process for consistent production of DP.

3.2.P.5.5 Characterization of Impurities

The impurity profile of the final DP is the same as that of the mRNA-1273 LNP DS because there are no new impurities anticipated to form or be introduced during DP manufacture. The (b) (4) mRNA-1273 LNP that (b) (4) DP manufacturing process does not impact nor alter mRNA or LNP degradation pathways.

3.2.P.6 Reference Standards or Materials {mRNA-1273}

The reference materials used to support testing of the mRNA-1273 DP are CX-024414 mRNA, (b) (4), and mRNA-1273 LNP DS and are described in the sections of the memo covering these (b) (4) and the DS.

3.2.P.7 Container-closure System {mRNA-1273}

The commercial multiple dose mRNA-1273 DP lots are supplied in a primary container-closure system consisting of three components (vial, stopper, and seal) configured as shown in [Table 75](#). The (b) (4) DP is dispensed into vials and closed with a 20-mm stopper and 20-mm aluminum seal (b) (4). Vials are then packaged in a secondary carton containing a total of 10 DP vials per carton. Each carton is then placed into a case containing a total of 12 cartons.

Table 75. Container-closure configurations for multiple dose mRNA-1273 DP vials

Container Closure Component	Description	Abbreviation
Vial	(b) (4) 10R clear Type 1 borosilicate glass vials	(b) (4)
Vial	(b) (4) 10-mL (b) (4) vial, RTU, sterile	
Vial	(b) (4) 10R clear Type 1 equivalent alkali aluminosilicate glass vial	
Vial	(b) (4) 10R clear Type 1 borosilicate glass vial	

Container Closure Component	Description	Abbreviation
Stopper	20 mm (b) (4) (b) (4) stopper	(b) (4)
Stopper	20 mm (b) (4) (b) (4) stopper	(b) (4)
Seal	(b) (4) 20 mm (b) (4) aluminum seal with flip-off plastic cap	20 mm aluminum seal

Stopper functionality testing

Data generated by the manufacturers support the use of the 20 mm (b) (4) stoppers (b) (4) as closure for multiple-dose product vials. Stopper functionality testing was performed on both stoppers in accordance with (b) (4) and includes evaluation of (b) (4). To assess the maximum (b) (4) allowed for the multiple-dose DP vial presentations, the container/closure system is (b) (4)

The stopper functionality testing showed that (b) (4) can be performed without impacting the quality of the product and functional performance of the stoppers.

Microbiological growth promotion characteristics

The final mRNA-1273 DP does not include a preservative since the integrity of LNP-based products are incompatible with common preservatives. A microbial challenge study was conducted to examine the ability of the multiple-dose DP vials to promote or hinder microbial growth over a timeframe corresponding to the proposed "In-Use Time" for the punctured vial. The study involved (b) (4)

Based on the results obtained, the proposed in-use time for the mRNA-1273 DP held at 20 - 25°C is ≤ 12 hours.

Extractables and leachables studies

A safety risk assessment for the DP primary closure systems was performed for each product-contact component of the container closure (vials and stoppers) based on material characterization studies performed as worst-case extraction profiles. Worst case estimates of the analytes (in µg) per dose (0.5 mL) of the DP were calculated based on extractables data provided for each material of construct by the vendor. Toxicology assessments were performed using worst-case estimates of Total Daily Intake (TDI). Because the DP is intended to be administered twice with an inter-injection interval of 1 month (30 days), worst-case estimates of TDI were equated to the estimates of analytes per dose. The Safety Concern Thresholds (SCTs) was assigned for each identified extractable based on permitted daily exposures (PDEs) as regulated by ICH Q3D(R1) (2019) guidance documents for parenteral routes of administration.

The obtained results demonstrated that all elemental extractables are well below the established PDEs for all tested materials of construction. No one analyte exceeded the SCT levels outlined in these assessments.

The potential compounds of container closures were evaluated for mutagenic potential using (b) (4) methodologies. The TDI per dose levels were limited to the SCT for all analytes that indicated them as non-mutagenic.

A simulated leachables study was conducted using (b) (4)

Although the leachables studies were simulated and were performed for (b) (4) the overall simulated leachables study and extractable study results are acceptable and support the use of the container closure systems.

Reviewer's Conclusion: Based on the extractables and leachables study results, the DP long-term storage at -20°C, up to 30 days at 2 – 8°C, and up to 24 hours storage at 25°C do not pose a risk of leachables.

3.2.P.8 Stability {mRNA-1273}

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

An initial shelf life of 9 months is proposed for the mRNA-1273 DP lots stored in the commercial container-closure system at the recommended long-term storage condition of -25°C to -15°C (-20°C). The proposed shelf life includes up to 1 month (30 days) of storage at 2 – 8°C (5°C) and up to 24 hours at room temperature (25°C) to support administration of the vaccine at the point of care site.

The shelf life is justified based on numerous characterization studies performed on development lots and lots manufactured at full scale under EUA. Summary information for a total of (b) (4) clinical and (b) (4) registration stability lots, including intended study temperature and duration, and data availability, is provided in **Table 76**.

Table 76. Summary of stability studies for clinical and registration mRNA-1273 DP lots

Lot	Purpose	Manufacturing Site	Lot Size (# vials)	Fill Volume (mL)	Container Closure	Temperature	Duration	Available Data
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(b) (4)

		Manufacturing	Lot Size	Fill Volume	Container			Available
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(b) (4)

The stability-indicating quality attributes include all specifications defined for DP release testing, except for identity, (b) (4) , and container content testing. However, the primary determinant of shelf life is mRNA purity. The product expiry is established using the degradation rates estimated as detailed in the Model Shelf-life Study described

below. The purity stability profiles are consistent and predictable for all vial fill volumes, container types, manufacturing scales, and individual lots assessed to-date.

Certain acceptance criteria ranges were revised during the process development and based on increased process knowledge. Therefore, stability-study results referred in this section were evaluated against the specification effective at the time of testing.

Clinical Stability Summary

For clinical lots listed in **Table 76**, stability data are provided as follows:

- Stability (b) (4) [redacted] time points were within the acceptance ranges; results for the (b) (4) timepoint were not provided. Results from lot (b) (4) are available for up to (b) (4), and all meet the defined specifications.
- Long-term stability at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$: all results from lots (b) (4) [redacted] measured at 1M, 2M, 3M, 4.5M, 6M, 9M, (b) (4) time points were within the acceptance ranges with the exception of missing data for RNA content at 6M, 9M, (b) (4), and lipid content and lipid impurities at 6M and 9M time points. Results from lot (b) (4) are available for up to 3M and met specifications. All results from lot (b) (4) are supportive for up to 3M of storage with additional interim purity data submitted for the 4.5M time point.
- Accelerated stability at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$: all results from all clinical lots met the acceptance criteria for all attributes tested at 1M, (b) (4) of storage with exception of RNA purity, (b) (4)
- Stability at room temperature (25°C): the results met all specifications for (b) (4) clinical lots stored at room temperature up to (b) (4) hours; however, (b) (4) [redacted]

Overall, available DP clinical data support long-term stability at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for up to (b) (4) months, accelerated stability at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for up to 1 month and in-use stability 25°C (b) (4) for up to 24 hours.

Commercial Stability Summary

The commercial Scale B PPQ lots placed on stability were manufactured at the (b) (4) mL and (b) (4) mL fill presentations at Catalent and Baxter and were filled into (b) (4) borosilicate glass vials, (b) (4) aluminosilicate glass vials, and (b) (4) vials. All registration lots have been placed in long-term stability studies at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and accelerated stability studies at $5 \pm 3^{\circ}\text{C}$ within less than one year in response to pandemic needs. In these circumstances, 6 different protocols for long-term storage and three protocols for accelerated storage have been employed to monitor the stability of (b) (4) commercial DP lots to support the intended shelf life. Some of these studies had not attained at least 3 timepoints when the model for shelf life was established.

Reviewer's comment:

With regard to ModernaTX Norwood site inspection (October 25-29, 2021), FDA issued the discussion point (3c) to recommend the implementation of the same stability protocol for the DS and DP.

In the response submitted in Amendment 25 on November 23, 2021, the sponsor committed to standardize the Stability Protocols across the Drug Substance and Drug Product commercial stability studies.

The availability of stability results for the registration DP lots is reflected in summary [Table 76](#). To date, long-term stability for up to 6 months of storage at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ was demonstrated for the DP lots filled in the Type 1 borosilicate glass vials, (b) (4) (lot (b) (4) , aluminosilicate glass vials, (b) (4) (lots (b) (4) , and (b) (4) vials, (b) (4) (lot (b) (4) . All test results were within specifications for all designated lots.

All results available for accelerated DP stability are supportive for up to 1 month of storage at $5 \pm 3^{\circ}\text{C}$ and for up to 24 hours at 25°C (b) (4) to enable administration of the vaccine at the point-of-care site.

Reviewer's conclusion: Overall, available DP long-term stability data for clinical and commercial lots support the proposed 9-month storage duration, which can include 8 months at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$, followed by 1 month at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and in-use stability at 25°C (b) (4) for up to 24 hours.

Model Shelf-life Study

A stability-modeling study was performed to support assumptions for modeling mRNA purity through storage or use at expected conditions. Degradation rates for DP purity were estimated for (b) (4) different storage temperatures, (b) (4) based on stability results available as of April 12, 2021. The rates along with their 95% confidence intervals are summarized in [Table 77](#). Additional results provided in the Degradation Rate and Variance Estimates Report DPAD-00880 for (b) (4) Scale B mRNA-1273 DP lots showed that the degradation rate depends significantly on temperature and ranges from (b) (4) (b) (4) (b) (4) (b) (4)

(b) (4)

Using these rates, the shelf life of the mRNA-1273 DP was estimated as the point where the lower 95% prediction interval for %purity crosses the %purity lower

specification limit of (b) (4). The totality of evidence supports a minimum (b) (4) purity shelf-life specification. The purity stability profiles available for clinical and registration DP lots are consistent and predictable for all vial fill volumes, container types, manufacturing scales, and individual lots assessed to-date.

Photostability

Photostability studies were performed on (b) (4)

(b) (4)

Based on the study results, a “Protect from Light” precautionary statement was included on the DP label.

Freeze/Thaw Stability Study

Freeze/thaw stability studies were performed using representative DP lots at (b) (4) mg/mL mRNA (lot (b) (4)) and (b) (4) mg/mL mRNA (lot (b) (4)). DP samples were subjected to (b) (4)

(b) (4)

Regardless of the freeze/thaw data, a precautionary statement in the DP label recommends not freezing the DP once thawed.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Moderna commits to placing a minimum (b) (4) DP (b) (4) on stability (b) (4) and test (b) (4) according to the protocol QC-STAB-PTL-0132 as summarized below.

Table 78 mRNA-1273 DP (b) (4) stability protocol

(b) (4)

Reviewer’s conclusion and recommendation: The CMC information submitted in the BLA 125752 and multiple BLA amendments provides data indicating that the mRNA-1273 DP manufacturing process and controls at the Catalent and Baxter facilities is well

characterized and qualified and the lots manufactured on different filling lines at the (b) (4) mL and (b) (4) mL fill presentations are comparable.

I recommend approval of this BLA.