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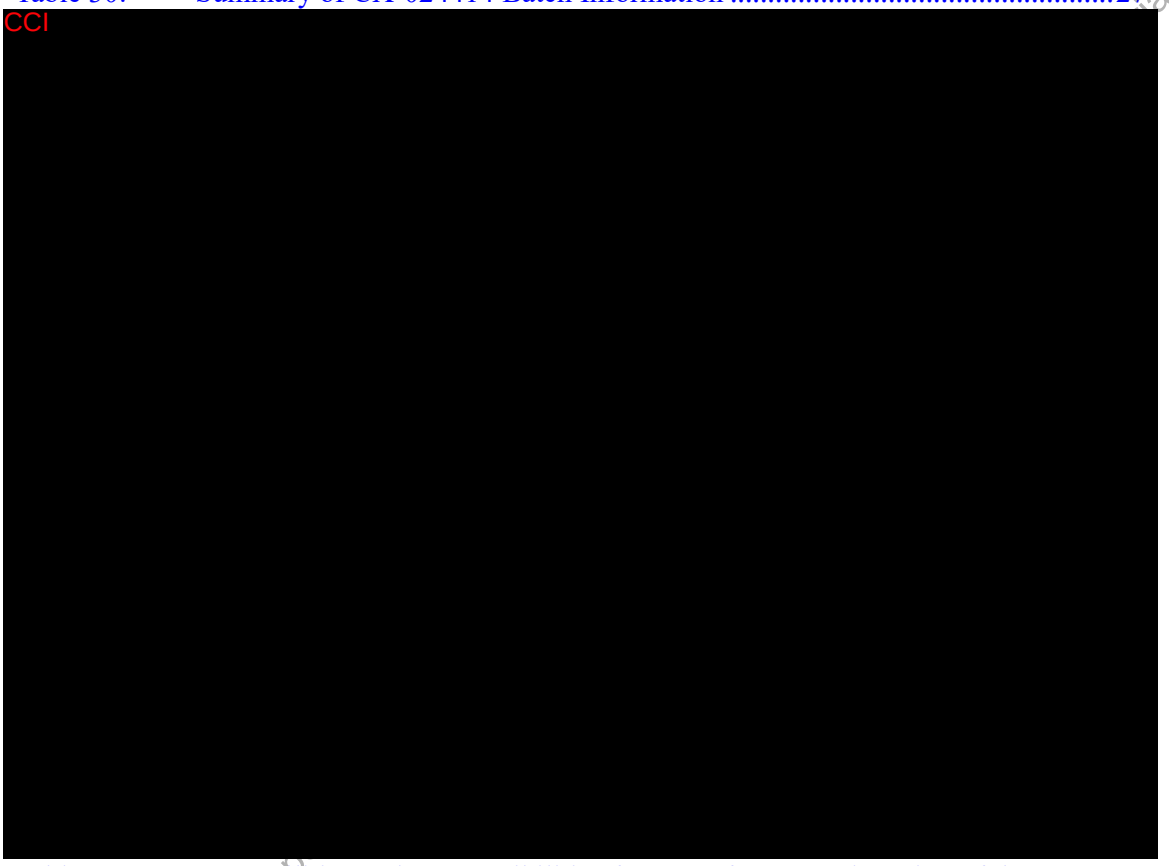

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DRUG SUBSTANCE CX-024414

MANUFACTURE CX-024414

MANUFACTURERS CX-024414

The US facilities and responsibilities for the manufacture and testing of CX-024414 are summarized in Table 1.

Table 1: US Facilities and Responsibilities for Manufacture and Quality Control Testing of CX-024414

Facility	Address	Responsibility
ModernaTX, Inc.	One Moderna Way Norwood, MA 02062 USA	• Manufacture of CX-024414 (10 L and 60 L IVT scales)
ModernaTX, Inc.	One Moderna Way Norwood, MA 02062 USA	• Release, stability, in-process testing of 10 L and 60 L IVT CX-024414 manufactured at ModernaTX Inc. Norwood. • Release, stability, in-process testing of 20 L and 60 L IVT CX-024414 manufactured at Lonza Biologics Inc. (excluding Bacterial endotoxin and bioburden)
ModernaTX, Inc. (Quality Control Laboratory Annex)	210 Rustcraft Road Dedham, MA 02026 USA	
Lonza Biologics, Inc.	101 International Drive Portsmouth, NH 03801 USA	• Manufacture of CX-024414 (20 L and 60 L IVT scale) • Release testing for Bacterial endotoxin and Bioburden for 20 L and 60 L IVT scales CX-024414 manufactured at site • Stability testing for Bacterial endotoxin 20 L and 60 L IVT scales CX-024414 manufactured at site

The European facilities and responsibilities for the manufacture and testing of CX-024414 are summarized in Table 2.

Table 2: European Facilities and Responsibilities for Manufacture and Quality Control Testing of CX-024414

Facility	Address	Responsibility
Lonza AG	Lonzastrasse 3930 Visp Switzerland	• Manufacture of CX-024414 (20 L IVT Scale) • Quality control testing (excluding Identity testing)
Lonza AG	Ibex Solutions Rottenstrasse 6 3930 Visp Switzerland	• Manufacture of CX-024414 (60 L IVT Scale)
Microsynth AG	Schützenstrasse 15 9436 Balgach Switzerland	• Quality control testing for identity of CX-024414

DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS CX-024414

Batch Scale and Definition

The nominal manufacturing batch size for CX-024414 mRNA at Lonza AG (Lonza Visp) (Visp, Switzerland) are a 20 L (Initial Scale B) and 60 L (Final Scale B) in vitro transcription (IVT) reaction volume and the nominal manufacturing batch size for CX-024414 mRNA at ModernaTX, Inc. (Norwood, MA, USA) and Lonza Biologics (Portsmouth, NH, USA) is 60 L (Final Scale B) IVT reaction volume. Batch size is maintained through the execution of approved, controlled batch records. Batch or lot numbers are unique identifiers for materials received or produced in the Systems, Applications, and Products enterprise resource planning software system (SAP). Batch numbers for commercial products will be generated utilizing the part number and the following logic 40075YYXXX, where "40075" represents the five-digit Item Number (Table 3), YY represents the year, and XXX represents a sequential number for CX-024414 mRNA at Lonza AG (Visp, Switzerland) and 40074YYXXX, where "40074" represents the five-digit Item Number (Table 3), YY represents the year, and XXX represents a sequential number for CX-024414 mRNA at Lonza AG (Visp, Switzerland).

Material manufactured at Lonza Biologics will also be assigned a Lonza Biologics-specific batch or lot number which is sequentially and automatically assigned by SAP. Material manufactured at Lonza AG will be given a Lonza Visp. The batch numbering for commercial batches produced at Lonza AG begins with 1000 for CX-024414 mRNA process 41001/51XXX/61XXX (Final Scale B). Batch numbers for each material increment consequently as batch production progresses.

Table 3: CX-024414 mRNA Item Numbers

Item Number	Nominal Batch Size	Manufacturing Site
40075 (Initial Scale- B)	20 L IVT	Lonza (Visp, Switzerland)
40074 (Final Scale- B)	60 L IVT	Lonza (Visp, Switzerland)
		Moderna Tx, Inc (Norwood, MA, USA)
		Lonza Biologics (Portsmouth, NH, USA)

Manufacturing Process Summary for CX-024414

The CX-024414 mRNA manufacturing process is shown in Figure 1, and in-process controls are listed in Table 4.

Figure 1: Process Flow Diagram

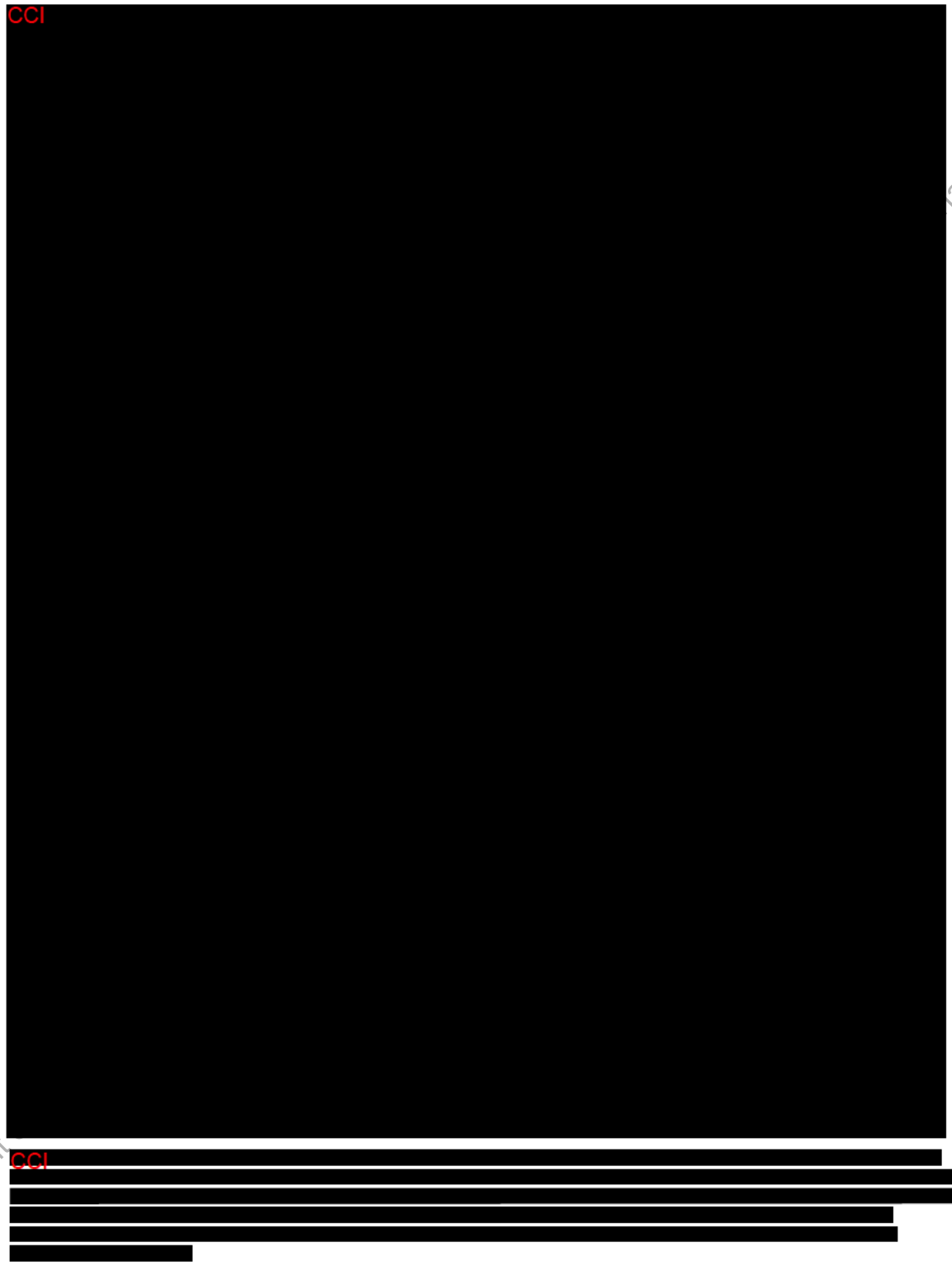

Table 4: In-process Controls

Attribute	Sample	Acceptance Criteria
mRNA content (Intact UV)	CCI	CCI Report Result CCI Report Result CCI
mRNA content (UV with Digest)		Report Result
Purity		Report Result
Product related impurities		Report Result
% Capped		Report Result
% Tailed		Report Result
% Tailless		Report Result
Residual DNA		Report Result
Residual protein		< 2.0% (w/w)
Bioburden		Report Result
Endotoxin		Report Result

Reprocessing

Reprocessing is not performed for any CX-024414 mRNA process step.

CONTROL OF MATERIALS CX-024414

Descriptions of the control of materials used in the manufacture of the CX-024414 are discussed in the following sections.

Control of Consumables

The quality management system describes the controls established for single-use consumables, including vendor selection and management; the identification, quarantine, storage, sampling, and acceptance of consumables; the documentation, investigation, and resolution of supplier-related non-conformances; and change control.

Single-Use Consumables

All single-use consumables used to manufacture CX-024414, consumable materials of construction (MOC), and the process step where they are used are listed in Module 3. Resins are multi-use materials and are discussed in the section below. Per procedures, all manufacturing consumables are sourced to be delivered gamma irradiated, steamed or sanitized in place, USP Class VI biocompatibility, and bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) conformance, at a minimum. The [redacted] affinity resin is tested in-house prior to use, but no other consumables used in the CX-024414 process are sampled or tested in-house. Some consumables, such as processing bags, transfer containers, and filters, are evaluated against additional criteria such as endotoxins/pyrogenicity, particulates, physical dimensions, and/or functionality testing by the supplier. All consumables are dispositioned by QC and QA prior to release in SAP.

Chromatography Media

The CCI resin used in CCI CX-024414 Oligo dT Affinity Chromatography operations consists of a polystyrene divinyl benzene backbone with a functionalized epoxy surface (immobilized Oligo dT ligand), received in a high-density polyethylene container. The resin, received as non-sterile, is packed and stored in 20% ethanol at 2 – 8°C. During incoming inspection, the resin is verified to conform with the material specification document, which includes certification of BSE/TSE compliance. Resin is received in pre-packed columns and tested as described in Table 5.

Table 5: CCI Pre-Packed Column Specification (Non-Compendial) [a]

Attribute	Specification
Vendor Specifications	
Column Efficiency (Plates / meter)	CCI
Column Asymmetry	
Endotoxins	
Bioburden	
Max. column hardware pressure	
Max. Packing pressure (bar)	Report
Max. packing flow rate (cm/hr)	Report
Additional In-House Specifications	
Product appearance	White to off-white slurry
Supplier batch number	Report
Comparison of certificate of analysis	Conforms
Valid BSE/TSE certificate available	Conforms

Abbreviations: BSE/TSE = bovine spongiform encephalopathy/transmissible spongiform encephalopathy; CFU = colony-forming unit(s); EU = endotoxin unit(s); FTIR = Fourier transform infrared spectroscopy; N/A = not applicable; NTU = nephelometric turbidity unit(s)

Control of Raw Materials

Quality of materials is assured through a rigorous system consisting of supplier evaluation, supplier qualification, audits, quality agreements, incoming goods testing, internal release procedure, package selection, shipping, storage conditions, expiry dates, and/or sterility requirements, based on the risk and criticality of supplier and/or material.

Raw materials are received from qualified suppliers. The supplier qualification process demonstrates the supplier has an effective and acceptable Quality Management System in place and can meet the minimum quality requirements of the process. Qualified suppliers have been assessed and qualified using a supplier risk level review and audit requirements based on the materials to be sourced from the supplier. At ModernaTX, Inc., qualification includes verification of release assay performance. Supplier performance is maintained and monitored through routine surveillance audits, periodic re-verification of release assay performance, quality agreements, and change notification agreements based on supplier risk level.

Incoming raw materials are released based on the Certificate of Acceptance and/or incoming goods testing. The Certificate of Acceptance and/or testing results are compared against the material specification prior to material release. All incoming raw materials are stored in a GMP warehouse.

Critical Raw Materials

The risks related to quality will drive the level of criticality. The risk factors that drive the levels of criticality with regards to quality are composed of:

1. The type of material and its origin (chemical, biological, complexity, animal/human origin)
2. Where and how it is used in the process
3. Contact between RM and drug substance or product as well as process time
4. Manufacturing process capabilities to reduce its amount to acceptable levels
5. Its variability in terms of quality under the standard manufacturing process used by suppliers
6. The quality agreement-audited quality systems and change control notification
7. The storage condition, use, and re-use

CMA is defined by the level of understanding of its quality attributes on process and product critical quality attributes (CQAs).

Microbial Control

All raw materials comply with appropriate specifications for microbiological testing that have been specified based on the process stage where the material is used and in conjunction with the process microbial control strategy.

Materials of Biological Origin

mRNA Cap 2' P-Methyltransferase, DNase I (RNase free), Pyrophosphatase, T7 RNA Polymerase, and Vaccinia Capping System are prepared using a bacterial fermentation process.

Materials Used in the Production of CX024414

Raw materials used in the production of CX-024414 mRNA are categorized as compendial and non-compendial. Raw materials are supplied from approved, qualified suppliers and are released prior to use per controlled incoming material specifications and current GMP (cGMP) guidelines. At a minimum, all raw materials are confirmed to conform with Certificates of Analysis (CoAs) or Certificates of Compliance, which includes verification of bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) certificates, either as part of raw material selection and/or during prelease prior to use, per site procedures. In addition, all non-compendial raw materials are tested for identification or other material attributes.

Table 6 lists the input materials for CX-024414 mRNA manufacture, identifies the process step where each material is used, and specifies the material type and criticality. Critical material attributes (CMAs) for critical raw materials are defined in Table 7.

Table 6: Process Inputs to CX-024414 mRNA Manufacturing Process

Input Material	Process Step	Material Type	Criticality
CCI [redacted]		Non-compendial	Not critical
		Buffer	Not critical
		Non-compendial	Not critical
		Buffer	Not critical
		Buffer	Not critical
		Buffer	Not critical
		Buffer	Not critical
		Buffer	Not critical
		Buffer	Not critical
		Non-compendial	Not critical
		Buffer/ Non-compendial	Not critical
		Buffer	Critical [(b)]
		Non-compendial	Not critical
		Non-compendial	Not critical
		Non-compendial	Not critical

CCI [redacted]

Table 7: Critical Material Attributes

Material	Critical Material Attribute
CCI [redacted]	Identity

CCI [redacted]

CCI [redacted] is manufactured by CCI [redacted] and is stored at CCI [redacted]

Buffer Compositions

Buffers used in the CX-024414 mRNA manufacturing process are listed in Table 8.

Table 8: CX-024414 mRNA In Process Buffers

Buffer	Where Used
CCI [redacted]	

CCI [redacted]

Compendial Raw Materials

All CX-024414 compendial raw materials (Table 9) are buffer components.

Table 9: CX-024414 mRNA Compendial Raw Materials

Raw Material Component	Grade
CCI [redacted]	Ph. Eur., BP, USP
	Ph. Eur., BP, JP, USP
	Ph. Eur, USP, JP
	Ph. Eur., BP, NF, JP
	Ph. Eur.
	Ph. Eur., BP, USP, JPC
	Ph. Eur., BP, USP, JP
	Ph. Eur., BP, USP, JP
	Ph. Eur., BP, JP, USP
	Ph. Eur., BP, JP, NF
	Ph. Eur., BP, ChP, JPC, USP

CCI [redacted]

Non-Compendial Raw Materials

Non-compendial raw materials used in the CX-024414 mRNA manufacturing process are listed in Table 10.

Recombinant proteins used in CX-024414 manufacturing include CCI [redacted]. These materials are produced in E. coli and are purchased from CCI [redacted]

Table 10: CX-024414 mRNA Non-Compendial Raw Materials

Non-Compendial Raw Materials	Where Used
CCI [redacted]	

Custom Raw Materials

There are no custom raw materials used in the CX-024414 mRNA manufacturing process.

Extractables and Leachables for CX-024414

The potential extractables and leachable from manufacturing components and container closure systems were evaluated for all materials with liquid product contact used in CX-024414 process, with the exception of the following.

- Stainless steel equipment, reusable flex lines, gaskets, and O-rings, as these components are assessed as part of equipment qualification activities.
- Single-use components for weighing and dispensing raw materials, as these are typically short contact duration, not exposed to product, and have very low contact area.
- Chromatography resins, as these are considered raw materials.

Risk Assessment

A systematic risk assessment was performed in alignment with the BioPhorum Operations Group best practice guides for evaluating extractables and leachable in biopharmaceutical manufacturing systems. An overall leachable risk rating (LRR) was calculated for each material as a weighted sum of risk parameters (distance along the process stream, exposure temperature, exposure duration, process fluid interaction, dilution ratio).

Buffer Storage Components

Buffer storage components were evaluated independently from the manufacturing processes because of the potential for prolonged exposure duration during storage relative to typical processing times. No high-risk materials were identified for buffer storage.

CX-024414 Manufacturing Process

The materials designated as medium risk are provided in Module 3. No high-risk materials were identified for the CX-024414 manufacturing process.

Control of starting materials

The starting materials in the manufacture of CX-024414 are the linearized plasmid template and the nucleotides ATP, CTP, GTP, N-1-Me-Pseudo UTP.

Linearized Plasmid Template

Critical material attributes (CMAs) for the linearized plasmid template are defined in Table 11. Table 12 identifies the process step where the material is used and specifies the material type and criticality.

Table 11: Critical Material Attributes

Material	Critical Material Attribute
Plasmid	Identity (sequence), % Linear

Table 12: Process Inputs to CX024414 mRNA Manufacturing Process

Input Material	Process Step	Material Type	Criticality
Linearized plasmid template	In Vitro Transcription	Custom	Critical

2.3.S.3.2.5.2 Nucleotides

Quality of materials is assured through a rigorous system consisting of supplier evaluation, supplier qualification, audits, quality agreements, incoming goods testing, internal release procedure, package selection, shipping, storage conditions, expiry dates, and/or sterility requirements, based on the risk and criticality of supplier and/or material.

Critical Materials

Starting materials used in the production of CX-024414 mRNA are categorized as Non compendial. These materials are supplied from approved, qualified suppliers and are released prior to use per controlled incoming material specifications and current GMP (cGMP) guidelines. At a minimum, all materials are confirmed to conform with Certificates of Analysis (CoAs) or Certificates of Compliance, which includes verification of bovine spongiform

encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) certificates, certificates either as part of raw material selection and/or during release prior to use, per site procedure. In addition, all Non compendial materials are tested for identification or other material attributes.

Table 13 lists the starting materials for CX-024414 mRNA manufacture, identifies the process step where each material is used, and specifies the material type and criticality. Critical material attributes (CMAs) for critical materials are defined in Table 14.

Table 13: Process Inputs to CX024414 mRNA Manufacturing Process

Input Material	Process Step	Material Type	Criticality
CCI [redacted]		Noncompendial	Critical
		Noncompendial	Critical
		Noncompendial	Critical
		Noncompendial	Critical

CCI [redacted]

Table 14: Critical Material Attributes

Material	Critical Material Attribute
CCI [redacted]	Identity, Purity
	Identity, Purity
	Identity, Purity
	Identity, Purity

CCI [redacted]

CCI [redacted]

Representative Certificate of Analyses and BSE/TSE statements for each starting material listed in Table 15 are provided in Module 3.

Specifications for non-compendial starting materials are provided in Module 3.

Table 15: CX-024414 mRNA Non-Compendial Starting Materials

Non-Compendial Starting Materials	Where Used
CCI [redacted]	

CONTROLS OF CRITICAL STEPS AND INTERMEDIATES CX-024414

This section presents the process control strategy and methods for critical in-process controls testing for the CX-024414 mRNA manufacturing process.

The control strategy for CX-024414 mRNA is a science- and risk-based approach to ensure consistent process performance and quality. It has been developed with a comprehensive understanding of the process and product to ensure critical quality attributes (CQAs) consistently remain within acceptable limits. Critical process parameters are classified as such. All characterized process parameters have target values or manufacturing limits represented by proven acceptable ranges (PARs).

Critical Process Parameters

CPPs and their PARs for the CX-024414 mRNA manufacturing process are provided in Table 16.

Table 16: Critical Process Parameters

Step	CPP	PAR	Rationale
CCI [redacted]			

CCI [redacted]

Microbial Control

The CX-024414 mRNA manufacturing process is carried out in a controlled manufacturing area. 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 in-house or are intended to be sanitized in place. The exceptions to this are the chromatography and tangential flow filtration (TFF) skids, which use clean in place cycles for equipment sanitization.

The operations and manufacturing controls specifically intended for microbial control of the CX-024414 mRNA manufacturing process are listed in Table 17.

Table 17: Microbial Controls

Step	Operation / IPC	Test / Description	Target
CCI [redacted]			N/A
			CCI [redacted]
			N/A
			CCI [redacted]
			Report results [b]
			Report results [c]
			CCI [redacted]
			N/A
			N/A
			CCI [redacted]
			N/A
			Report results
			Report results [c]
			N/A
			N/A
			CCI [redacted]
			N/A
			CCI [redacted]
			Report results
			Report results [c]
			CCI [redacted]
			N/A
			N/A
			Report results
			Report results
			N/A
			CCI [redacted]

CCI [redacted]

In-process Holds

Process intermediate hold limits are provided in Table 18.

Table 18: In-process Hold Times

Step	Operation	Activity/Description	Duration
CCI [redacted]			

CCI [redacted]

Resin and Membrane Lifecycles and Column Reuse

The chromatography resin in the CX-024414 mRNA manufacturing process may be re-used for processing multiple batches. Scale-down models were developed and used to evaluate the maximum number of cycles that the resin can be used and to provide justification for the reuse of the TFF membrane for the four TFF operations that occur in a single batch. The acceptable resin and membrane lifecycles are provided in Table 19.

Table 19: Resin and Membrane Lifecycles

Unit Operation	Resin / Membrane	Maximum Lifetime/Cycles
CCI [redacted]		

CCI [redacted]

Critical In process- Controls Testing

The critical in-process testing and associated method references for the CX-024414 mRNA manufacturing process are summarized in Table 20. In-process sample matrices were qualified and/or validated for the appropriate criteria as described in ICH Q2.

Table 20: Critical In-process Controls

Step	CIPC	Acceptance Criteria	Method Reference
CCI			SOP-0882
			Lonza AG: GROUP-107932

CCI

PROCESS VALIDATION AND/OR EVALUATION CX-024414

A Process Validation Master Plan was developed to ensure that the commercial manufacturing process for CX-024414 mRNA will reliably and consistently produce product of appropriate quality.

Product development of CX-024414 mRNA was accelerated in response to the COVID-19 pandemic. To accelerate the collection of scientific data that demonstrate process consistency, the process performance qualification (PPQ) was executed concurrently with process development activities. The process parameters and proven acceptable ranges (PARs) evaluated during PPQ were determined prior to the completion of the process development activities. The final determination of critical process parameters (CPPs) and PARs will be based on the results of PPQ and the process development data.

Three PPQ lots (10 L IVT scale) were completed at ModernaTX, Inc. in Norwood, to demonstrate process consistency for CX-024414 mRNA manufacturing process at ModernaTX, Inc., in Norwood, MA, Suite 1183 (Table 21).

PPQ has been completed for 60 L IVT scale to demonstrate process consistency for CX024414 mRNA manufacturing at ModernaTX, Inc. in Norwood, MA, (Suite 1280, Suite 1183 and Suite 1268) (Table 21). The process parameters and PARs were determined prior to the initiation of PPQ activities.

Table 21: CX-024414 mRNA Process Performance Qualification Lots

Manufacturing Location	Scale	Moderna Lot Number (Lonza Lot Number)	Date of Manufacture
ModernaTX, Inc. Norwood, MA	10 L	4007220003	20-May-20
	10 L	4007220004	04-Jun-20
	10 L	4007220005	18-Jun-20
	60 L	4007420003	19-Oct-20
	60 L	4007420004	31-Oct-20
	60 L	4007420006	10-Nov-20
	60 L	4007420007	12-Nov-20
	60 L	4007420021	06-Jan-21

Full details of the PPQs are available in summary report PV-VAL-RPT-006 Process Performance Qualification summary report for CX-024414 mRNA (PN 40074)

Three PPQ lots (20 L IVT scale) were completed at Lonza Biologics, Inc. in Portsmouth, NH to demonstrate process consistency for CX-024414 mRNA manufacturing process (Table 22).

PPQ for the 60 L IVT scale CX-024414 mRNA manufacturing process at Lonza Biologics, Inc. (Portsmouth, NH, USA) has been completed (Table 1). The process parameters and PARs were determined prior to the initiation of PPQ activities.

Table 22: CX-024414 mRNA Process Performance Qualification Lots

Manufacturing Location	Scale	Moderna Lot Number (Lonza Lot Number)	Date of Manufacture
Lonza, Biologics, Inc. Portsmouth, NH	20 L	4007520002 (922693)	12-Aug-20
	20 L	4007520003 (928769)	25-Aug-20
	20 L	4007520004 (930143)	31-Aug-20
	60 L	4007421013 (960389)	12-Jan-21
	60 L	4007421017 (963102)	21-Jan-21
	60 L	4007421022 (963103)	28-Jan-21

For the 20 L and 60 L IVT PPQ scales at Lonza (Portsmouth, NH), all process parameters and in-process controls were evaluated during the PPQ and confirmed to be within target ranges.

Full details of the PPQ are available in summary report USPO-28706 (60 L IVT scale).

MANUFACTURING PROCESS DEVELOPMENT CX-024414

The initial development of CX024414 mRNA was conducted using equipment in ModernaTX, Inc.'s small-scale Personalized Vaccine Unit (PVU). In the PVU, the manufacturing operations for mRNA are completed as part of an integrated comprehensive process encompassing both CX-024414 mRNA and mRNA1273 Lipid Nanoparticle (LNP) processes for each lot of mRNA1273 Drug Product and does not include a separate release of the mRNA.

A lot of mRNA1273 mRNA Process Intermediate (MPI) (Lot 8410000101) was prepared to manufacture mRNA1273 Drug Product (Lot 8520100101) for use in the Phase 1 clinical studies. Subsequently, three additional lots mRNA1273 MPI were prepared (Lot 8410000102, Lot 8410000103 and Lot 8410000104) to support the manufacture of mRNA1273 Drug Product (Lot 8520100102, Lot 8520100103 and Lot 8520100104) for the Phase 2 clinical studies. As noted in Table 1, the batch sizes for these mRNA1273 MPI lots ranged from CCI scale to CCI scale.

Large-scale manufacturing process development was completed in the laboratories at ModernaTX, Inc. to establish unit operations and process parameter ranges for the manufacture of CX024414 mRNA at a 10 L IVT scale (Scale A) utilizing Moderna TX, Inc's 10 L IVT scale mRNA platform process. The mRNA process was developed to achieve targeted strength,

safety, and purity product quality attributes and to be comparable to previously manufactured MPI lots (8410000101, 8410000102, 8410000103, and 8410000104).

This process was subsequently transferred to the GMP manufacturing area to enable the manufacture of CX024414 mRNA (lot 4007220001 through lot 4007220005) at the 10 L IVT scale for the use in the manufacture of mRNA1273 DP for use in clinical studies. Small-scale studies were conducted, and process changes implemented after the manufacture of CX024414 mRNA Lot 4007220001 with the aim to increase the expected productivity of the 10 L IVT manufacturing process. Lots 4007220003 through 400722005 represent the PPQ lots for the Scale A CX-024414 mRNA process.

The process was transferred to Lonza Biologics, Inc. (Portsmouth, NH) for an additional scale-up to a 20 L IVT scale (PN 40075, Initial Scale B). One development lot, one GMP lot (prior to PPQ), and three PPQ lots were performed to establish the 20 L IVT scale process at Lonza. One development lot and one GMP lot were performed prior to PPQ as this was the first time Moderna's CX-024414 mRNA process was transferred to Lonza.

Initial Scale B was also transferred to Lonza, Visp (20 L IVT) (PN 40075) and several changes were made to accommodate the site and scale changes (Table 6). Changes were made to material sourcing due to regional availability, operations to maintain aseptic processing aligned with
facility fit, and operational improvements. This manufacturing process is described in Section 3.2.S.2.2 {CX024414 – Lonza Visp}.

The full commercial scale has been increased and has been implemented at the US manufacturing sites (with implementation planned for Lonza Visp) to the 60 L IVT scale (PN 40072) (Scale B Final). Plans to execute the 60 L IVT scale process at Lonza Visp are currently ongoing and data will be shared once implementation of the 60 L IVT scale process at Lonza Visp site will be completed.

Overview - CX-024414 mRNA

A summary of CX-024414 mRNA lots manufactured to date is provided in Table 23.

Table 23: Manufacturing History – CX-024414 mRNA

CX-024414 mRNA/MPI Lot	DOM	Manufacturer	IVT Scale/Process	Process Train	Disposition / Use
8410000101	07 Feb 2020 [a]	Moderna (Norwood, MA)	CCI	NA	Phase 1 (DMID Protocol 20-0003)
8410000102	19 Mar 2020 [a]	Moderna (Norwood, MA)		NA	Phase 2
8410000103	23 Mar 2020 [a]	Moderna (Norwood, MA)		NA	Phase 2
8410000104	02 Apr 2020 [a]	Moderna (Norwood, MA)		NA	Phase 2
MTDS20002	26 Mar 2020	Moderna (Norwood, MA)		NA	Developmental lot Reference standard
4007220001	03 Apr 2020	Moderna (Norwood, MA)	10 L/Scale A	NA	Not currently used in clinical materials
4007220002 [b]	04 May 2020	Moderna (Norwood, MA)	10 L/Scale A	NA	Phase 3
4007220003 [b]	20 May 2020	Moderna (Norwood, MA)	10 L/Scale A	NA	PPQ
4007220004 [b]	04 Jun 2020	Moderna (Norwood, MA)	10 L/Scale A	NA	PPQ
4007220005 [b]	18 Jun 2020	Moderna (Norwood, MA)	10 L/Scale A	NA	PPQ
01_5156DEV	10 Jul 2020	Lonza (Portsmouth, NH)	20 L/ Initial Scale B	NA	Developmental lot
Lonza Lot 918988 (4007520001)	28 Jul 2020	Lonza (Portsmouth, NH)	20 L/ Initial Scale B	NA	GMP
Lonza Lot 922693 (4007520002)	12 Aug 2020	Lonza (Portsmouth, NH)	20 L/ Initial Scale B	NA	PPQ
Lonza Lot 928769 (4007520003)	25 Aug 2020	Lonza (Portsmouth, NH)	20 L/ Initial Scale B	NA	PPQ
Lonza Lot 930143 (4007520004)	31 Aug 2020	Lonza (Portsmouth, NH)	20 L/ Initial Scale B	NA	PPQ
Lonza Lot 1000 (4007520801)	11 Nov 2020	Lonza AG (Visp, Switzerland)	20 L/Initial Scale B	Lonza Train 4a	GMP
Lonza Lot 1001 (4007520802)	30 Nov 2020	(Visp, Switzerland)	20 L /Initial Scale B	Lonza Train 4a	PPQ
Lonza Lot 1002 (4007520803)	16 Dec 2020	Lonza AG (Visp, Switzerland)	20 L /Initial Scale B	Lonza Train 4a	PPQ
Lonza Lot 1003) (4007520804)	23 Dec 2020	Lonza AG (Visp, Switzerland)	20 L /Initial Scale B	Lonza Train 4a	PPQ

Abbreviations: DOM = date of manufacture; PVU = personalized vaccine unit; RCB = research cell bank; WCB = working cell bank
Drug Product DOM
Additional process enhancements made prior to lot 4007220002

Summary of manufacturing process changes

Summary of manufacturing process changes from development through PPQ is provided in Module 3.

CX-024414 mRNA Process Characterization

In accordance with ICH Q9, a systematic assessment of the potential risk to CX-024414 mRNA product quality was performed with respect to the manufacturing process. A science-based approach was used to identify Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Critical In-Process Controls to inform process design studies and to establish the manufacturing control strategy. The proposed CQAs for CX-024414 mRNA are summarized below in Table 9. The CPPs for the CX024414 mRNA manufacturing process are provided in Table 10. The CIPC for the CX024414 mRNA manufacturing process is provided in Table 11.

Table 24: CX-024414 mRNA Critical Quality Attributes

Attribute	Target Acceptance Criteria
Appearance	Clear, colorless solution, essentially free of visible particulates
Identity	Sequence matches 100% of description coding region
pH	CCI
Purity	
Product Related Impurities	
% 5' Capped	
% PolyA Tailed RNA	
% Tailless RNA	
Residual DNA Template	
Residual Protein	
Bacterial Endotoxins	
Bioburden	

CCI

Table 25: CX-024414 mRNA Critical Process Parameters

Step	Process Variable	Target	PAR	Potential CQA Impact	Rationale
CCI					

CCI

Table 26: Critical In-Process Controls Tests

Step	CIPC	Acceptance Criteria	Method Reference
CCI			SOP0882

CCI

BATCH ANALYSIS CX-024414

CX-024414 GMP lots are intended for further manufacturing into mRNA-1273 Drug Product GMP lots.

Batch analysis date is generated for CX-024414 according to an approved specification as presented in Section 3.2.S.4.1 CX-024414

Refer to Section 3.2.S.2.4.4 {CX-024414} for full details concerning batch analysis data.

CONTAINER CLOSURE SYSTEM CX-024414

CX-024414 mRNA is stored frozen in gamma irradiated, single-use storage bags as a low bioburden material. The CX-024414 mRNA is dispensed into bags utilizing aseptic connections. The filled bags are directly processed or stored at -15°C to -25°C prior to mRNA-1273 LNP manufacture. A microbial control strategy and stability protocols are in place to ensure that bioburden limits remain below specifications during storage. Two storage bag options are available as described below.

Storage Bags

The Mobius storage bag assemblies are manufactured from PureFlex film, which is composed of ultra-low density polyethylene (ULDPE) product contact and ethylene vinyl acetate (EVA) support structure. The bags are equipped with three ports with C-Flex and silicone tubing. 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>.

The CCI storage bag assemblies are manufactured from CCI film, which is composed of ultra-low density polyethylene (ULDPE) product contact and ethylene vinyl acetate (EVA) and polyamide (PA) support structure. The bags are equipped with three ports with silicone tubing. 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>.

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 materials also meet the requirements for physicochemical testing as described in USP <661> (Plastic Packaging Systems and their Materials of Construction).

The storage bags meet the USP Class VI requirements and is determined to be nonpyrogenic at a level of < 0.25 EU/mL per USP <85>.

Each incoming lot is received with a Certificate of Quality, which documents completion of the gamma irradiation cycle. The storage system is rated at an operating range of -80°C to 60°C (CCI max operating temperature of 40°C), which accommodates the CX-024414 manufacturing process parameters. The manufacturer has assigned a post gamma irradiation sterilization shelf life of two years (3 years for CCI).

There are no functional secondary packaging components.

Materials of Construction

Materials of construction for the primary container closure are provided in Table 27 and Table 28. No animal-derived materials are used in the manufacture of the Mobius product fluid pathway raw materials.

Table 27: Mobius Bag Materials of Construction

Primary Container Component	Material of Construction
Bag	PureFlex film (ULDPE, EVA), 10 mil, gamma-stable
Tubing Connection	AseptiQuick G, polycarbonate, USP Class VI
Tubing	Silicone/C-Flex

Table 28: CCI Bag Materials of Construction

Primary Container Component	Material of Construction
Bag	CCI [redacted]
Tubing Connection	
Tubing	

Suitability

The suitability of the selected primary container closure for CX-024414 has been demonstrated through a combination of long-term stability studies conducted with comparable platform-based product and real-time/accelerated stability studies currently in progress.

Extractables and Leachables

An extractables and leachable assessment was performed for the storage bags.

Component Risk Assessment

The overall leachables risk rating (LRR) is calculated as follows:

$$LRR = DAS * Weight(0.4) + ET * Weight(0.15) + ED * Weight(0.15) + PFI * Weight(0.15) + DR * Weight(0.15)$$

The storage bags resulted in a Leachables Risk Ranking (LRR) of Medium (Table 29). For Medium Risk materials, the following verification was performed through a review of available vendor documentation to mitigate the risk:

- Conformance to USP Class VI requirements confirmed.
- Conformance to EP 3.1.5 and EU 10/2011 confirmed for primary container.

Based on the risk assessment performed, it is concluded that the storage bags pose negligible safety risk to humans.

Table 29: LRR Assessment for Storage Bags

Unit Operation	Component	DAS	ET	ED	PFI	DR	LRR	DAS Note	ET Note	ED Note	PFI Note	DR Note	USP Class VI Check	Comments
Storage	Bag, Mobius Select 2D, AQ	CCI											Passed	N/A
Storage	CCI												Passed	N/A

Abbreviation: DAS = Distance along the production stream; DR = Dilution ratio; ED = Exposure duration; ET = Exposure temperature; LRR = Leachables risk rating; PFI = Process fluid interaction

STABILITY SUMMARY AND CONCLUSIONS CX-024414

The CX-024414 mRNA 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.

Stability and characterization studies were designed to evaluate product stability under various stressed and long-term storage conditions. All lots were manufactured using the manufacturing process described in Section 3.2.S.2.2 {CX-024414}. Stability samples were stored in containers made of the same materials (high-density polyethylene bottle with a polyethylene terephthalate glycol cap) as the commercial closure system.

An overview of the CX-024414 mRNA stability program is outlined in Table 30.

Table 30: Summary of CX-024414 Batch Information

Lot Number	Usage	Manufacturing Site	Date of Manufacture
MTDS20002	Toxicology, Development	ModernaTX, Inc. Cambridge, MA	March 26, 2020
4007220001	Phase 3 Clinical Supplies	ModernaTX, Inc. Norwood, MA	April 03, 2020
4007220002	Phase 3 Clinical Supplies	ModernaTX, Inc. Norwood, MA	May 04, 2020
4007220003	Phase 3 Clinical Supplies (10 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	May 20, 2020
4007220004	Phase 3 Clinical Supplies (10 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	June 04, 2020
4007220005	Phase 3 Clinical Supplies (10 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	June 18, 2020
4007520001	GMP	Lonza Biologics, Inc. Portsmouth, NH	July 28, 2020
4007520002	GMP (20 L IVT PPQ)	Lonza Biologics, Inc. Portsmouth, NH	August 12, 2020
4007520003	GMP (20 L IVT PPQ)	Lonza Biologics, Inc. Portsmouth, NH	August 25, 2020
4007520004	GMP (20 L IVT PPQ)	Lonza Biologics, Inc. Portsmouth, NH	August 31, 2020
4007420003	GMP (60 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	October 19, 2020
4007420004	GMP (60 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	October 31, 2020
4007420006	GMP (60 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	November 10, 2020
4007420007	GMP (60 L IVT PPQ)	Norwood, MA	November 12, 2020

CX-024414 material stored in the commercial container closure system is assigned a shelf life of 12 months when stored at the recommended long-term storage condition of -20 ± 5°C.

The shelf life is justified from the composite of data generated from 3 PPQ lots, 2 clinical lots, and 1 development lot. The release and stability testing results at T = 6 month for MTDS20002 stored at -20 ± 5°C have met target attributes as presented in Section 3.2.S.7.3 {CX-024414}. The release and stability testing results at T = 3 month for the 3 PPQ lots and 2 clinical lots stored at -20 ± 5°C have met target attributes as presented in Section 3.2.S.7.3 {CX-024414}.

Refer to Section Section 3.2.S.7.3 {CX-024414} for full detailed results on stability studies conducted for CX-024414.

CCI

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CCI

CCI

CCI

CCI

CCI

CCI [redacted]

DRUG SUBSTANCE mRNA-1273 LNP

MANUFACTURE mRNA-1273 LNP

MANUFACTURERS mRNA-1273 LNP

The name and address for the US manufacturing and testing facilities of mRNA-1273 Lipid Nanoparticle (LNP) are listed in Table 51.

Table 51: US Facilities and Responsibilities for Manufacture and Testing of the mRNA1273 Lipid Nanoparticle (LNP)

Facility	Address	Responsibility
CCI [redacted]		• Manufacture of mRNA-1273 LNP (CCI [redacted] and 200 g Scale)
		• Release, stability and in-process testing of mRNA-1273 LNP manufactured at ModernaTX, Inc. Norwood (excluding bacterial endotoxin testing) • Release, stability and in-process testing of mRNA-1273 LNP manufactured at Lonza Biologics, Inc. Portsmouth (excluding bacterial endotoxin and bioburden testing)
		• Manufacture of mRNA-1273 LNP (200 g Scale) • Release testing for Bioburden of mRNA-1273 LNP manufactured at site
		• Release and stability testing of mRNA-1273 LNP (Bacterial endotoxin)

The name and address for the European manufacturing and testing facilities of mRNA-1273 Lipid Nanoparticle (LNP) are listed in Table 52.

Table 52: European Facilities and Responsibilities for Manufacture and Testing of the mRNA1273 Lipid Nanoparticle

Facility	Address	Responsibility
CCI		• Manufacture of mRNA-1273 LNP (CCI Scale) • Quality control testing (excluding Identity testing)
		• Manufacture of mRNA-1273 LNP (200 g Scale)
		• Quality control testing for identity of mRNA-1273 LNP
		• Quality control testing
List of Testing Exceptions		
CCI		• Bacterial Endotoxin testing

DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS MRNA-1273 LNP

Batch Scale and Definition

mRNA-1273 Lipid Nanoparticle (LNP) is manufactured at Lonza AG (Lonza Visp) (Visp, Switzerland) at CCI and 200 g batch sizes and at ModernaTX, Inc. (Norwood, MA, USA) and Lonza Biologics (Portsmouth, NH, USA) at 200 g batch size. Batch size is maintained through the execution of approved, controlled batch records. Batch or lot numbers are unique identifiers for materials, received or produced, in the SAP (Systems Applications and Products in Data Processing) and computer system. Batch numbers will be generated using the part number and the following logic: 500AAYYXXX, where "500AA" represents the five-digit Item Number and AA represents the scale (Table 3) YY represents the year, and XXX represents a sequential number.

Lonza Visp is given a Lonza Visp-specific batch number, which is assigned by SAP. The batch numbering for commercial batches produced at Lonza Visp begins with 3000 for CCI mRNA-1273 LNP manufacturing process. For 200 g scale mRNA-1273 LNP manufacturing process, commercial batch numbering will begin with X3001, where X represents the identifier for the Process Train or production line used in the manufacture of the batch (Process Train 4, Process Train 5, and Process Train 6). Batch numbers for each material increment consequently as batch production progresses.

Table 53: mRNA-1273 Lipid Nanoparticle Item Numbers

Item Number	Nominal Batch Size	Manufacturing Site
50073	CCI	Lonza AG (Lonza Visp) (Visp, Switzerland)
50075	200 g	Lonza AG (Lonza Visp) (Visp, Switzerland) ModernaTX, Inc. (Norwood, MA, USA) Lonza Biologics (Portsmouth, NH, USA)

mRNA1273 Lipid Nanoparticle Process Summary

The purpose of the mRNA-1273 LNP manufacturing process CCI CCI 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 CCI (Figure 3): CCI manufacture of mRNA-1273 LNP, and manufacture of mRNA-1273 Drug Product; in process controls are provided in Table 54. CCI

Figure 3: mRNA-1273 Manufacturing Overview

Abbreviation: LNP = lipid nanoparticle

This mRNA-1273 LNP manufacturing process includes: CCI fill, freezing, and storage as shown in Figure 4, and process parameters are described in the associated tables, with detailed descriptions of each unit operation in subsections below.

CCI

CCI ; the resulting mRNA-1273 LNP dispersion is filled into bags for frozen storage between 60ºC to -90ºC until the fill/finish operation for mRNA1273 Drug Product.

Figure 4: mRNA-1273 LNP Process Flow Diagram

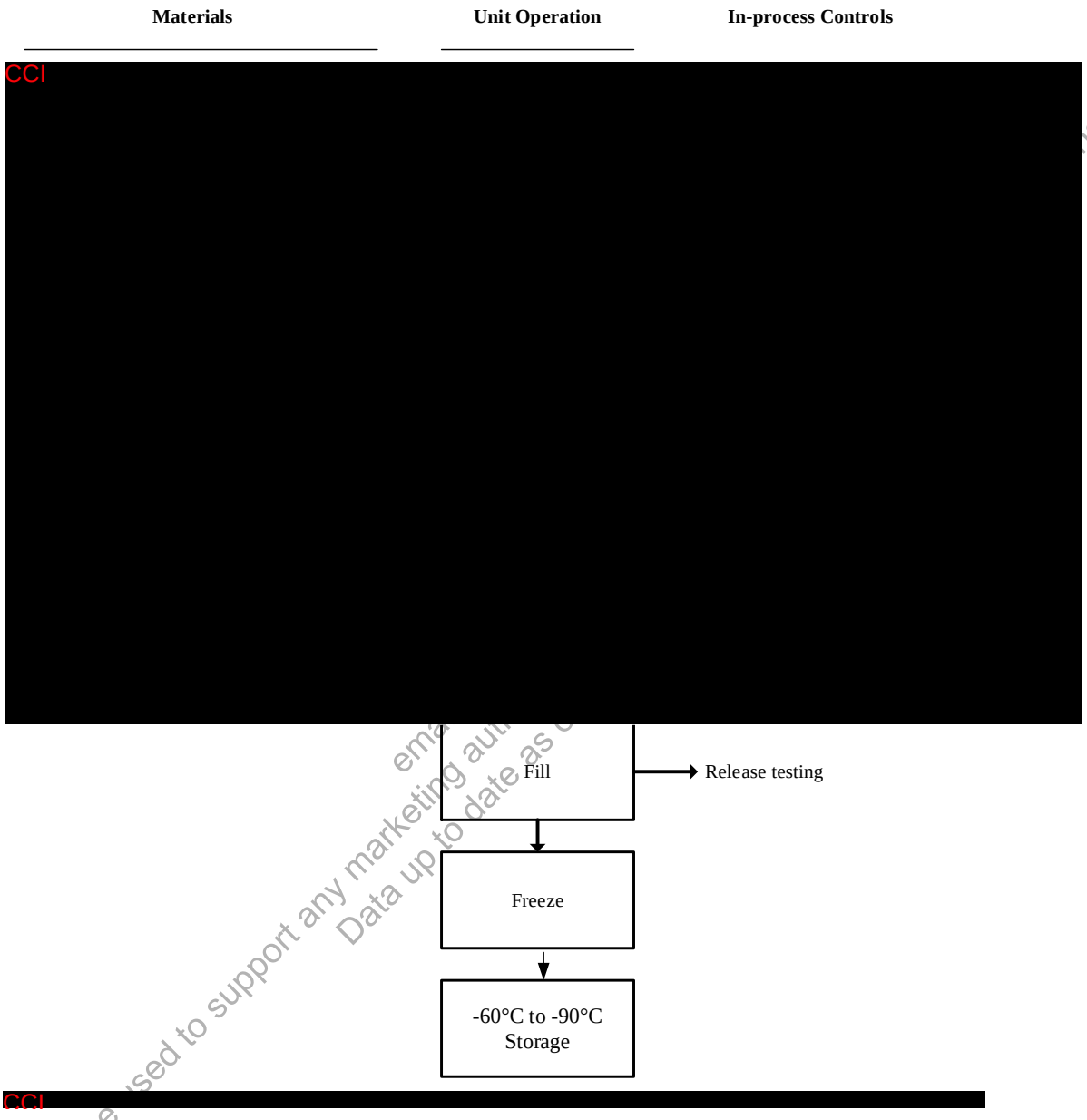

Table 54: In-process Controls

Attribute	Sample	Acceptance Criteria
mRNA concentration (AEX chromatography)	CCI	
mRNA concentration (AEX chromatography)		
Lipid content (UPLC-CAD)		
Bioburden	CCI	Report Results[a]
Bacterial Endotoxins		Report Results

Abbreviations: AEX = anion exchange chromatography; UPLC-CAD = reversed-phase ultra high-performance liquid chromatography with charged aerosol detection
a) Lonza Biologics: CCI

Shipping

The mRNA-1273 LNP is shipped in qualified dry ice passive shippers for road freight or by air. The maximum allowable transportation time will be constrained within the qualified duration of the shipper. Temperature loggers will be utilized to monitor the worst-case locations within the shipper; the worst-case location is determined by hot spots identified from operational qualification data.

Reprocessing

Reprocessing is not performed for any mRNA-1273 LNP process step.

CONTROL OF MATERIALS mRNA-1273 LNP

Descriptions of the control of materials used in the manufacture of the mRNA-1273 Lipid Nanoparticle (LNP) are discussed in the following sections.

Control of Consumables

Refer to Control of Consumables section for CX-024414.

mRNA-1273 Lipid Nanoparticle Single-Use Consumables

All single-use consumables used to manufacture mRNA-1273 LNP, consumable MOC, and the related process step are listed in Table 55 ([CCI] and 200 g Scales, Lonza Visp, Moderna Tx and Lonza Biologics). Per procedures, all manufacturing consumables are sourced to be delivered gamma irradiated, steamed, or sanitized in place, USP VI biocompatibility, and BSE/TSE requirements, at a minimum. No consumables used in the mRNA-1273 LNP manufacturing process are sampled or tested in-house. Some consumables, such as processing bags, transfer containers, and filters, are evaluated against additional criteria such as endotoxins/pyrogenicity, particulates, physical dimensions, and/or functionality testing by the supplier. All consumables are dispositioned by QC and QA prior to release in SAP.

Table 55: mRNA-1273 LNP Drug Substance Consumables CCI 200 g Scales, Lonza Visp)

Consumable	Fluid Path Primary Materials of Construction	Commercial Process Description Process Step
CCI		

Abbreviations: HDPE = high-density polyethylene; LLDPE = linear-low density polyethylene; PE = polyethylene; PES = Polyethersulfone; PC = polycarbonate; PP = polypropylene; PTFE = polytetrafluoroethylene; PVDF = polyvinylidene fluoride; ULDPE = ultra-low density polyethylene

Control of Raw Materials

Refer to Control of Raw Materials section for CX-024414.

Critical Raw Materials

Refer to Critical Raw Materials section for CX-024414.

Microbial Control

Refer to Microbial Control section for CX-024414.

Materials of Biological Origin

There are no materials of animal or human origin used in the manufacture of mRNA1273 LNP.

Raw Materials

Raw materials used in the production of mRNA-1273 LNP are categorized as compendial or noncompendial.

Table 56 lists the input materials for mRNA-1273 LNP manufacture, identifies the process step where each material is used, and specifies the material type and criticality. CMAs for critical raw materials are defined in Table 57.

Table 56: Process Inputs to mRNA-1273 LNP Manufacturing Process

Input Material	Process Step	Material Type	Criticality
CCI			N/A [(a)]
			Critical
			N/A [(a)]
			Critical
			Critical

a) Quality of the drug substances is assured by the release testing of those materials

Table 57: Critical Material Attributes

Material	CMAs
CCI	

Buffer Compositions

Buffers are prepared in-house according to approved, controlled manufacturing batch records that specify raw material quantity and addition sequence. All buffers are prepared using dispensed WFI and charged to either stainless steel or disposable, single-use mixing systems. Following sampling and in process testing, all buffers are filtered through sterilizing-grade filters and stored per defined storage times and conditions. Buffers are filtered in-line prior to use.

Buffers used in the mRNA-1273 LNP manufacturing process are listed in Table 58.

Table 58: mRNA-1273 LNP In Process Buffers

Buffer	Where Used
CCI	

a) Buffer used for equipment sanitization
b) Buffer used for equipment storage.

Compendial Raw Materials

Table 59: mRNA-1273 LNP Compendial Raw Materials

Raw Material Component	Grade
CCI	

All compendial raw materials are buffer components. Buffer compositions are provided in Section 0 {mRNA-1273 LNP – Lonza Visp}.

Non-Compendial Raw Materials

Non-compendial materials used in the manufacture of mRNA-1273 LNP are CCI

Custom Raw Materials

There are two vendors used to manufacture the PEG2000-DMG lipid component. A comparability assessment of the two materials has been performed. PEG2000-DMG is commercially available but is not contained in any approved products. PEG2000-DMG (Option A) is manufactured under cGMPs by CCI and by CCI (Option B). The product specifications are shown in Table 60 and Table 61. PEG2000-DMG is stored at -15ºC to -25ºC.

Table 60: Lipid, 1,2-Dimyristoyl-rac-glycero-3-methylpolyoxyethylene (PEG 2000-DMG) (Option A)

Attribute	Acceptance Criteria
Vendor Specifications	
Appearance	White to off-white powder
Identification	Conforms structure
Average molecular weight	CCI
Purity GM-020 (%)	
Content of Monomyristoylglycerol-PEG2000 (%)	Report value
Content of other PEG derivatives (%)	Report value
Content of free fatty acid (%)	Report value
Content of unknown (%)	Report value
Moisture (%)	CCI
Residual solvent (ppm) Acetonitrile Hexane Ethyl acetate Chloroform Toluene	
Endotoxin (EU/g)	
TAMC (CFU/g)	
TYMC (CFU/g)	
Cadmium (µg/g)	
Lead (µg/g)	
Inorganic arsenic (µg/g)	
Inorganic mercury (µg/g)	
In-House Specifications (Lonza Visp)	
Appearance	White to off-white
Colour	Powder
Identification (IR)	Conforms
BSE/TSE statement	Valid BSE/TSE statement is available
Excipient ID test on every container	Conforms
Results of full testing received	Conforms
InHouse Specifications (ModernaTX)	
Identification	Sample consistent with reference standard retention time criteria
BSE/TSE statement	Verify BSE/TSE statement has been received with each shipment
InHouse Specifications (Lonza Biologics)	
Appearance	White to off-white solid
Identification - FTIR	Conforms

Abbreviations: BSE/TSE = bovine spongiform encephalopathy/transmissible spongiform encephalopathy; CFU = colony-forming unit(s); EU = endotoxin unit(s); N/A = not applicable; TAMC = total aerobic microbial count; TYMC = total yeast and mold count

Table 61: Lipid, 1,2-Dimyristoyl-rac-glycero-3-methylpolyoxyethylene (PEG 2000-DMG) (Option B)

Attribute	Acceptance Criteria
Vendor Specifications	
Appearance	Solid, white to off-white
Identification	Conforms structure
Average molecular weight	CCI
Purity (% w/w)	
mPEG2000-Dimer (% w/w)	
mPEG2000-DMG-Myristoate (% w/w)	
mPEG2000-DMG-MMG (% w/w)	
mPEG2000-DMG-Glycerol+mPEG2000 (% w/w)	
Myristic acid (% w/w)	
Myristic anhydride (% w/w)	
Total impurities (% w/w)	
Moisture (%)	
Residual solvent (ppm) Toluene 2-propanol Methyl Tert-butyl Ether (MTBE) Methanol Acetonitrile n-Heptane Ethanol Acetone	
Endotoxin (EU/g)	
TAMC (CFU/g)	
TYMC (CFU/g)	
Cadmium (µg/g)	
Lead (µg/g)	
Inorganic arsenic (µg/g)	
Inorganic mercury (µg/g)	
In-House Specifications (Lonza Visp)	
Appearance	White to off-white
Colour	Powder
Comparison of CoA	Conforms
Identification (IR)	Conforms
BSE/TSE statement	Valid BSE/TSE statement is available
Excipient ID test on every container	Conforms
Retained sample received	Conforms
Results of full testing received	Conforms
InHouse Specifications (ModernaTX)	
Identification	Sample consistent with reference standard retention time criteria
BSE/TSE statement	Verify BSE/TSE statement has been received with each shipment
InHouse Specifications (Lonza Biologics)	
Appearance	White to off-white solid
Identification - FTIR	Conforms

Abbreviations: BSE/TSE = bovine spongiform encephalopathy/transmissible spongiform encephalopathy; CFU = colonyforming unit(s); EU = endotoxin unit(s); N/A = not applicable; TAMC = total aerobic microbial count; TYMC = total yeast and mold count

Extractables and Leachable for mRNA-1273 LNP

Refer to Extractable and Leachable section for CX-024414.

Risk Assessment

Refer to Risk Assessment section for CX-024414.

Buffer Storage Components

Buffer storage components were evaluated independently from the manufacturing processes because of the potential for prolonged exposure duration during storage relative to typical processing times. No high-risk materials were identified for buffer storage.

CCI [redacted]

mRNA-1273 LNP Manufacturing Process

The materials designated as medium risk are provided in Module 3. No high-risk materials were identified for the mRNA-1273 LNP manufacturing process.

CONTROLS OF CRITICAL STEPS AND INTERMEDIATES mRNA-1273 LNP

During the mRNA-1273 Lipid Nanoparticle (LNP) manufacturing process, in-process tests are performed to provide control over the inputs to the process. mRNA-1273 LNP is manufactured at CCI [redacted] 200 g batch sizes. This section presents the microbial control strategy, and methods for critical in-process controls testing for the mRNA-1273 LNP manufacturing process. Unless otherwise noted, these in-process controls are identical between the CCI [redacted] 200 g manufacturing processes. Refer to Controls of Critical Steps and Intermediates section CCI [redacted] for process control strategy.

Critical Process Parameters

CPPs and their PARs for the mRNA-1273 LNP manufacturing process are provided in Table 62. Excursions outside of these established ranges are reported, investigated, and assessed by the Quality Unit per established standard operating procedures.

Table 62: Critical Process Parameters

Step	CPP	PAR	Rationale
CCI [redacted]			

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

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 CCI and it is verified to be clean post-use (Refer to Table 63). Manufacturing controls specifically intended for microbial control of the mRNA-1273 LNP manufacturing process are listed in Table 64. Note that additional microbial controls may be present. Any deviations incurred in the implementation of these microbial controls are assessed for product quality impact.

Table 63: Microbial Controls

Step	Operation / IPC	Test / Description	Limit
CCI			

In-process Holds

Process intermediate hold conditions are provided in Table 64.

Table 64: In-process Hold Conditions

Step	Operation	Activity/Description	Duration (Temperature)
CCI			
Collection, Filling and Storage[a]	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) L Lonza Biologics: CCI
b) Lonza Biologics: Endotoxin not tested

Resin and Membrane Reuse

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.

PROCESS VALIDATION AND/OR EVALUATION mRNA-1273 LNP

A Process Validation Master Plan (mRNA-1273 PVMP) was developed to ensure that the commercial manufacturing process for mRNA-1273 LNP would reliably and consistently produce product of appropriate quality.

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}.

Three PPQ lots were completed to demonstrate process consistency for the (CCI scale) mRNA1273 LNP manufacturing process at ModernaTX, Inc., in Norwood, MA, Suite 1295 (Table 1).

Three PPQ lots were also completed to demonstrate process consistency for the (CCI scale) mRNA1273 LNP manufacturing process at ModernaTX, Inc., in Norwood, MA, Suite 1295 (Table 1).

PPQ for the 200 g scale mRNA-1273 LNP manufacturing process at ModernaTX, Inc. (Norwood, MA) is currently on-going.

Table 65: mRNA-1273 Lipid Nanoparticle Process Performance Qualification Lots (CCI Scale and CCI Scale)

Scale	Lot Number	Date of Manufacture
CCI	5006820005	02 Jul 2020
	5006820006	11 Jul 2020
	5006820007	17 Jul 2020
	5007320005	11 Oct 2020
	5007320006	17 Oct 2020
	5007320007	23 Oct 2020

All process parameters and in-process controls defined in Section 3.2.S.2.2 {mRNA-1273 LNP} were evaluated during the PPQ and confirmed to be within target ranges.

PPQ for the 200 g scale mRNA-1273 LNP manufacturing process at Lonza Biologics, Inc (Portsmouth, NH, USA) has been completed (Table 1).

Table 66: mRNA-1273 LNP Process Performance Qualification Lots

Manufacturing Location	Scale	Moderna Lot Number (Lonza Lot Number)	Date of Manufacture
Lonza Biologics. Portsmouth, NH	200 g	5007521502 (962902)	05-Jan-21
	200 g	5007521020 (962903)	08-Jan-21
	200 g	5007521028 (962904)	12-Jan-21

For the 200 g PPQ scale at Lonza Biologics (Portsmouth, NH), all process parameters and in-process controls defined in Section 3.2.S.2.2 {mRNA-1273 LNP} were evaluated during the PPQ and confirmed to be within target ranges.

Full details of the PPQ are available in summary report USPO-28756.

MANUFACTURING PROCESS DEVELOPMENT mRNA-1273 LNP

mRNA-1273 Lipid Nanoparticle (LNP) CCI

The mRNA-1273 LNP is then filtered through a clarification filter CCI and filled into singleuse, disposable bags (described in Section 3.2.S.6 {mRNA-1273 LNP - Lonza Visp}).

The initial process for mRNA-1273 was conducted using equipment utilized in ModernaTX, Inc.'s personal vaccine unit (PVU). The PVU process for mRNA1273 Drug Product did not incorporate freezing and storage of the bulk mRNA1273 LNP. The process was completed in a sequential integrated-batch manner for each lot of mRNA1273 Drug Product CCI Product intermediates were held inprocess prior to proceeding to each subsequent step. CCI

To enable scale-up of the mRNA1273 LNP manufacturing process (Scale A), the neutralization and component addition operations were incorporated downstream CCI 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 mRNA1273 LNP was produced using the process described in Section 3.2.S.2.2 {mRNA-1273 LNP - Lonza Visp} (Lot AMPDP200022). The process was subsequently transferred to the GMP manufacturing area, and lots 5006820002 through 5006820008 of mRNA1273 LNP were produced.

Overview – mRNA1273 LNP

A summary of mRNA1273 lots manufactured to date that are described in this section are provided in Table 67.

Table 67: Manufacturing History - mRNA1273 LNP

mRNA-1273 LNP Lot #	DOM	CX-024414 Lot#	[redacted]	Manufacturer	Process/Scale (g)	Yield (g)	Disposition/Use
AMPDP-200022	01 Apr 2020	MTDS20002	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	Development
5006820002 [a]	15 May 2020	4007220002	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	Phase 3
5006820003	16 Jun 2020	4007220003	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	Phase 3
5006820004	24 Jun 2020	4007220004	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	Phase 3
5006820005	02 Jul 2020	4007220005	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	PPQ
5006820006	11 Jul 2020	4007220003	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	PPQ
5006820007	17 Jul 2020	4007220004 4007220005	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	PPQ
5007320002	24 Sep 2020	4007220002 4007220004	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	GMP
5007320004	30 Sep 2020	4007220003 4007220005	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	GMP
5007320005	09 Oct 2020	4007520002	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	PPQ
5007320006	15 Oct 2020	4007520002 4007520003	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	PPQ
5007320007	20 Oct 2020	4007420001	[redacted]	Moderna (Norwood, MA)	[redacted]	[redacted]	PPQ
5007320009 Lonza Lot 3000	22 Nov 2020	4007520801 Lonza Lot 1000	[redacted]	Lonza (Visp, Switzerland)	[redacted]	[redacted]	GMP
5007320300 Lonza Lot 3001	11 Dec 2020	4007520802 Lonza Lot 1001	[redacted]	Lonza (Visp, Switzerland)	[redacted]	[redacted]	PPQ
5007320803 Lonza Lot 3002	26 Dec 2020	4007520803 Lonza Lot 1002	[redacted]	Lonza (Visp, Switzerland)	[redacted]	[redacted]	PPQ
5007320804 Lonza Lot 3003	31 Dec 2020	4007520804 Lonza Lot 1003	[redacted]	Lonza (Visp, Switzerland	[redacted]	[redacted]	PPQ
5007321002 Lonza Lot 3004	06 Jan 2021	4007520804 Lonza Lot 1003	[redacted]	Lonza (Visp, Switzerland)	[redacted]	[redacted]	PPQ
5007320009 Lonza Lot 43001	22 Nov 2020	Lonza Lot 41001	[redacted]	Lonza Visp, Switzerland	200	[redacted]	PPQ

Abbreviations: DOM = date of manufacture
N/A = yield not applicable for pre-GMP development lot
Lot 500680001 was an engineering batch and not used for clinical trial material.

Summary of manufacturing changes

A summary of manufacturing changes implemented through the manufacturing process development activities is provided in Module 3.

mRNA-1273 LNP Process Characterization

In accordance with ICH Q9, a systematic assessment of the potential risk to mRNA-1273 lipid nanoparticle (LNP) product quality was performed with respect to the manufacturing process. A science-based approach was used to identify Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), and Critical In-Process Controls (CIPCs) to inform process design studies, and to establish the manufacturing control strategy. The proposed CQAs for mRNA-1273 LNP are summarized below in Table 68. The CPPs for the mRNA-1273 LNP manufacturing process are provided in Table 69

Table 68: mRNA-1273 LNP Critical Quality Attributes

Test Category	Attribute	Target Acceptance Criteria
CCI		

CCI

Table 69: mRNA-1273 LNP Critical Process Parameters

Step	Process Variable	Parameter	Target	PAR	Potential CQA Impact	Rationale
CCI						

Abbreviations: CQA = critical quality attribute; LNP = lipid nanoparticle; PDI = polydispersity index

Full details of the characterization studies are provided in Module 3.

SPECIFICATION mRNA-1273 LNP

The specification for mRNA-1273 Lipid Nanoparticle (LNP) is described in Table 70.

Table 70: mRNA-1273 LNP Specification

Test	Analytical Method	Acceptance Criteria	
Appearance	Visual Ph. Eur. 2.2.1, 2.2.2 (SOP-0278 ModernaTX, Inc.) (CHVI-101557 Lonza AG) (SOP-0278 Eurofins BioPharma)	White to off-white dispersion.	
		May contain visible, white or translucent product-related particulates.	
Identity	Reverse Transcription/Sanger Sequencing (SOP-1032 ModernaTX, Inc.) (SOP-1032 Eurofins BioPharma)	Sequence matches description	
Total RNA content	Anion Exchange HPLC (SOP-0999 ModernaTX, Inc.) (GROUP-107933 Lonza AG) (SOP-0999 Eurofins BioPharma)	CCI [redacted]	
Purity Product-related impurities	RP- HPLC (SOP-0996 ModernaTX, Inc.) (GROUP-107927 Lonza AG) (SOP-0996 Eurofins BioPharma)		
% RNA encapsulation	Fluorescence CCI [redacted] (SOP-1000 ModernaTX, Inc.) (GROUP-108245 Lonza AG) (SOP-1000 Eurofins BioPharma)		
Mean particle size Polydispersity	Dynamic Light Scattering (SOP-0998 ModernaTX, Inc.) (GROUP-109237 Lonza AG) (SOP-0998 Eurofins BioPharma)		
Lipid identification			
SM-102	UPLC-CAD (SOP-1001 ModernaTX, Inc.) (GROUP-107937 Lonza AG) (SOP-1001 Eurofins BioPharma)	Matches RT of Standard	
Cholesterol		Matches RT of Standard	
DSPC		Matches RT of Standard	
PEG2000-DMG		Matches RT of Standard	
Lipid content			
SM-102 Cholesterol DSPC PEG2000-DMG	UPLC-CAD (SOP-1001 ModernaTX, Inc.) (GROUP-107937 Lonza AG) (SOP-1001 Eurofins BioPharma)	CCI [redacted]	
Lipid impurities	UPLC-CAD (SOP-1001 ModernaTX, Inc.) (GROUP-107937 Lonza AG) (SOP-1001 Eurofins BioPharma)	Individual impurities:	CCI [redacted] area (Report RRT)
		Total impurities:	CCI [redacted][a]
pH	USP <791>, Ph. Eur. 2.2.3 (SOP-0288 ModernaTX, Inc.) (CHVI-82391 Lonza AG) (SOP-0288 Eurofins BioPharma)	CCI [redacted]	
Osmolality	USP <785>, Ph. Eur. 2.2.35 (SOP-0279 ModernaTX, Inc.) (CHVI-50752 Lonza AG) (SOP-0279 Eurofins BioPharma)		
Bacterial endotoxin	USP <85>, EP 2.6.14 (M-CTS-CS-0929 Associates of Cape Cod) (CHVI-6303 Lonza AG)		
Bioburden	USP <61>, EP 2.6.12 (SOP-0480 ModernaTX, Inc.) (CHVI-8889 Lonza AG)		

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

BATCH ANALYSES MRNA-1273 LNP

mRNA-1273 LNP GMP lots are intended for further manufacturing into mRNA-1273 Drug Product GMP lots.

Batch analysis date is generated for mRNA-1273 Lipid Nanoparticle (LNP) according to an approved specification as presented in section 3.2.S.4.1 (mRNA-1273 LNP).

Refer to Section 3.2.S.2.4.4 {mRNA-1273 LNP} for full details concerning batch analysis data

STABILITY SUMMARY AND CONCLUSIONS mRNA-1273 LNP

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. mRNA-1273 LNP material is stored in the commercial container closure.

An overview of the mRNA-1273 LNP stability program is provided in Table 71.

Table 71: mRNA-1273 Lipid Nanoparticle Stability Program Lots

Lot	Purpose	Date of Manufacture	Lot Size	Conditions		Available Longterm Data
				Temperature	Duration	
AMPDP-200022 (sublot DHM-47432)	Development	01 Apr 2020	CCI	60 to 90°C	24 mo	6 mo
5006820002	Clinical	15 May 2020		60 to 90°C	36 mo	6 mo [a]
				5 ± 3°C	2 mo	2 mo
5006820005	PPQ	02 Jul 2020		60 to 90°C	36 mo	6 mo [b]
				5 ± 3°C	2 mo	2 mo
5006820006	PPQ	11 Jul 2020		60 to 90°C	36 mo	6 mo [c]
				5 ± 3°C	2 mo	2 mo
5006820007	PPQ	17 Jul 2020		60 to 90°C	36 mo	6 mo [d]
				5 ± 3°C	2 mo	Initial
5007520002	PPQ	06 Nov 2020	200 g	70 to 90°C	36 mo	Initial
				5 ± 3°C	2 mo	Initial
5007520003	PPQ	11 Nov 2020	200 g	70 to 90°C	36 mo	3 mo [e]
				5 ± 3°C	2 mo	2 mo [f]
5007520004	PPQ	13 Nov 2020	200 g	70 to 90°C	36 mo	Initial
				5 ± 3°C	2 mo	Initial
5007520009	PPQ	20 Nov 2020	200 g	70 to 90°C	36 mo	3 mo [g]
				5 ± 3°C	2 mo	2 mo [h]
5007520013	PPQ	27 Nov 2020	200 g	70 to 90°C	36 mo	3 mo [i]
				5 ± 3°C	2 mo	2 mo [j]

Abbreviations: PPQ = process performance qualification; mo = month
Not all tests were conducted at the T = 6 month time point.
Not all tests were conducted at the T = 6 month time point
Not all tests were conducted from T = 6 month time point
Not all tests were conducted at the T = 6 month time point
Not all tests were conducted from T = 1 to T = 3 month timepoints
Not all tests were conducted from T = 1 to T = 2 month timepoints
Not all tests were conducted from T = 1 to T = 3 month timepoints
Not all tests were conducted from T = 1 to T = 2 month timepoints
Not all tests were conducted from T = 1 to T = 3 month timepoints
Not all tests were conducted from T = 1 to T = 2 month timepoints

mRNA-1273 LNP has been assigned a use period of 3 months when stored at the recommended long-term storage condition between 60°C to 90°C.

The shelf life is justified from the composite of data generated from one development lot (Section 3.2.7.1.2.1 {mRNA-1273 LNP}), one clinical lot (Section 3.2.7.1.2.2 {mRNA-1273 LNP}), and three PPQ lots (Section 3.2.7.1.2.3 {mRNA-1273 LNP}). Stability and characterization studies designed to evaluate product stability under various stressed conditions (freeze/thaw) are discussed in Section 3.2.7.1.2.4 {mRNA-1273 LNP}. All lots were manufactured at ModernaTX, Inc. using the manufacturing process as described in Section 3.2.S.2.2 {mRNA-1273 LNP} for PPQ and clinical lots and the processes described in Section 3.2.S.2.6 {mRNA-1273 LNP} for the development lot.

Refer to Section Section 3.2.S.7.3 {mRNA-1273 LNP} for full detailed results on stability studies conducted for mRNA-1273 LNP.

FACILITIES AND EQUIPMENT

Refer to section 3.2.A.1.