TABLE OF CONTENTS

2.3.S DRUG SUBSTANCE [mRNA-1273.529 LNP] 3
2.3.S.1 General Information 3
2.3.S.1.1 Nomenclature 3
2.3.S.1.2 Structure 3
2.3.S.1.3 General Properties 3
2.3.S.2 Manufacture 4
2.3.S.2.1 Manufacturer(s) 4
2.3.S.2.2 Description of Manufacturing Process and Process Controls 5
2.3.S.2.3 Control of Materials 7
2.3.S.2.4 Controls of Critical Steps and Intermediates 9
2.3.S.2.5 Process Validation and/or Evaluation 10
2.3.S.2.6 Manufacturing Process Development 11
2.3.S.3 Characterisation 11
2.3.S.3.1 Elucidation of Structure and Other Characteristics 11
2.3.S.3.2 Impurities 13
2.3.S.4 Control of the Drug Substance 13
2.3.S.4.1 Specification 13
2.3.S.4.2 Analytical Procedures 14
2.3.S.4.3 Validation of Analytical Procedures 14
2.3.S.4.4 Batch Analyses 15
2.3.S.4.5 Justification of Specification 15
2.3.S.5 Reference Standards or Materials 16
2.3.S.6 Container Closure System 16
2.3.S.7 Stability 16
2.3.S.7.1 Stability Summary and Conclusions 16
2.3.S.7.2 Post-Approval Stability Protocol and Stability Commitment 20
2.3.S.7.3 Stability Data 20

LIST OF TABLES

Table 1: General Properties of mRNA1273.529 Lipid Nanoparticle - B 3
Table 2: European Facilities and Responsibilities for Manufacture and Testing of the mRNA-1273 LNPs-B 4
Table 3: List of Testing Exceptions 4
Table 4: US Facilities and Responsibilities for Manufacture and Testing of the mRNA 1273 LNPs – B 5
Table 5: mRNA-1273 Lipid Nanoparticles (LNPs) Utilizing Moderna Platform 5
Table 6: Critical Process Parameters 9
Table 7: Elucidation of Structure Summary for mRNA 1273 Lipid Nanoparticle 12
Table 8: Specification for mRNA-1273 LNPs - B 13
Table 9: Critical Quality Attribute Assessment for mRNA-1273 LNP 15
Table 10: Additional mRNA-1273 LNP Stability Modelling Lots 19
Table 11: mRNA-1273 LNP Registration Stability Program Lots 19

LIST OF FIGURES

Figure 1: mRNA-1273 LNPs-B Process Flow Diagram 7
Figure 2: Raw Material Control Process Overview 8

2.3.S DRUG SUBSTANCE [mRNA-1273.529 LNP]

2.3.S.1 General Information

This product is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion containing CX-031302 mRNA that encodes for the prefusion stabilized Spike protein of the SARS-CoV-2 B.1.1.529 Omicron Variant. The LNP is composed of the following four lipid components:

- Cholesterol,
- SM102 (a custom-manufactured ionizable lipid),
- DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), and
- PEG2000-DMG (1monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000).

2.3.S.1.1 Nomenclature

International Non-proprietary Name (INN):	N/A
Proprietary name:	N/A
Company product codes:	mRNA-1273.529
Drug Product name:	mRNA-1273
Synonymous name:	mRNA-1273.529 Lipid Nanoparticle (LNP), mRNA-1273.529 LNP - B

2.3.S.1.2 Structure

mRNA-1273.529 Lipid Nanoparticle (LNP) - CCI [redacted], which protects the mRNA from nucleolytic degradation in biological fluids. Additionally, encapsulation of the RNA in a lipid particle of appropriate composition is critical to cellular uptake of the nanoparticle, endosomal escape, and ultimately productive cytosolic display of the mRNA such that protein translation may occur. CCI [redacted]

2.3.S.1.3 General Properties

The general properties of mRNA-1273.529 Lipid Nanoparticle (LNP) – B are summarized in Table 1.

Table 1: General Properties of mRNA1273.529 Lipid Nanoparticle - B

Description	mRNA-1273.529 LNP - B has a CCI [redacted]
Appearance	White to off-white LNP dispersion. The mRNA-1273.529 LNP – B may contain visible, white or translucent product-related particulates.
pH	CCI [redacted]

Osmolality	CCI
Density	CCI
Particle Size	CCI

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer(s)

The name and address for the manufacturing and testing facilities of mRNA-1273 Lipid Nanoparticle (LNP)s-B are listed in Table 2, Table 3 and Table 4.

.

Table 2: European Facilities and Responsibilities for Manufacture and Testing of the mRNA-1273 LNPs-B

Facility	Address	Responsibility
CCI		• Manufacture of mRNA-1273 LNPs-B (200 g Scale) • Quality control testing (excluding identity testing)
		• Quality control testing for identity
		• Quality control testing
		• Manufacture of mRNA-1273 LNPs-B (200 g Scale) • Quality control testing (except identity testing)
		• Quality control testing for identity

Table 3: List of Testing Exceptions

Facility	Address	• Responsibility
CCI		• Bacterial endotoxin testing

Table 4: US Facilities and Responsibilities for Manufacture and Testing of the mRNA 1273 LNPs – B

Facility	Address	Responsibility
CCI [redacted]		• Manufacture of mRNA-1273 LNPs-B (200g Scale) • Quality control testing (excluding bacterial endotoxin testing) • Storage
		• Quality control testing (excluding bacterial endotoxin)
		• Bacterial endotoxin testing

2.3.S.2.2 Description of Manufacturing Process and Process Controls

For mRNA-1273, Moderna has established and qualified a global manufacturing network and has demonstrated analytical comparability in enabling process scale-up and the introduction of new manufacturing sites, and new manufacturing equipment lines. Moderna's manufacturing history, knowledge of the risk of sequence changes to process performance and product quality, and rigorous suite of analytical methods to detect functionally significant changes in product attributes justify a streamlined platform approach to CMC development.

It is this established vaccine platform that Moderna has utilized to develop, manufacture, and scale-up mRNA-1273 variant vaccines in response to the emergence of SARS-CoV-2 variants of concern. The following section defines the manufacturing process for mRNA-1273 LNPs noted in Table 5. The manufacturing process and control strategies for all mRNA-1273 LNPs manufactured using the platform approach detailed below are identical, unless specifically noted. As new SARS-CoV-2 variants vaccines are developed utilizing the platform approach, the information in the Table 5 will be updated.

Table 5: mRNA-1273 Lipid Nanoparticles (LNPs) Utilizing Moderna Platform

mRNA-1273 LNP Name	COVID Variant
mRNA-1273 LNP	Prototype (Wuhan-Hu-1)
mRNA-1273 LNP-B (Process B)	Prototype (Wuhan-Hu-1)
mRNA-1273.529 LNP -B (Process B)	Omicron (B.1.1.529)

mRNA-1273 (LNPs) are white to off-white LNP dispersions CCI [redacted]. The mRNA-1273 LNP is intended for further processing into mRNA-1273 Drug Product.

Note: the manufacturing process and process controls described in this Section are applicable to any CCI [redacted] (also referred to as mRNA-1273 LNP-B), regardless of the mRNA-1273 RNA sequence.

Narrative Description of the Manufacturing Process

The purpose of the manufacturing process CCI [redacted], which provides biological functionality including enabling cellular uptake and endosomal escape, and to add components to stabilize the dispersion of mRNA-loaded LNPs.

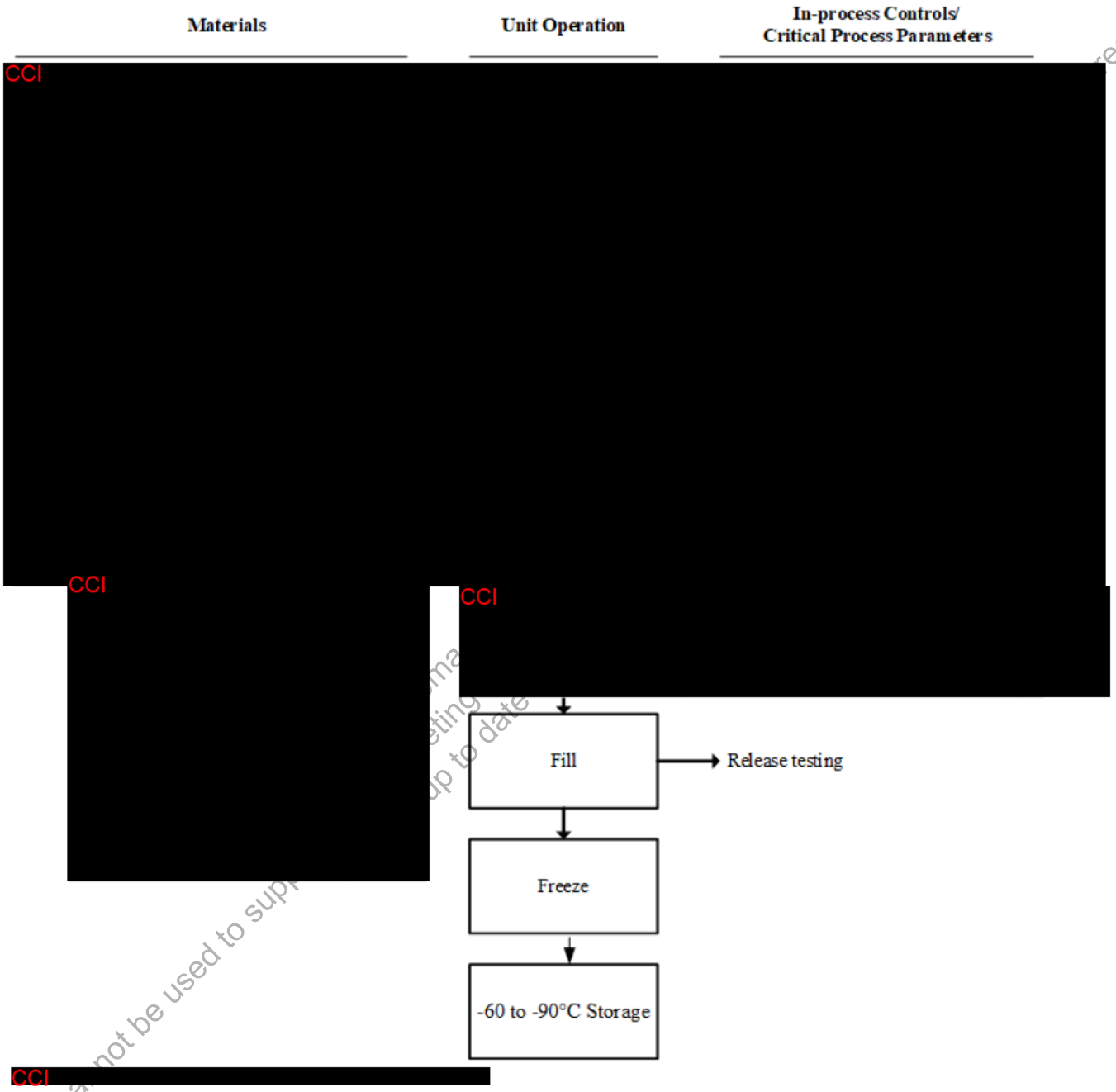
This document describes the mRNA-1273 LNPs-B manufacturing process, which includes CCI [redacted], fill, freezing, and storage as shown in Figure 1.

CCI [redacted] CCI [redacted] the resulting mRNA-1273 LNPs-B dispersion is filled into bags (Section 3.2.S.6 {mRNA-1273 LNPs}) for frozen storage between -60ºC to -90ºC until the fill/finish operation for mRNA-1273 Drug Product.

Detailed description of the manufacturing process including in-process controls and process parameters is provided in Section 3.2.S.2.2 {mRNA-1273 LNPs-B}.

A Failure Mode and Effects Analysis was performed to determine in-process control and parameter criticality based on impact to mRNA-1273 LNP Critical Quality Attributes. The Failure Mode and Effects Analysis and critical parameter range characterization studies are described in Section 3.2.S.2.6 {mRNA-1273 LNPs}.

Figure 1: mRNA-1273 LNPs-B Process Flow Diagram



2.3.S.2.3 Control of Materials

Descriptions of the control of materials used in the manufacture of the mRNA-1273 Lipid Nanoparticle (LNP) and mRNA-1273 LNP – B are discussed in Section 3.2.S.2.3 {mRNA-1273 LNPs - B}.

All the raw materials used for both mRNA-1273 LNP and mRNA-1273 LNP-B are similar. The CCI -

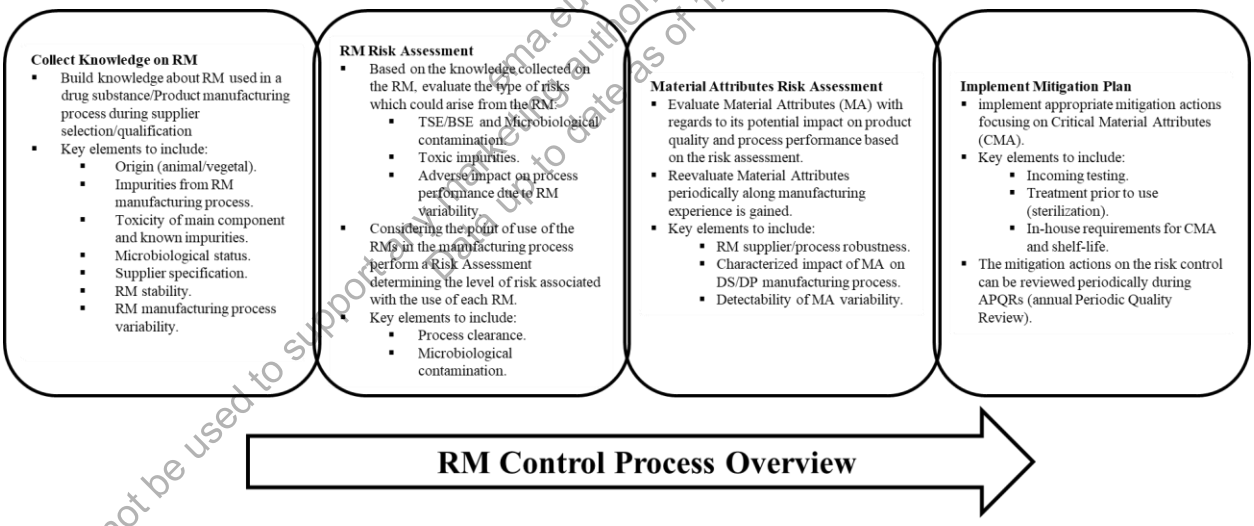
CCI [redacted]

Raw Materials

Raw materials used in the production of mRNA-1273 LNP are categorized as compendial or non-compendial. Raw materials are supplied from approved vendors or suppliers and are released prior to use per controlled incoming material specifications and cGMP guidelines. At a minimum, all raw materials are confirmed to conform with CoAs or Certificates of Compliance, which includes verification of BSE/TSE safety. In addition, all non-compendial raw materials are tested for identification or other material attributes. Specifications for non-compendial materials are provided.

All incoming raw materials are stored in a GMP warehouse. An overview of the RM control process is provided in Figure 2. In instances of material transfer within the global manufacturing network, raw materials initially received at a manufacturing site and released may be transferred to another manufacturing site and received as released goods for manufacturing based on a risk based approach that will managed through the Quality Management System accordingly.

Figure 2: Raw Material Control Process Overview



Adapted from Concept Paper: Management and control of raw materials. Version 1 Nov 29th 2017

More detailed information on raw materials is provided in Section 3.2.S.2.3 {mRNA-1273 LNPs -B}.

Materials or Starting Materials of Biological Origin

There are no materials or starting materials of animal or human origin used in the manufacture of mRNA-1273 LNP.

2.3.S.2.4 Controls of Critical Steps and Intermediates

During the mRNA-1273 LNP manufacturing process, in-process tests are performed to provide control over the inputs to the process.

Note: the process controls described in this Section are applicable to any mRNA-1273 LNP using 9.0 g/L PEG2000-DMG addition buffer (also referred to as mRNA-1273 LNP-B), regardless of the mRNA-1273 RNA sequence.

Critical Process Parameters

Critical process parameters (CPPs) and their proven acceptable range (PARs) for the mRNA-1273 LNPs manufacturing process are provided in Table 11. Excursions outside of these established ranges are reported, investigated, and assessed by the Quality Unit per established standard operating procedures.

Table 6: Critical Process Parameters

Step	CPP	PAR	Rationale
CCI			

Abbreviation: CPP = critical process parameter; PAR = proven acceptable range; PDI = Polydispersity

Microbial Control

The mRNA-1273 LNPs manufacturing process is carried out in a Grade C manufacturing area. Process buffers are formulated and then filtered through CCI filters prior to use. Microbial control limits are established for raw materials used in the manufacturing process. Manufacturing operations utilize single-use, disposable materials for product contact equipment whenever possible. These materials are either received as gamma irradiated/autoclaved by the manufacturer or are intended to be sanitized in place. Aseptic connections are used where possible to minimize open processing. Pre-use and post use sanitization are performed on the Mix skid, and it is verified to be clean post use. Manufacturing controls specifically intended for microbial control of the mRNA-1273 LNPs manufacturing process are listed in Section 3.2.S.2.4 {mRNA-1273 LNPs}.

Note that additional microbial controls may be present. Any deviations incurred in the implementation of these microbial controls are assessed for product quality impact.

In-Process Holds

Process intermediate hold conditions are provided in Section 3.2.S.2.2 {mRNA-1273 LNPs-B}.

Membrane Re-use

No resins or membranes are used in the mRNA-1273 LNPs manufacturing process.

Critical In-process Controls Testing

There are no critical in-process control tests required during mRNA-1273 LNPs manufacturing.

2.3.S.2.5 Process Validation and/or Evaluation

Process validation for mRNA-1273 lipid nanoparticles (LNPs) – B is performed in compliance with European Medicines Agency (EMA), United States Food and Drug Administration (FDA), International Council for Harmonization (ICH), and international regulatory expectations. Process validation comprises Process Design (Phase 1), Process Performance Qualification (PPQ; Phase 2), and Continued Process Verification (CPV; Phase 3). The elements of Process Design (Phase 1) are described in Section 3.2.S.2.4 {mRNA-1273 LNPs} for control strategy and Section 3.2.S.2.6.1 {mRNA-1273 LNPs} for process development. PPQ (Phase 2) and CPV (Phase 3) are discussed in Section 3.2.S.2.5 {mRNA-1273.529 LNPs-B}. All material referenced in these sections is mRNA-1273 LNP-B (2.5% PEG2000-DMG).

For mRNA-1273 LNPs-B variant processes that use a manufacturing process and control strategy equivalent (equivalent excepting for mRNA sequence specific control elements) to the prototype mRNA-1273 process, one confirmatory PPQ verification lot was performed to demonstrate process consistency per site per the requirements specified in the Process Validation Master Plan. Moderna has successfully completed PPQ verification of the mRNA-1273 variant manufacturing process as a means of demonstrating that the commercial-scale manufacturing process is capable of consistently delivering quality product. The PPQ verification has generated data at commercial scale to support and complement concurrent laboratory-scale studies.

The commercial control strategy (Section 3.2.S.2.4 {mRNA-1273 LNPs}) defines critical quality attributes (CQAs) and identifies critical process parameters (CPPs). The commercial control strategy is the basis of the defined acceptance criteria for PPQ verification and no further revision to the commercial control strategy was deemed necessary following PPQ verification.

Validation results are presented in Section 3.2.S.2.5.1 {mRNA-1273.529 LNPs – B}. The CPV Plan is described in Section 3.2.S.2.5.1.2.3 {mRNA-1273.529 LNPs – B}.

Based on the outcome of the PPQ exercise, the mRNA-1273 LNPs - B manufacturing process has

been successfully validated at the 200 g scale at Moderna Norwood, Lonza Visp and Rovi Granada. . More complete information on process validation is provided in Section 3.2.S.2.5 {mRNA-1273.529 LNPs - B}.

2.3.S.2.6 Manufacturing Process Development

The mRNA-1273.529 Lipid Nanoparticle (LNP) CCI [redacted]. CCI [redacted]. The mRNA-1273 LNP is then filtered through a clarification filter CCI [redacted] and filled into single-use, disposable bags (described in Section 3.2.S.6 {mRNA-1273 LNPs}).

The development of additional mRNA-1273 vaccines was initiated in response to the emergence of SARS-CoV-2 variants of concern. Sequences for mRNA-1273 vaccines are designed based upon the S-2P encoding sequence for CX-024414 mRNA. Changes relative to this sequence are made only to incorporate the specific mutations of the variant S protein sequence encoded by the specific mRNA-1273 RNA. The manufacturing process and process and analytical control strategies established for the prototype mRNA-1273 LNP are applied directly to all mRNA-1273 LNPs.

Subsequent process characterization beyond that described in Section 3.2.S.2.6 {mRNA-1273 LNP - Process Characterization} was performed for mRNA-1273 LNPs, with the intent of verifying the applicability of the process description and process control strategy defined in Section 3.2.S.2.2 {mRNA-1273 LNPs-B} and Section 3.2.S.2.4 {mRNA-1273 LNPs}, respectively, to all mRNA-1273 LNPs. Characterization results are provided in 3.2.S.2.6.1 {mRNA-1273 LNPs}.

The comparability demonstration, including evaluation of process change impact on critical quality attributes, is included in Section 3.2.S.2.6.3 {mRNA-1273 LNPs}.

The mRNA-1273.529 LNP-B manufacturing process was successfully established at ModernaTX (Norwood, MA), Rovi (Granada, Spain), and Lonza (Visp, Switzerland) at a 200 g mRNA scale to provide commercial material. A process performance qualification (PPQ) batch at ModernaTX, and PPQ verification batches at Rovi and Lonza were manufactured according to the Process Validation Master Plan and comparability was assessed against the expected ranges per DPAD-PRO-0797. More details are provided in Section 3.2.S.2.6 {mRNA-1273LNPs}

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and Other Characteristics

In addition to the standard release panel of analytical assays, additional characterization was performed on the mRNA-1273 LNP and the results of these studies are summarized in Table 7. These lots were manufactured using process Scale A (representative of the commercial Scale B

lots) and were stored at the intended storage condition (-70°C).

Table 7: Elucidation of Structure Summary for mRNA 1273 Lipid Nanoparticle

Attribute/Characteristic	Method	Results Summary
CCI [redacted]		

CCI [redacted]

A discussion of the methods and results of the characterization studies is provided in Section 3.2.S.3.1 {mRNA-1273.529 LNP - B}.

2.3.S.3.2 Impurities

Product-Related Impurities

Product-related impurities are molecular variants arising during manufacture or storage with properties different from those of the desired product with respect to activity, efficacy, and safety. Due to the unique mRNA 1273 Lipid Nanoparticle (LNP) production process and complex molecular characteristics of the mRNA and the lipids, mRNA-1273 LNP can also include several molecular entities or variants. These variants are formed during the manufacturing process and/or storage and have properties comparable to the desired product; therefore, they are considered product-related substances and not impurities.

Characterization of mRNA-1273 LNP identified the presence of minor amounts of product variants and degradants derived from mRNA-1273 LNP covalently linking to lipid impurities and degradants. These adducts render mRNA inactive and thus affect the potency of the mRNA 1273 LNP. The presence, impact, and ability of the process to control such impurities are discussed. The particulate matter was demonstrated to be product-related and having no impact on the overall characteristics for the SM-102 formulated RNA, is assessed by USP <788> Method 2.

More detailed information is provided in Section 3.2.S.3.2 {mRNA-1273 LNPs}.

Process-Related Impurities

There are no process-related impurities introduced to or generated during the mRNA-1273 LNP manufacturing process that are not already described in CCI [redacted].

2.3.S.4 Control of the Drug Substance

2.3.S.4.1 Specification

The specification for mRNA-1273 Lipid Nanoparticle (LNPs) - B is described in Table 8.

Table 8: Specification for mRNA-1273 LNPs - B

Test	Analytical Method	Acceptance Criteria
Appearance	Visual Ph. Eur. 2.2.1, 2.2.2	White to off-white dispersion. May contain visible, white or translucent product-related particulates.
Identity	Reverse Transcription/Sanger Sequencing	Sequence matches description
Total RNA content	Anion Exchange HPLC	CCI [redacted]
Purity Product-related impurities	RP-IP- HPLC	

Test	Analytical Method	Acceptance Criteria
% RNA encapsulation	Absorbance-based Assay	CCI
Mean particle size	Dynamic Light Scattering	
Polydispersity		
Lipid identification		
SM-102	HPLC-CAD	Matches RT of Standard
Cholesterol		Matches RT of Standard
DSPC		Matches RT of Standard
PEG2000-DMG		Matches RT of Standard
Lipid content		
SM-102	HPLC-CAD	CCI
Cholesterol		
DSPC		
PEG2000-DMG		
Lipid impurities	HPLC-CAD	CCI individual impurities: Total impurities:
pH	USP <791>, Ph. Eur. 2.2.3	CCI
Osmolality	USP <785>, Ph. Eur. 2.2.35	
Bacterial endotoxin	USP <85>, Ph. Eur. 2.6.14	
Bioburden	USP <61>, Ph. Eur. 2.6.12	

Abbreviations: RT = retention time; RRT = relative retention time

2.3.S.4.2 Analytical Procedures

The proposed drug substance specification has been designed to ensure safety and quality of the product, with the objective of patient safety. Acceptance criteria for tests for appearance, identity, strength, purity, impurities and microbiological quality of mRNA-1273 LNPs were established based on compliance with regulations, guidances and compendial methods, and are justified based on characterization studies, the manufacturing process, available batch analyses data, and stability results using validated analytical methods.

The analytical methods used for release testing of mRNA-1273.529 LNPs and the prototype mRNA-1273 LNP are identical with the exception of the identity method, since this is the only method that is sequence-specific. For descriptions of the common methods please refer to Section 3.2.S.4.2 {mRNA-1273 LNP}. A description of the mRNA-1273.529 LNPs identity method is provided in Section 3.2.S.4.2 {mRNA-1273.529 LNPs}.

2.3.S.4.3 Validation of Analytical Procedures

The analytical procedures used for testing mRNA-1273 LNP have been validated by ModernaTX, Inc. at the Norwood, MA Quality Control (QC) Laboratory. The analytical methods were subsequently transferred to ModernaTX, Inc. QC laboratory (Dedham, MA), Lonza AG (Visp, Switzerland), and Rovi (Granada, Spain).

The analytical procedures for testing of the mRNA-1273 LNP were confirmed as suitable for their intended use through method validation experiments. A summary of the validation parameters provided in Section 3.2.S.4.3 {mRNA-1273.529 LNPs}.

The analytical methods used for release testing of mRNA-1273 LNP – B and mRNA-1273.529 LNP - B are identical with the exception of the identity method, since this is the only method which is sequence-specific. For information on validation of common methods, please refer to Section 3.2.S.4.3 {mRNA-1273 LNP}. A validation summary of the identity testing method for mRNA-1273.529 LNP – B is provided in Section 3.2.S.4.3 {mRNA-1273.529 LNPs}.

2.3.S.4.4 Batch Analyses

The mRNA-1273 Lipid Nanoparticle (LNPs) lots are intended for further manufacturing into mRNA-1273 Drug Product lots. Batch analysis data is generated for mRNA-1273 Lipid Nanoparticle (LNPs) according to an approved specification and is presented in Section 3.2.S.4.4 {mRNA-1273.529 LNPs-B}.

2.3.S.4.5 Justification of Specification

Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities. Specifications are chosen to confirm the quality of the mRNA 1273 LNP and mRNA-1273 LNP – B rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the mRNA-1273 LNP (ICH Q6B and Q11). Please note that in the present section, mRNA-1273 LNP refers to both mRNA-1273 LNP and mRNA-1273 LNP-B unless otherwise stated.

A Critical Quality Attribute is defined as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality per ICH Q8(R2) - Pharmaceutical Development.

Table 9 summarizes the CQAs and the corresponding justifications for the mRNA 1273 LNP (prototype and associated variant LNPs) based on risk assessment performed and process and product characterization knowledge gained for mRNA-1273 and general SM-102 lipid formulated drug product with other mRNAs.

Table 9: Critical Quality Attribute Assessment for mRNA-1273 LNP

Quality Attribute	Classification	Justification
CCI		

Quality Attribute	Classification	Justification
CCI [redacted]		

CCI [redacted]

The rationale for the establishment and justification of the release specification is provided in Section 3.2.S.4.5 {mRNA-1273 LNPs-B}.

2.3.S.5 Reference Standards or Materials

For information on the reference standard refer to Section 3.2.S.5 {mRNA-1273 LNP}.

2.3.S.6 Container Closure System

For information regarding the container closure system please refer to Section 3.2.S.6 {mRNA-1273 LNP}.

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

The mRNA-1273 Lipid Nanoparticle (LNP) registration stability program was executed according to ICH Q1A (R2*), Stability Testing of new Drug Substances and Products, and ICH Q5C, Stability Testing of Biotechnological/Biological Products*. An initial shelf life of 12 months is proposed for mRNA-1273 LNP material stored in the commercial container closure defined in Section 3.2.S.6 {mRNA-1273 LNP}, when stored at the recommended long-term storage condition of -60°C to -90°C.

The properties of mRNA-loaded lipid nanoparticles with respect to the attributes that affect product potency has been systematically and thoroughly assessed. These attributes include the quantity of mRNA delivered; the fidelity of the mRNA sequence, including cap, tail, and open reading frame; the integrity of the mRNA; and various biophysical attributes of the lipid nanoparticles, particularly including the state of mRNA encapsulation and the size distribution of the particles. Direct measurements of those attributes of greatest significance have been established and has included those assays in the routine release panel for mRNA-1273 prototype and variant LNPs. The stability of mRNA-1273 variant LNPs will be evaluated against a broad set of stability data and modelling encompassing both prototype registration lots and additional variant RNAs associated with the mRNA-1273 program (Table 10 and Table 11).

The product quality attribute expected to vary during the manufacturing and distribution of the product is mRNA integrity as assessed by mRNA purity. The degradation of mRNA in the product has been extensively studied by applying a sensitive chromatographic assay to assess the formation of RNA degradants. The principal routes of degradation are hydrolytic chain scission, which is measured by the species which elute prior to the main peak (RNA fragments); and the formation of covalent adducts between the RNA and degradants of the cationic lipid, which are relatively hydrophobic and elute after the main peak (RNA-lipid adduct). There is a strong quantitative correlation between RNA degradation as measured directly and the resulting protein levels. Direct measure of mRNA degradation utilizing the mRNA purity assay by RP-HPLC is precise, accurate, and the most stability-indicating measure of product activity.

The degradation rates can be determined from the purity analysis over different stability timepoints. Based on the stochastic nature of the degradation mechanism, there is a dependence on the rate of degradation on RNA size (length). Since mRNA-1273 prototype and variant RNAs have approximately the same overall length (~4,000 nt), a similar rate of degradation is expected across these mRNA-1273 prototype and variant LNPs.

The stability profiles for all the stability-indicating attributes are being evaluated and monitored, but purity is the primary determinant of shelf-life, since it is the most stability-indicating attribute. Degradation rates for purity at each temperature of interest (-60°C to -90°C and 5 ± 3°C) are reported in Section 3.2.S.7.1.1 {mRNA-1273 LNPs}.

The shelf life is justified from the purity modelling analysis. Stability and characterization studies designed to evaluate product stability under various stressed conditions (freeze/thaw) have been performed. The mRNA-1273 LNP lots used in the purity modelling analysis (Table 10) used a development process and the Scale B process (Section 3.2.S.2.6 {mRNA-1273 LNPs}). Modelling analysis also included additional lots not listed that were manufactured outside the United States as part of Moderna's global network. The purity modelling results are provided in Section 3.2.S.7.1.1 {mRNA-1273 LNPs} and the purity data from these studies are presented in Section 3.2.S.7.3 {mRNA-1273.529 LNPs}.

Registration lots, Scale B Process Performance Qualification (PPQ) lots manufactured using the process described in Section 3.2.S.2.2 {mRNA-1273 LNPs-B}, were also placed on stability studies (Table 11). The data from these studies are presented in Section 3.2.S.7.3 {mRNA-1273.529 LNPs} and protocols are provided in Section 3.2.S.7.1.2 {mRNA-1273 LNPs}.

Stability samples were stored in a scaled-down container closure system (50-mL Aramus bag). The scaled down bag is representative of the storage container used for commercial manufacture with the same product contact surfaces. Based on the sample volume and size of the scaled-down container, the surface area:volume ratio is considered worst case in the stability studies. Samples stored at the recommended condition of -60°C to -90°C are evaluated against the specification current at the time of testing. Samples stored at alternate storage conditions use the specification as a reference point to characterize stability trends at that condition.

Stability protocols are described in Section 3.2.S.7.1 {mRNA-1273 LNPs}. The data from the stability studies are presented in Section 3.2.S.7.3 {mRNA-1273.529 LNP}.

Table 10: Additional mRNA-1273 LNP Stability Modelling Lots

Lot	Product	Purpose	Manufacturing Site	Lot Size	Fill Volume (mL)	Container Closure	Conditions		Status
							Temperature	Duration	
DH-06191.1	mRNA-1273.351	Development	ModernaTX	CCI	6 mL	50 mL Aramus Bag	-60°C to -90°C	9 months	Completed
							5°C ± 3°C	1 month	Completed
DH-06191.2	mRNA-1273.211	Development	ModernaTX	CCI	6 mL	50 mL Aramus Bag	-60°C to -90°C	9 months	Completed
							5°C ± 3°C	1 month	Completed
5011122003	mRNA-1273.529	PPQ Comparability	ModernaTX	200 g	15 mL	50 mL Aramus Bag	-60°C to -90°C	36 months	Ongoing
							5°C ± 3°C	2 months	Completed

Abbreviations: PPQ = process performance qualification

Table 11: mRNA-1273 LNP Registration Stability Program Lots

Lot	Product	Purpose	Manufacturing Site	Lot Size	Fill Volume (mL)	Scale	Process Train	Container Closure	Conditions	
									Temperature	Duration
5011122003	mRNA-1273.529 LNP-B	Stability[(a)]	ModernaTX (Norwood, MA)	200 g	15	B	8	50 mL Aramus bag	-60°C to -90°C	36 months
									5°C ± 3°C	2 months
5011522001	mRNA-1273.529 LNP-B	PPQ Comparability	Rovi (Granada, Spain)	200 g	40	B	10	50 mL Aramus bag	-60°C to -90°C	36 months
									5°C ± 3°C	3 months
5011422001	mRNA-1273.529 LNP-B	PPQ Comparability	Lonza (Visp, Switzerland)	200 g	30	B	5	50 mL Aramus bag	-80°C ± 10°C	36 months
									5°C ± 3°C	2 months

Abbreviations: PPQ = process performance qualification

[a] Lot 5011122003 was manufactured using the identical process as the PPQ verification batch 5011122001.

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

For information on post-approval stability, please refer to Section 3.2.S.7.2 {mRNA-1273 LNP}.

2.3.S.7.3 Stability Data

All stability data available are provided in Section 3.2.S.7.3 {mRNA-1273.529 LNPs}.