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2.3.S DRUG SUBSTANCE [mRNA-1273 LNP]

2.3.S.1 General Information

The mRNA-1273 Lipid Nanoparticle (LNP) and mRNA-1273 LNP – B are an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains an mRNA (CX-024414) that encodes for the pre-fusion stabilized Spike protein of 2019-novel Coronavirus (SARS-CoV-2). CCI [redacted]

The only difference regarding the materials used for manufacture of mRNA-1273 LNP and mRNA-1273 LNP – B is that the mRNA-1273 LNP uses CCI [redacted] of the production process while mRNA-1273 LNP - B is manufactured using CCI [redacted].

The mRNA-1273 LNP has CCI [redacted]

The mRNA-1273 LNP - B has CCI [redacted].

2.3.S.1.1 Nomenclature

International Non-proprietary Name (INN):	N/A
Proprietary name:	N/A
Company product codes:	mRNA-1273
Drug Product name:	mRNA-1273
Synonymous name:	N/A

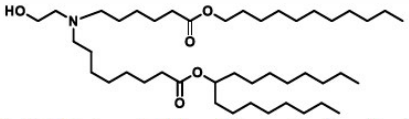
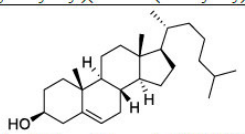
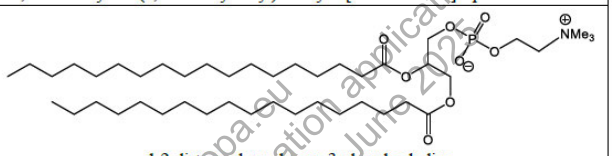
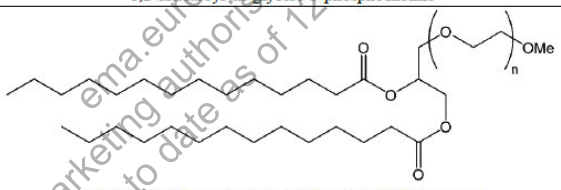
2.3.S.1.2 Structure

Structure of CX-024414

The molecular sequence of CX-024414, including the 5' cap, the 5' untranslated region (UTR), the Open Reading Frame (ORF), the 3' UTR, and the 3' polyA tail, is provided in Section 2.3.S.1.2 {CX-024414}. CX-024414 is the mRNA that encodes for the pre-fusion stabilized Spike protein of 2019-novel Coronavirus (SARS-CoV-2). The S protein is stabilized in the so-called pre-fusion conformation by two amino acid mutations, K986P and V987P.

CCI [redacted]

Table 1: Structure of Lipid Components

Lipid	Molecular Weight	Chemical Structure and Name
SM-102	710.2	 Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy) hexyl) amino)octanoate
Cholesterol	386.65	 2,15-dimethyl-14-(1,5-dimethylhexyl)tetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptadec-7-en-5-ol
DSPC	790.15	 1,2-distearoyl-sn-glycero-3-phosphocholine
PEG2000-DMG	2475 (avg.)[a]	 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol

a) approximately n = 45 PEG units, corresponding to an approximate PEG chain molecular weight of 2000

2.3.S.1.3 General Properties

The general properties of mRNA-1273 LNP and mRNA-1273 LNP – B are summarized in Table 2. More detailed information is provided in Section 3.2.S.1.2 {mRNA-1273 LNP}.

Table 2: General Properties of mRNA-1273 LNP

Description	mRNA-1273 LNP has CCI [redacted]
	mRNA-1273 LNP - B has CCI [redacted]
Appearance	White to off-white LNP dispersion.
pH	CCI [redacted]
Osmolality	
Density	
Particle Size	

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer(s)

Each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing process are described in Table 3 and Table 6.

Table 3: Manufacturers of mRNA-1273 LNP

Manufacturer	Address	Responsibility
[redacted]		Manufacture of mRNA-1273 LNP [redacted] Scale) Quality control testing (excluding identity testing)
		Manufacture of mRNA-1273 LNP (200 g Scale
		Quality Control testing for identity of mRNA-1273 LNP
ModernaTX, Inc.	One Moderna Way Norwood, MA, 02062 USA	Manufacturer of mRNA-1273 LNP ([redacted] 200 g Scale) Lot release of mRNA-1273 LNP Storage of mRNA-1273 LNP
ModernaTX, Inc.	One Moderna Way Norwood, MA, 02062 USA	Release, stability, in-process testing mRNA-1273 LNP (excluding bacterial endotoxin testing as well as bioburden testing for mRNA-1273 LNP manufactured at Lonza)
[redacted]		
Lonza Biologics, Inc.	101 International Drive Portsmouth, NH, 03801 USA	Manufacture of mRNA-1273 LNP (200 g Scale) Release testing (bioburden testing of mRNA-1273 LNP manufactured at site) Storage mRNA-1273 LNP
[redacted]		Release and stability testing of mRNA-1273 LNP (Bacterial endotoxin)

Table 4: Manufacturers of mRNA-1273-LNP - B

Facility	Address	Responsibility
[redacted]		• Manufacture of mRNA-1273 LNP - B (200 g Scale) • Quality control testing (excluding identity testing)
		• Quality control testing for identity
		• Quality control testing
		• Manufacture of mRNA-1273 LNP - B (200 g Scale) • Quality control testing (except identity testing)
		• Quality control testing for identity

* For EU and UK.

Table 5: List of Testing Exceptions

Facility	Address	• Responsibility
CCI		• Bacterial endotoxin testing

Table 6: US Facilities and Responsibilities for Manufacture and Testing of the mRNA 1273 LNP – B

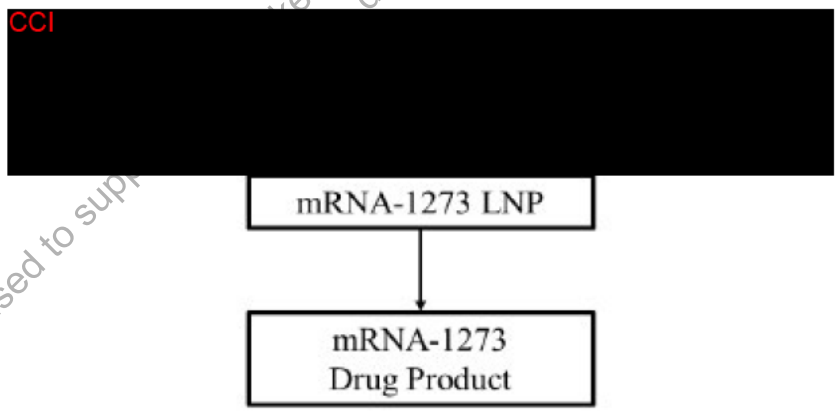
Facility	Address	Responsibility
CCI		• Manufacture of mRNA-1273 LNP-B (200g Scale) • Quality control testing (excluding bacterial endotoxin testing) • Storage
		• Quality control testing (excluding bacterial endotoxin)
		• Bacterial endotoxin testing

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

Flow Diagram

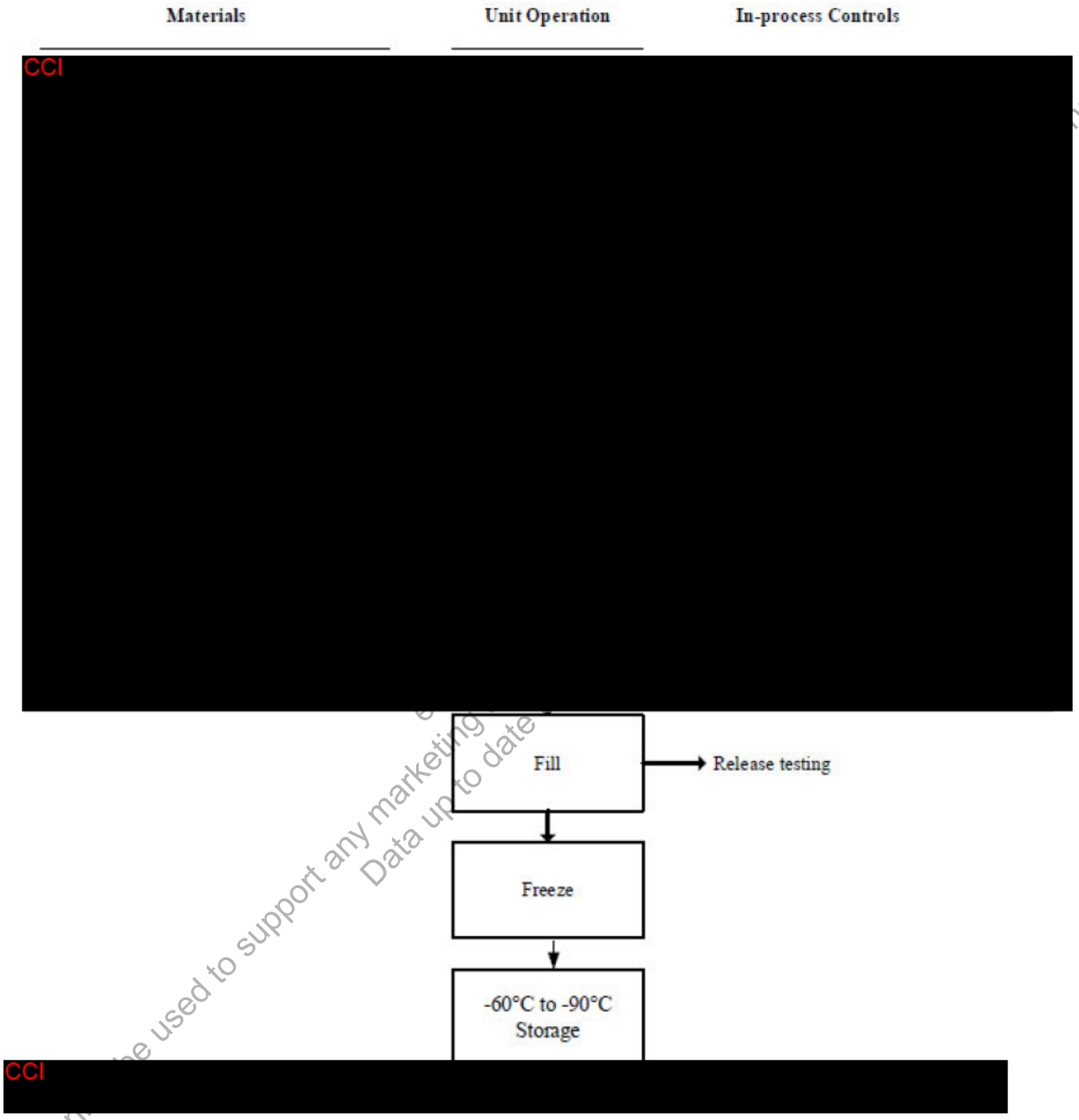
The manufacturing process scheme and a flow diagram of the manufacturing process is provided in Figure 1 and Figure 2.

Figure 1: mRNA-1273 Manufacturing Process Scheme



Abbreviation: LNP = lipid nanoparticle

Figure 2: mRNA-1273 LNP Process Flow Diagram



Narrative Description of the Manufacturing Process

The purpose of the mRNA-1273 LNP 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.

The manufacture of mRNA-1273 is comprised of four processes as shown in Figure 1.

- Manufacture of CX-024414 mRNA,

CCI

- Manufacture of mRNA-1273 LNP, and
- Manufacture of mRNA-1273 Drug Product.

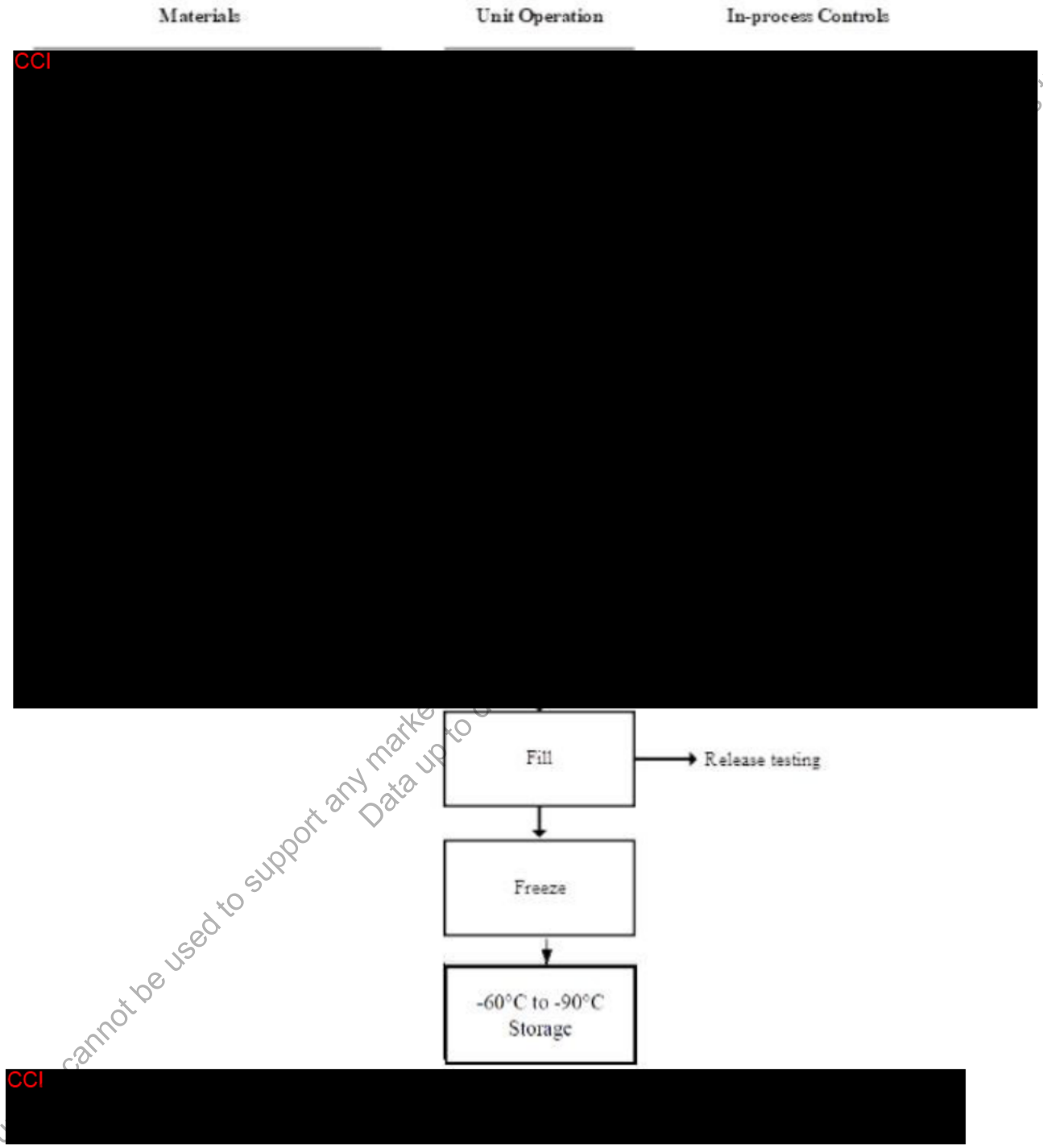
CCI

This mRNA-1273 LNP manufacturing process includes: CCI fill, freezing, and storage. CCI the resulting mRNA-1273 LNP dispersion is filled into bags (Section 3.2.S.6 {mRNA-1273 LNP}) for frozen storage between -60ºC to -90ºC until the fill/finish operation for mRNA-1273 Drug Product.

Detailed description of the manufacturing process is provided in Section 3.2.S.2.2 {mRNA-1273 LNP}.

The manufacturing process for mRNA-1273 LNP – B, CCI total lipid is the same as described for mRNA-1273 LNP except for the use of CCI The process utilizes same raw materials, intermediates, equipment, process parameters, hold times and in-process controls. The mRNA-1273 LNP - B manufacturing process (Version B process) is shown in Figure 3.

Figure 3: mRNA-1273 LNP-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 LNP}.

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

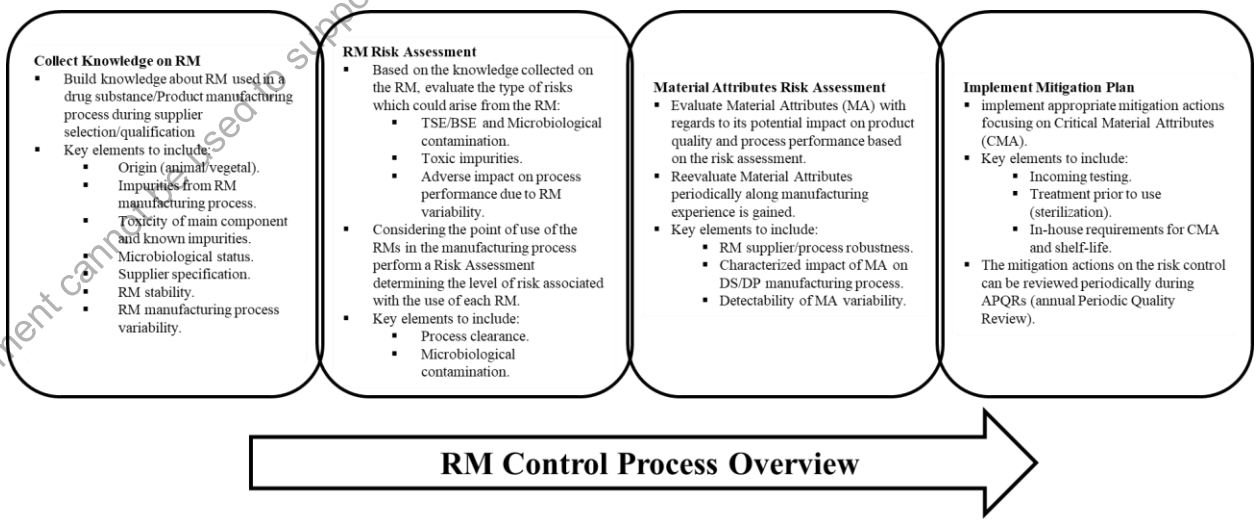
[redacted]

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 4. 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 4: 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 LNP}.

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

Critical Process Parameters

Critical process parameters (CPPs) and their proven acceptable range (PARs) for the mRNA-1273 LNP manufacturing process are provided in Table 7. Excursions outside of these established ranges are reported, investigated, and assessed by the Quality Unit per established standard operating procedures.

Table 7: Critical Process Parameters

Step	CPP	PAR	Rationale
CCI			

Abbreviation: CPP = critical process parameter; PAR = proven acceptable range; PDI = Polydispersity
a) CPP distinction for ModernaTX and Lonza Biologics was changed per PD-MEM-0769
CCI

Microbial Control

The mRNA-1273 LNP 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. 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 times for mRNA-1273 LNP manufacturing process are provided in Table 8.

Table 8: In-process Hold Times

Step	Operation	Activity/Description	Duration (Temperature)
CCI			
Collection, Filling and Storage[b]	End of filtration until start of mRNA-1273 LNP at CCI hold duration (end of filtration until start of CCI storage)	Hold time between end of filtration until start of mRNA-1273 LNP hold duration	CCI
Clarification and Freezing Operation	mRNA-1273 LNP hold storage conditions	Hold time between start of CCI storage and freezing of final bag	

Abbreviation: LNP = lipid nanoparticle
a) ModernaTX and Lonza Biologics: CCI
b) Lonza -specific in-process hold condition

Microbial Control

At, ModernaTX, Inc., testing was performed after hold periods for batches manufactured as part of the process performance qualification (PPQ) activities of the mRNA-1273 LNP production process. No bioburden was observed during the PPQ execution.

Membrane Re-use

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

Critical In-process Controls Testing

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

2.3.S.2.5 Process Validation and/or Evaluation

A Process Validation Master Plan (PVMP) was developed to ensure that the commercial manufacturing process for mRNA-1273 LNP will reliably and consistently produce product of appropriate quality. Per the PVMP, a minimum of 3 PPQ lots is required if a new process is established, a new scale is established, or an existing, qualified process is transferred to a new site.

Product development of mRNA-1273 LNP was accelerated in response to the COVID-19 pandemic. To accelerate the collection of scientific data that demonstrates process consistency, the process performance qualification (PPQ) was executed concurrently with process-development activities; the process-development studies are discussed in Section 3.2.S.2.6 {mRNA-1273 LNP}, for the initial CCI scale. The process parameters and proven acceptable ranges (PARs) were evaluated during PPQ and were determined prior to the completion of the process-development activities. The final determination of critical process parameters (CPPs) and PARs were based on the process development characterization data and confirmed based on the results of the PPQ and summarized in Section 3.2.S.2.6 {mRNA-1273 LNP}.

Based on the outcome of the PPQ exercise, the mRNA-1273 LNP manufacturing process has been successfully validated at the CCI scale (initial Scale B) and at the 200 g scale (final Scale B).

More complete information on process validation is provided in Section 3.2.S.2.5 {mRNA-1273 LNP}.

The mRNA-1273 LNP-B manufacturing process was validated at the 200g scale as per the approved protocols. The validation results are provided in Section 3.2.S.2.5 {mRNA-1273 LNP - B}.

2.3.S.2.6 Manufacturing Process Development

The mRNA-1273 Lipid Nanoparticle (LNP) is prepared 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 LNP}).

The initial process for mRNA-1273 was conducted using equipment utilized in ModernaTX, Inc.'s personal vaccine unit (PVU). The PVU process for mRNA-1273 Drug Product did not incorporate freezing and storage of the bulk mRNA-1273 LNP. The process was completed in a sequential integrated-batch manner for each lot of mRNA-1273 Drug Product CCI [redacted] Product intermediates were held in-process prior to proceeding to each subsequent step. CCI [redacted]

In order to support ongoing clinical development, scale-up of the mRNA-1273 Drug Product process was required. To facilitate supply logistics, a bulk freezing step was developed and implemented. Comparison of characteristics of mRNA-1273 Drug Product with the previously manufactured mRNA-1273 Drug Product is provided in Section 3.2.P.2.3 {Rovi}. Due to the introduction of the mRNA-1273 LNP, no such comparison is available for previously manufactured mRNA-1273 LNP material.

To enable scale-up of the mRNA-1273 LNP manufacturing process (Scale A), the neutralization and component addition operations were incorporated downstream CCI [redacted] in a continuous process. CCI [redacted] Process hold times were evaluated and adjusted to accommodate continuous processing. Following laboratory scale process development, a development lot of mRNA-1273 LNP was produced using the process described in Section 3.2.S.2.2 {mRNA-1273 LNP} (Lot AMPDP-200022). The process was subsequently transferred to the GMP manufacturing area, and lots 5006820002 through 5006820008 of mRNA-1273 LNP were produced.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Though the mRNA-1273 LNP intermediate was not generated prior to the implementation of the Scale A process, the process steps of CCI [redacted] were included in the small-scale process to generate the mRNA-lipid. Minor changes were implemented between the PVU process and the Scale A process.

CCI [redacted]

The CCI [redacted] Initial Scale B process has been transferred to Lonza, Visp. Changes were made to materials for regional availability, operations and equipment to maintain aseptic processing aligned with facility fit, and equipment availability. This manufacturing process is described in Section 3.2.S.2.2 {mRNA-1273 LNP}.

The full commercial scale has been increased and has been implemented at the US manufacturing sites and Lonza Visp site by scaling mRNA-1273 LNP from CCI [redacted] 200 g (Scale B, PN 50075). All changes associated with this process change are related to scale-up, including equipment size and implementation of parallel processing skids. Scale up has occurred in parallel at Norwood and Lonza Portsmouth.

A subsequent process improvement was implemented at Norwood on the final Scale B (PN 50089), using CCI [redacted].

Comparison of mRNA-1273 LNP manufacturing changes for all sites and all processes are provided in Section 3.2.S.2.6 { mRNA-1273 LNP}.

The mRNA-1273 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 materials outside of the United States. Process performance qualification (PPQ) batches were manufactured according to the Process Validation Master Plan and comparability was assessed against the baseline expected ranges per DPAD-PRO-0446. More details are provided in Section 3.2.S.2.6 {mRNA-1273 LNP -B}

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and Other Characteristics

Extended physicochemical and biological characterization was performed on mRNA-1273 LS Lipid Nanoparticle (LNP) which was produced according to manufacturing process as described in Section 3.2.S.2.2 {mRNA-1273 LNP}. Unless noted, this testing was performed on mRNA-1273 LS Lot 5006820002 stored at the intended storage condition between -60°C to -90°C. Lot 5006820002, CCI [redacted], was manufactured at the ModernaTX, Inc. GMP facility in Norwood, MA.

The set of analytical tests employed for the extended characterization of the mRNA-1273 LS LNP is detailed in Table 10. The selection of these assays was intended to complement and, in some cases, be orthogonal to the analytical data as part of lot release as described in Section 3.2.S.4.1 {mRNA-1273 LNP}.

Table 10: List of Assays used for Extended Analytical Characterization of mRNA-1273 LNP

Product Attribute	Method	Comments
CCI [redacted]		

A discussion of the methods and results of the characterization studies is provided in Section 3.2.S.3.1 {mRNA-1273 LNP}.

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. In addition to the impurities and degradation described in Section 3.2.S.3.2 {CX-024414}, and the lipid impurities and degradants described in this section, characterization of mRNA 1273 LNP identified the presence of minor amounts of product variants and degradants derived from CX 024414 mRNA 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 mRNA, is assessed by USP <788> Method 2.

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

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 Section 3.2.S.3.2 {CX-024414}.

2.3.S.4 Control of the Drug Substance

2.3.S.4.1 Specification

The testing of the mRNA-1273 Lipid Nanoparticle (LNP) is performed in accordance with the specification listed in Table 11.

The specification for mRNA-1273 LNP – B is described in Table 12.

Table 11: Specification for mRNA-1273 LNP

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	
Purity	RP-IP-HPLC		
Product-related impurities			
% RNA encapsulation	Absorbance-based Assay		
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	UPLC-CAD	Individual impurities:	CCI area (Report RRT)
		Total impurities:	CCI area
pH	USP <791>, Ph. Eur. 2.2.3	CCI	
Osmolality	USP <785>, Ph. Eur. 2.2.35		
Bacterial endotoxin	USP <85>, EP 2.6.14		
Bioburden	USP <61>, EP 2.6.12		

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

Table 12: Specification for mRNA-1273 LNP - 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
Purity	RP- HPLC	
Product-related impurities		
% RNA encapsulation	Absorbance-based Assay	
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	Individual impurities: CCI area (Report RRT) Total impurities: CCI area
pH	USP <791>, Ph. Eur. 2.2.3	CCI
Osmolality	USP <785>, Ph. Eur. 2.2.35	
Bacterial endotoxin	USP <85>, EP 2.6.14	
Bioburden	USP <61>, EP 2.6.12	

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 LNP and mRNA-1273 LNP – B 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. A full description of each method used is provided in Section 3.2.S.4.2 { mRNA-1273 LNP}.

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 LNP} is included in Table 13.

The same analytical methods are also used for testing of mRNA-1273 LNP – B and therefore additional method validation was not required.

Table 13: Method Validation Summary for the mRNA-1273 Lipid Nanoparticle

Attribute	Method	Method Parameter
Identity	Reverse Transcription/Sanger Sequencing	Specificity
RNA Content	AEX-HPLC	System Suitability, Specificity, linearity, accuracy, precision (repeatability and intermediate), range and robustness
Purity	RP-IP-HPLC	System Suitability, Specificity, accuracy, precision (repeatability and intermediate), linearity, range, QL, sample and standard stability and robustness
% RNA Encapsulation	Absorbance-based Assay	System Suitability, specificity, linearity, precision (repeatability and intermediate), reproducibility, range, accuracy, QL, DL and prepared solution stability
Particle Size and Polydispersity	Dynamic Light Scattering	System suitability, specificity, accuracy, precision (repeatability and intermediate), range and robustness
Lipid Content, Identification and Impurities	HPLC-CAD	Specificity, linearity, accuracy, precision (repeatability and intermediate), range QL, DL, sample stability and robustness

QL=quantitation limit, DL=detection limit

2.3.S.4.4 Batch Analyses

The mRNA-1273 Lipid Nanoparticle Particle (LNP) and mRNA-1273 LNP – B GMP lots are intended for further manufacturing into mRNA-1273 Drug Product GMP lots. Batch analysis data generated for mRNA-1273 Lipid Nanoparticle (LNP) and mRNA-1273 LNP – B according to specification approved at time of release are presented in Section 3.2.S.4.4 {mRNA-1273 LNP} and Section 3.2.S.4.4 {mRNA-1273 LNP - 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).

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 14 summarizes the CQAs and the corresponding justifications for the mRNA 1273 LNP and mRNA-1273 LNP – B 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. The specifications of mRNA-1273 LNP and mRNA-1273 LNP– B, are the same with the exception of the acceptance criterium for PEG2000-DMG lipid contents.

Table 14: Critical Quality Attribute Assessment for mRNA 1273 LNP and mRNA-1273 LNP - B

CCI		
CCI		

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

2.3.S.5 Reference Standards or Materials

The reference standard for the mRNA-1273 Lipid Nanoparticle (LNP) for the total RNA content method by AEX-HPLC and the reference material for the % purity method by RP-HPLC is described in Section 3.2.S.5 {CX-024414}.

The reference material for mRNA-1273 LNP for the Ultra-High Performance Liquid Chromatography with Charged Aerosol Detection (UPLC-CAD) method for lipid identification, lipid content and lipid impurity CCI

2.3.S.6 Container Closure System

The mRNA-1273 LNP (-B) is stored frozen in single-use storage bags as a low-bioburden material.

It is frozen in Aramus™ bags CCI : Aramus™ CCI 5 L Bag Assemblies or Aramus™ CCI 10 L Bag Assemblies or Aramus™ CCI 15 L Bag Assemblies CCI CCI CCI The inlet tubing to the Aramus™ bag is sealed utilizing a non-product contact CCI device by CCI , while the inlet tubing to the CCI bag is sealed utilizing an aseptic CCI disconnect by CCI . The mRNA-1273 LNP (-B) is stored at CCI before further processing.

The Aramus™ storage bag is manufactured from high-purity fluoropolymer film. The bags are equipped with two or more fluoropolymer ports with silicone tubing. Bag assembly is performed in an ISO Class 5 certified cleanroom by trained operators. The single-use systems are individually packaged prior to being gamma-irradiated at a minimum exposure of 25 kGy, capable of ensuring a sterility assurance level of 10-6. Liquid particle count levels are certified in compliance with USP <788> and Ph.Eur. 2.9.19.

The results of USP <87> (in vitro Biological Reactivity) and USP <88> (in vivo Biological Reactivity) and ISO 10993-4 (Hemolysis) testing conducted by the manufacturer indicates that the primary container materials of construction are non-cytotoxic. The Aramus™ storage bag meets the USP Class VI and 21 CFR 177.1550 requirements. The LNP storage bag is determined to be non-pyrogenic at a level of CCI (based on 40 mL rinse) per USP <85> and Ph.Eur. 2.6.14.

Each incoming lot is received with a Certificate of Processing, which documents completion of the gamma irradiation cycle. The storage system is rated at an operating range of CCI which accommodates the mRNA-1273 LNP (-B) manufacturing process parameters. The manufacturer has assigned a post-sterilization shelf life of two years based on real-time and accelerated aging studies conducted per ASTM F1980.

The CCI storage bag is manufactured from Ultra Low Density Polyethylene film. The bags are equipped with two or more High Density Polyethylene ports with platinum cured silicone tubing. Bag assembly is performed in an ISO Class 7 certified cleanroom by trained operators. The single-use systems are individually packaged prior to being gamma-irradiated at a minimum exposure of 27.5 kGy, capable of ensuring a sterility assurance per (ANSI/AAMI/) ISO 11137-2 and ISO/TS 13004. Liquid particle count levels are certified in compliance with USP <788>.

The results of USP <87> (in vitro Biological Reactivity) and USP <88> (in vivo Biological Reactivity) conducted by the manufacturer indicates that the primary container materials of construction are non-cytotoxic.

The CCI storage bag meets the USP Class VI and 21 CFR 177 requirements. The LNP storage bag is determined to be non-pyrogenic at a level of ≤ 0.25 EU/mL per USP <85>.

Each incoming lot is received with a Certificate of Processing, which documents completion of the gamma irradiation cycle. The storage system is rated at an operating range of CCI , which accommodates the mRNA-1273 LNP (-B) manufacturing process parameters. The

manufacturer has assigned a post-sterilization shelf life of two years based on real-time and accelerated aging studies.

There are no functional secondary packaging components.

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

The mRNA-1273 Lipid Nanoparticle (LNP) and mRNA-1273 LNP-B 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. CCI [redacted] The mRNA-1273 LNP and mRNA-LNP – B material are stored in the commercial container closure defined in Section 3.2.S.6 {mRNA-1273 LNP}.

The shelf life is justified from the composite of data generated from development lot, clinical lot, and PPQ lots of mRNA-1273 LNP and mRNA-1273 LNP - B. Stability and characterization studies designed to evaluate product stability under various stressed conditions (freeze/thaw) have been performed. All lots were manufactured at ModernaTX, Inc., Lonza AG (Visp, Switzerland), and Rovi (Granada, Spain) using the manufacturing process as described in Section 3.2.S.2.2 {mRNA-1273 LNP} and Section 3.2.S.2.2 {mRNA-1273 LNP - B} for PPQ and clinical lots and the processes described in Section 3.2.S.2.6 {mRNA-1273 LNP} for the development lot. Stability samples were stored in a container made of the same materials (i.e., Aramus bag) as the commercial closure system. Also, a fill volume that is at or less than 30% of the container volume was used as the worst case.

Purity, as assessed by reverse-phase high-performance liquid chromatography (RP HPLC); % RNA encapsulation, as assessed by CCI [redacted] fluorescence; particle size and polydispersity, as assessed by dynamic light scattering (DLS); and lipid impurities, as assessed by ultra-high-performance liquid chromatography with charged aerosol detection (UPLC CAD) have been demonstrated to be stability-indicating (refer to Section 3.2.S.4.2 {mRNA-1273 LNP} for analytical procedures).

The recommended storage condition for mRNA-1273 LNP and mRNA-1273 LNP – B is between -60°C to -90°C. Based on the available stability data presented in Section 3.2.S.7.3 {mRNA-1273 LNP -ROW}, a shelf life of 12 months is proposed for mRNA-1273 LNP and mRNA-1273 LNP – B.

An overview of the mRNA-1273 LNP and mRNA-1273 LNP -– B stability program is provided in Table 15. The data from these studies are presented in Section 3.2.S.7.3 {mRNA-1273 LNP -ROW}.

Table 15: mRNA-1273 Lipid Nanoparticle Stability Program Lots

Lot	Purpose	Date of Manufacture	Manufacturing Site	Conditions		Available Long-term Data
				Temperature	Duration	
mRNA-1273 LNP lots						
AMPDP-200022 (sublot DHM-47432)	Development	01 Apr 2020	ModernaTX (Norwood, MA)	-60 to -90°C	24 mo	12 mo
5006820002	Clinical	15 May 2020	ModernaTX (Norwood, MA)	-60 to -90°C	36 mo	18 mo
				5 ± 3°C	2 mo	2 mo
5006820005	PPQ	02 Jul 2020	ModernaTX (Norwood, MA)	-60 to -90°C	36 mo	18 mo
				5 ± 3°C	2 mo	2 mo
5006820006	PPQ	11 Jul 2020	ModernaTX (Norwood, MA)	-60 to -90°C	36 mo	18 mo
				5 ± 3°C	2 mo	2 mo
5007520002	PPQ	06 Nov 2020	ModernaTX (Norwood, MA)	-60 to -90°C	36 mo	12 mo
5007520003	PPQ	11 Nov 2020	ModernaTX (Norwood, MA)	-60 to -90°C	36 mo	12 mo
5007520004	PPQ	13 Nov 2020	ModernaTX (Norwood, MA)	-60 to -90°C	36 mo	12 mo
5007520009	PPQ	20 Nov 2020	ModernaTX (Norwood, MA)	-60 to -90°C	36 mo	12 mo
5007520013	PPQ	27 Nov 2020	ModernaTX (Norwood, MA)	-60 to -90°C	36 mo	12 mo
				5 ± 3°C	2 mo	1 mo
5007521502	PPQ	05 Jan 2021	Lonza (Portsmouth, NH)	-60 to -90°C	36 mo	9 mo
5008921002	PPQ	28 Aug 2021	ModernaTX (Norwood, MA)	5 ± 3°C	24 mo	3 mo
				-60 to -90°C	2 mo	2 mo
5007320009 (3000)	GMP	22Nov2020	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
3001	PPQ	11 Dec 2020	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
3002	PPQ	26 Dec 2020	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
3003	PPQ	31 Dec 2020	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
3028	PPQ	11 May 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	3 mo
				5 ± 3°C	6 mo	3 mo
43001	PPQ	12 Fev 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
43002	PPQ	19 Feb 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo

Lot	Purpose	Date of Manufacture	Manufacturing Site	Conditions		Available Long-term Data
				Temperature	Duration	
43003	PPQ	24 Feb 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
43004	PPQ	28 Feb 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
43005	PPQ	07 Mar 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
43006	PPQ	16 Mar 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
53001	PPQ	03 Mar 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	6 mo
				5 ± 3°C	6 mo	6 mo
53003	PPQ	16 Mar 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	3 mo
				5 ± 3°C	6 mo	3 mo
63001	PPQ	27 Apr 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	3 mo
				5 ± 3°C	6 mo	3 mo
63005	PPQ	16 May 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	2 mo
				5 ± 3°C	6 mo	2 mo
63021	PPQ	29 Jul 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	2 mo
				5 ± 3°C	6 mo	2 mo
1136900121	PPQ	14 Nov 2021	Rovi, Granada Spain	-60 to -90°C	36 mo	Initial
				5 ± 3°C	3 mo	Initial
1136900221	PPQ	19 Nov 2021	Rovi, Granada Spain	-60 to -90°C	36 mo	Initial
				5 ± 3°C	3 mo	Initial
1136900321	PPQ	25 Nov 2021	Rovi, Granada Spain	-60 to -90°C	36 mo	Initial
				5 ± 3°C	3 mo	Initial
mRNA-1273 LNP-B lots						
5009221001	PPQ	07 Oct 2021	ModernaTX (Norwood, MA)	-60 to -90°C	24 mo	3 mo
				5 ± 3°C	2 mo	2 mo
5010421001	PPQ	27 Nov2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	2 mo
				5 ± 3°C	6 mo	2 mo
5010421002	PPQ	29 Nov 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	2 mo
				5 ± 3°C	6 mo	2 mo
5010421003	PPQ	29 Nov 2021	Lonza, Visp Switzerland	-60 to -90°C	24 mo	2 mo
				5 ± 3°C	6 mo	2 mo
5010821001	PPQ	15-Dec-2021	Rovi, Granada Spain	-60 to -90°C	36 mo	1 mo
				5 ± 3°C	3 mo	1 mo
5010822001	PPQ	19-Dec-2021	Rovi, Granada Spain	-60 to -90°C	36 mo	1 mo
				5 ± 3°C	3 mo	1 mo
5010822003	PPQ	17-Jan-2022	Rovi, Granada Spain	-60 to -90°C	36 mo	Initial
				5 ± 3°C	3 mo	

Stability Protocols

Stability protocols for mRNA-1273 LNP lots are described in Table 16 to Table 20. Stability protocols for mRNA-1273 LNP-B lots are described in Table 22 to Table 24.

Table 16: Stability Protocol for Development mRNA-1273 LNP Lot AMPDP-200022

Condition[a]	Time Interval (Months)							
	0	1	3	4	6	9	12	24
-60°C to -90°C	X ,Y, Z,	XY	XY	XYC	XY	XY	XY	XY

a) Container is a 50 mL Aramus Bag
X = Appearance, Filtered mean particle size, Polydispersity
Y = Encapsulation, RNA Purity, RNA content, Lipid content, Lipid purity
Z = pH, Osmolality, Bacterial Endotoxins, Residual Solvent (Ethanol)
C = pH

Table 17: Stability Protocol for Clinical GMP mRNA-1273 LNP

Condition[a]	Time Interval (Months)										
	0	1	2	3	6	9	12	18	24	30	36
-60 to -90°C	A, B, C	A	A	A	A	A	AB	A	AB	A	AB
5°C ± 3°C		A	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

a) Container is a 50 mL Aramus Bag
A = Appearance, pH, RNA content, %RNA encapsulation, %Purity and %Impurities, %Lipid content and lipid impurities, mean particle size and polydispersity
B = Bacterial endotoxin
C = Bioburden, lipid identification, lipid identity, osmolality, residual solvent: Ethanol
N/A = Not tested per the stability protocol

Table 18: Stability Protocol for GMP mRNA-1273 LNP

Condition[a]	Time Interval (Months)									
	0	1	2	3	6	9	12	18	24	36
-60 to -90°C	ABC	A	A	A	A	A	AB	A	AB	AB
5°C ± 3°C		A	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

a) Container is a Aramus Bag at ambient relative humidity
A = Appearance, pH, filter mean particle size and polydispersity, RNA content, %RNA encapsulation, %Purity and %Impurities, %Lipid content and lipid impurities,
B = Bacterial endotoxin
C = Bioburden, lipid identification, identity, osmolality
N/A = Not tested per the stability protocol

Table 19: Stability Protocol for GMP mRNA-1273 LNP Lot 5008921002

Condition[a]	Time Interval (Months)						
	0	1	2	3	6	12	24
-60 to -90°C	ABC	N/A	N/A	A	A	ABC	ABC
5°C ± 3°C		A	ABC	N/A	N/A	N/A	N/A

a) Container is a Aramus Bag at ambient relative humidity
A = Appearance, pH, filter mean particle size and polydispersity, %RNA encapsulation, %Purity and %Impurities,
B = %Lipid content and lipid impurities, RNA content
C = Bacterial endotoxin

Table 20: Stability Protocol for GMP mRNA-1273 LNP Manufactured at Lonza AG (Visp, Switzerland)

Condition[(a)]	Time Interval (Months)								
	0	1	2	3	6	9	12	18	24
-60 to -90°C	ABCD	A	A	A	A	A	AB	A	ABD
5°C ± 3°C		A	A	A	A	N/A	N/A	N/A	N/A

a) Container is an Aramus Bag at ambient relative humidity
A = Appearance, pH, filter mean particle size and polydispersity, RNA content, %RNA encapsulation, %Purity and %Impurities, %Lipid content and lipid impurities
B = Bacterial endotoxin
C = Lipid identification, identity, osmolality
D = Bioburden
N/A = Not tested per the stability protocol

Table 21: Stability Protocol for GMP mRNA-1273 LNP Manufactured at Rovi (Granada, Spain)

Condition[(a)]	Time Interval (Months)									
	0	1	2	3	6	9	12	18	24	36
-60 to -90°C	ABCD	A	A	A	A	A	AB	A	ABC	AB
5°C ± 3°C		A	A	A	N/A	N/A	N/A	N/A	N/A	N/A

a) Container is a CCI Bag at ambient relative humidity
A = Appearance, pH, %Purity and %Impurities, particle size, polydispersity, Total RNA concentration, %RNA encapsulation, %Lipid identity, content and lipid impurities
B = Bacterial endotoxins
C = Bioburden
D = Identity, osmolality
N/A = Not tested per the stability protocol

Table 22: Stability Protocol for GMP mRNA-1273 LNP – B Manufactured at ModernaTX, Inc. (Norwood, USA)

Condition[(a)]	Time Interval (Months)							
	0	1	2	3	6	12	24	36
-60 to -90°C	AB	A	N/A	A	A	AB	AB	AB
5°C ± 3°C		A	AB	N/A	N/A	N/A	N/A	N/A

a) Container is an Aramus Bag at ambient relative humidity
A = Appearance, pH, filter mean particle size and polydispersity, %RNA encapsulation, %Purity and %Impurities
B = RNA Concentration, Lipid content and lipid impurities, Bacterial endotoxin
N/A = Not tested per the stability protocol

Table 23: Stability Protocol for GMP mRNA-1273 LNP – B Manufactured at Lonza AG (Visp, Switzerland)

Condition[(a)]	Time Interval (Months)								
	0	1	2	3	6	9	12	18	24
-60 to -90°C	ABCD	A	A	A	A	A	AB	A	ABD
5°C ± 3°C		A	A	A	A	N/A	N/A	N/A	N/A

a) Container is an Aramus Bag at ambient relative humidity
A = Appearance, pH, filter mean particle size and polydispersity, RNA content, %RNA encapsulation, %Purity and %Impurities, %Lipid content and lipid impurities
B = Bacterial endotoxin
C =Identity, osmolality
D = Bioburden
N/A = Not tested per the stability protocol

Table 24: Stability Protocol for GMP mRNA-1273 LNP – B Manufactured at Rovi (Granada, Spain)

Condition[a]	Time Interval (Months)								
	0	1	2	3	6	12	18	24	36
-60 to -90°C	ABCD	A	A	A	A	AB	A	ABC	AB
5°C ± 3°C		A	A	A	N/A	N/A	N/A	N/A	N/A

a) Container is an Aramus Bag at ambient relative humidity
A = Appearance, pH, %Purity and %Impurities, filter mean particle size and polydispersity, RNA content, %RNA encapsulation, %Lipid identity, content and lipid impurities
B = Bacterial endotoxin
C = Bioburden
D = Identity, osmolality
N/A = Not tested per the stability protocol

Stress Studies

A freeze-thaw stability study was performed using a representative lot of mRNA-1273 LNP, Lot AMPDP-200022. The mRNA-1273 LNP samples were subjected to a series of five freezing and thawing cycles and assessed for appearance, %RNA encapsulation, mean particle size and polydispersity.

No notable differences were observed in the mRNA-1273 LNP attributes after stored between -60°C to -90°C and thawed to either ambient temperature, room temperature or 2°C to 8°C. The data results presented in Section 3.2.S.7.3 {mRNA-1273 LNP}, show that the mRNA-1273 LNP biophysical attributes (particle size, polydispersity, encapsulation) are not impacted by the different freeze-thaw processes or 5 cycle times.

Stability Conclusion

The recommended storage condition for mRNA-1273 LNP is between -60°C to -90°C. Based on the available stability data , a shelf life of 12 months is proposed for mRNA-1273 LNP and mRNA-1273 LNP - B.

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

As stability studies are on-going to determine expiry for mRNA-1273 LNP, post-marketing stability commitments will be provided when available.

2.3.S.7.3 Stability Data

All stability data available are provided in Section 3.2.S.7.3 {mRNA-1273 LNP}.