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2.3.S DRUG SUBSTANCE {CX-031302}

2.3.S.1 General Information

CX-031302 is the mRNA that encodes for the pre-fusion stabilized Spike protein of 2019-novel Coronavirus (SARS-CoV-2) B.1.1.529 Omicron Variant.

2.3.S.1.1 Nomenclature

International Non-proprietary Name (INN):	imelasomeran
Proprietary name:	N/A
Company product codes:	CX-031302
Drug Product name:	mRNA-1273
Synonymous name:	N/A

2.3.S.1.2 Structure

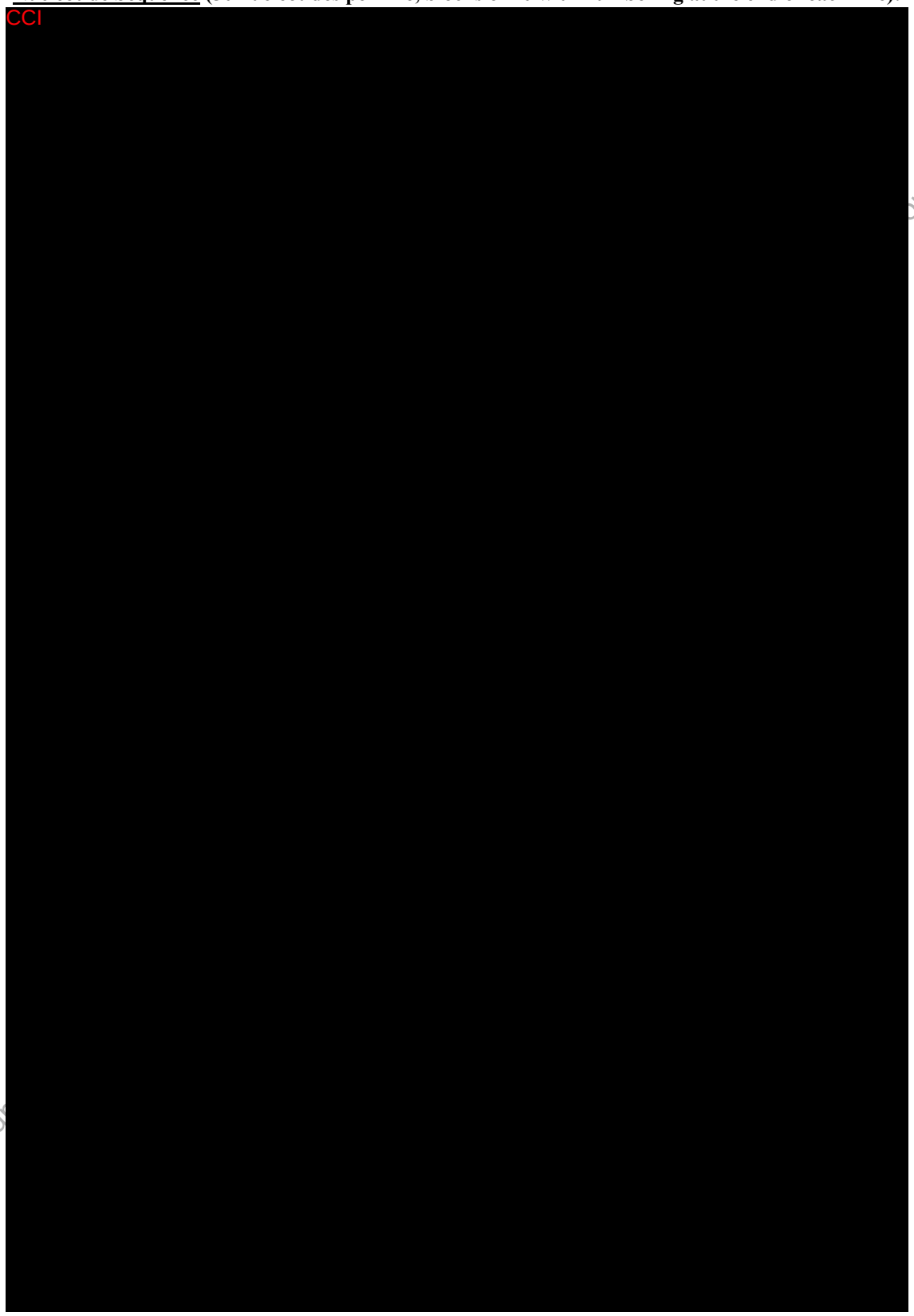
The B.1.1.529 or Omicron variant has emerged recently in South Africa and is currently circulating globally and was designated as a Variant of Concern on November 26, 2021. B.1.1.529 has multiple mutations in the S-protein including several that increase the likelihood of transmissibility and cause a reduction in susceptibility to neutralization. The mutations in the S protein of the B.1.1.529 variant include some, or all, among: A67V, Δ69-70, T95I, G142D/Δ143- 145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F. Moderna has designed mRNA-1273.529 containing CX-031302 which encodes for the S-2P of B.1.1.529.

CX031302 mRNA is chemically identical to naturally occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N1methylpseudouridine, a naturally occurring pyrimidine base present in mammalian tRNAs. This nucleoside is included in the CX-031302 mRNA in place of the normal uridine base to minimize the indiscriminate recognition of CX-031302 mRNA by pathogen associated molecular pattern (PAMP) receptors (e.g., Toll-like receptors). The molecular sequence of CX-031302 is provided in Figure 1, including the 5' cap (in purple), the 5' untranslated region (UTR) (in yellow), the Open Reading Frame (ORF) (in green), the 3' UTR (in yellow), and the 3' polyA tail (in grey).

Figure 1: Full mRNA Sequence of CX-031302

Nucleotide Sequence (50 nucleotides per line, blocks of 10 with numbering at the end of each line):

CCI



Where: A, C, G and U = AMP, CMP, GMP and & N1-Me-ΨMP, respectively;
Me = methyl; p = inorganic phosphate.

2.3.S.1.3 General Properties

CX-031302 mRNA is intended for further processing into mRNA-1273.529 LNP Drug Substance, an mRNA/lipid-based product. The general properties of CX-031302 mRNA are summarized in Table 1.

Table 1: General Properties of CX-031302 mRNA

Appearance	Clear, colorless solution, essentially free of visible particulates
pH	Formulated at a target pH of 5.0
Partition coefficient	Due to the high aqueous solubility and charge density, the partition coefficient is considered negligible for mRNAs like CX-031302
Aqueous solubility	Readily soluble in water and salts, demonstrated solubility >2 mg/mL to around 6 mg/mL in 32.5 mM sodium acetate, pH 5.0, solution
Extinction coefficient	A sequence specific coefficient is calculated using the formula as described in Section 3.2.S.3.1 {CX-031302}. The SSC for mRNA-1273 is CCI

Abbreviations: SSC = sequence specific coefficient

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 are described in Table 2.

Table 2: Manufacturers of CX-031302

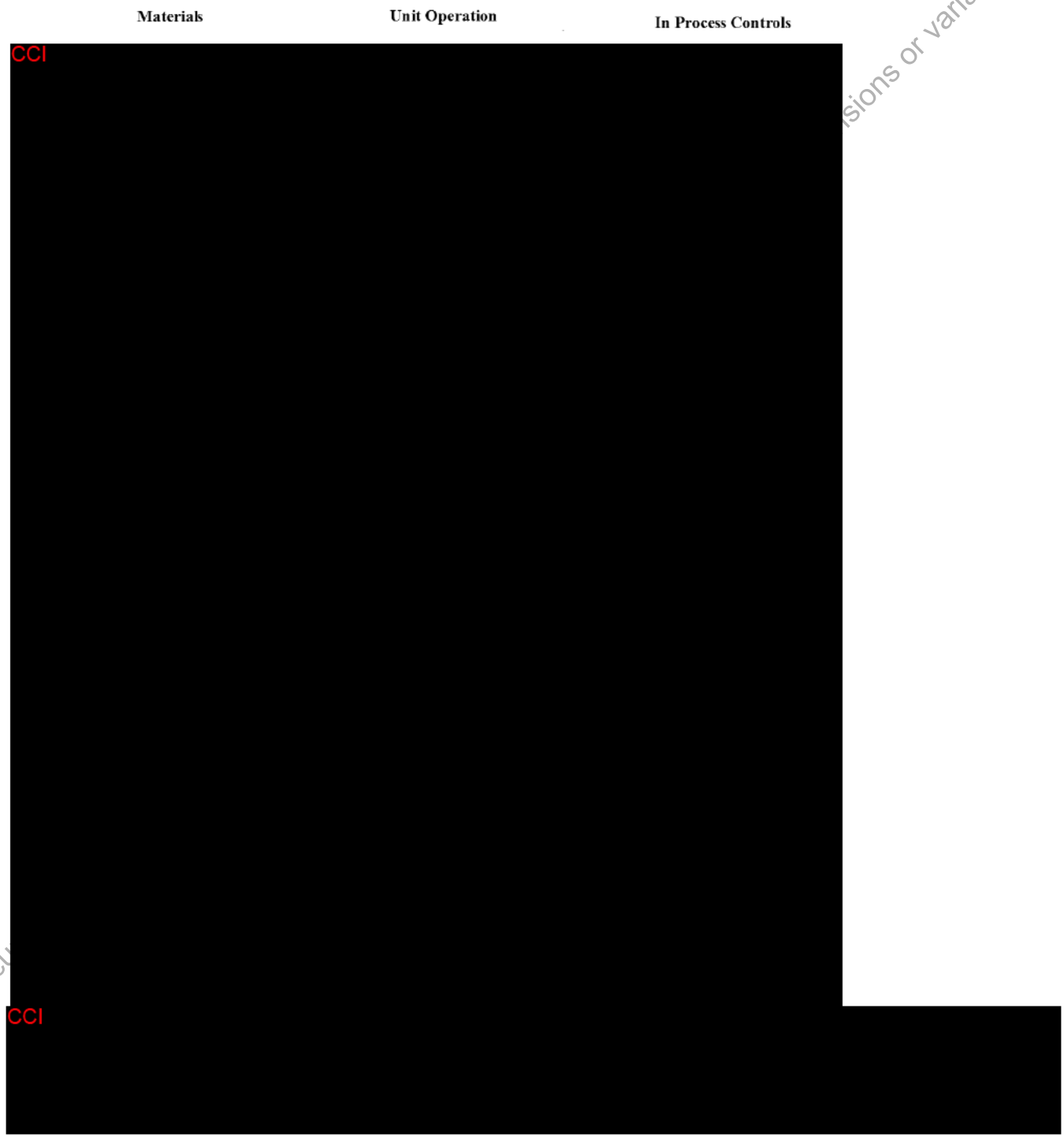
Manufacturers	Location	Responsibility
CCI		

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

Flow Diagram

A flow diagram of the manufacturing process is provided in Figure 2.

Figure 2: Overview of the Manufacturing Process



Manufacturing Process Summary

CCI

[redacted]

Detailed description of the manufacturing process is provided in Section 3.2.S.2.2 {CX-031302}.

2.3.S.2.3 Control of Materials

Raw Materials

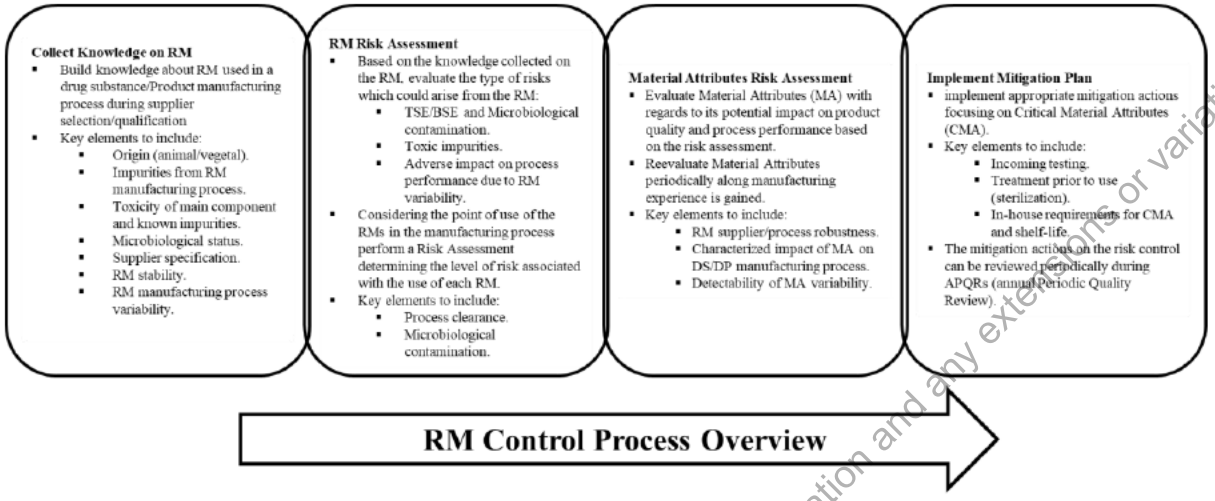
Quality of materials is assured through a rigorous system consisting of supplier evaluation, supplier qualification, audits, quality agreements, incoming goods testing, internal release procedure, package selection, shipping, storage conditions, expiry dates, and/or sterility requirements, based on the 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. An overview of the Raw Material control process is provided in Figure 3. 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 3: Raw Material Control Process Overview



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

The CX-031302 manufacturing process uses the same raw materials as for the prototype CX-024414 mRNA. For more details, please refer to Section 3.2.S.2.3.4 {CX-024414} – Raw Materials.

Materials of Biological Origin

There are no starting materials of animal or human origin used in the manufacture of CX-031302.

Starting Materials

The starting materials in the manufacture of CX-031302 are the linearized plasmid template and the nucleotides ATP, CTP, GTP, N1-Me-ΨTP. The nucleotides are the same nucleotides as used for manufacture of CX-024414. For more information refer to Section 3.2.S.2.3 {CX-024414 - Starting Materials - CCI [redacted]}. This Section will focus on the plasmid and its cell banking system.

Linearized Plasmid Template

A unique linearized DNA plasmid template specific for CX-031302 was designed at ModernaTX, Inc. (Norwood, MA, USA). The plasmid contains the molecular elements of the CX-031302 mRNA including the 5' untranslated region, the coding region [open reading frame (ORF)], the 3' untranslated region and the polyA tail. CCI [redacted]

CCI [redacted] The plasmid only contains elements necessary for plasmid selection and replication in E. coli and for in vitro transcription of CX-031302.

The full plasmid DNA sequence and the plasmid map are provided in Section 3.2.S.2.3 {CX-031302} – Starting Materials.

Generation of Host Cell Line

The lineage of the host cell line is illustrated in Figure 4.

Figure 4: Lineage of Host Cell Line

CCI [redacted]

CCI [redacted]

A description of the genetic modifications, transformation and purification of the host cell line are provided in Section 3.2.S.2.3 {CX-031302} – Starting Materials.

Plasmid Cell Banking System

The cell banking system is two-tiered, including a master cell bank (MCB) and a working cell bank (WCB).

An overview of the cell banking process is provided in Figure 5.

Figure 5: Overview of Plasmid Cell Banking

Further details of the manufacturing of the cell banks, their release results, stability testing and qualifications are provided in Section 3.2.S.2.3 {CX-031302} – Starting Materials.

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 CX-031302 manufacturing process are provided in Table 3. Excursions outside of these established ranges are reported, investigated, and assessed by the Quality Unit per established standard operating procedures.

Table 3: Critical Process Parameters

Step	CPP	PAR	Rationale
CCI [redacted]			

CCI [redacted]

Microbial Control

The CX-031302 manufacturing process is carried out in a controlled manufacturing area. Raw materials are tested as described in Section 3.2.S.2.3 {CX-031302 - Raw Materials}. CCI [redacted].

The operations and manufacturing controls specifically intended for microbial control of the CX-031302 manufacturing process are provided in Section 3.2.S.2.4 {CX-031302}. Any deviations incurred in the implementation of these microbial controls are assessed for product impact.

In-Process Holds

The maximum duration that process intermediates may be held at CCI [redacted]; the maximum intermediate hold duration at CCI [redacted].

Resin and Membrane Lifecycles and Column Reuse

Scale-down models were developed and used to evaluate the maximum number of cycles that the resin can be used and to provide justification CCI [redacted]. These studies demonstrated that the resin may be re-used for processing multiple batches to a maximum of CCI [redacted]. CCI [redacted]

Critical In-Process Controls

The critical in-process testing and associated method references for the CX-031302 manufacturing process are summarized in Table 4. In-process sample matrices were qualified and/or validated for the appropriate criteria as described in ICH Q2.

Table 4: Critical In-process Controls

Step	CIPC	Acceptance Criteria	Method Reference
CCI			
CCI			

2.3.S.2.5 Process Validation and/or Evaluation

Process validation for CX-031302 is performed in compliance with European Medicines Agency, United States Food and Drug Administration, International Conference on Harmonization, and international regulatory expectations. Process validation comprises Process Design (Phase 1), Process Performance Qualification (PPQ; Phase 2), and Continued Process Verification (CPV; Phase 3). The elements of Process Design (Phase 1) are described in Section 3.2.S.2.4 {CX-024414} for control strategy and Section 3.2.S.2.6 {CX-031302}. PPQ (Phase 2) and CPV (Phase 3) are discussed in Section 3.2.S.2.5 {CX-024414}.

Moderna has successfully completed process verification of the CX-031302 mRNA manufacturing process as a means of demonstrating that the commercial-scale manufacturing process platform is capable of consistently delivering quality product. The qualification has generated data at commercial scale to support and complement concurrent laboratory-scale studies. Process verification acceptance criteria were defined in the associated protocol and are provided in Section 3.2.S.2.5 {CX-031302}. For mRNA-1273 variant processes that use a manufacturing process and control strategy equivalent (equivalent except for mRNA sequence specific control elements) to the prototype mRNA-1273 process, one confirmatory process verification lot was performed to demonstrate process consistency per site per the requirements specified in the Process Validation Master Plan. The introduction of CX-031302 mRNA also included the qualification of the additional identical Train 8 (Moderna TX, Norwood); enabling Train 8 for prototype mRNA-1273 and variants at Moderna TX, Norwood. Moderna has successfully completed process verification of the CX-031302 mRNA manufacturing process as a means of demonstrating that the commercial-scale manufacturing process is capable of consistently delivering quality product. The process verification has generated data at commercial scale to support and complement laboratory-scale studies.

Based on the outcome of the PPQ exercise, the CX-031302 mRNA manufacturing process has

been successfully validated at Moderna Norwood and Lonza Visp.

More complete information on process validation is provided in Section 3.2.S.2.5 {CX-031302}.

2.3.S.2.6 Manufacturing Process Development

Following the initial development of mRNA-1273 vaccines at ModernaTX, Inc.'s small-scale Personalized Vaccine Unit (PVU), the manufacturing process was successfully established at CCI [redacted] at a 75 L IVT scale to provide commercial materials outside of the United States. The manufacturing process for CX-031302 is described in Section 3.2.S.2.2 {CX-031302}.

Manufacturing process development for the prototype CX-024414 is described in Section 3.2.S.2.6{CX-024414}. An overview of the omicron variant CX-031302 is provided in Section 3.2.S.2.6 {CX-031302}. The process characterization and comparability demonstration, including evaluation of process change impact on critical quality attributes, are included in Section 3.2.S.2.6 {CX-031302}.

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and Other Characteristics

The structure, physicochemical properties of CX-031302 mRNA, were studied using a variety of techniques applicable to mRNAs. Unless otherwise indicated, data were generated from GMP lot 84112C0702. The data generated from these analyses confirm the physico- chemical structure of CX-031302 mRNA, as described in more details in Section 3.2.S.3.1 {CX-031302}.

2.3.S.3.2 Impurities

Product-Related Impurities

Product-related impurities (Table 5) are molecular variants arising during manufacture or storage with properties different from those of the desired product with respect to activity, efficacy, and safety. Characterization of CX-031302 identified the presence of minor amounts of product variants representative of those commonly found in the profile of mRNA-based therapeutics, such as short RNA impurities, high molecular impurities and polyA tail variants, double-stranded RNA (dsRNA), and cap variants. The presence, impact, and ability of the process to control such impurities is discussed in Section 3.2.S.3.2 {CX-024414}.

An overview of product-related impurities is presented in Table 5.

Table 5: Overview of CX-031302 Product-related Impurities

Product-Related Impurities	Description	Control Strategy
	CX-031302	
CCI	[redacted]	

Process-Related Impurities

Process-related impurities (Table 6) that may be present in CX-031302 include residual process material and in vitro transcription (IVT) impurities derived from or generated during the manufacturing process. Please refer to Section 3.2.S.3.2 {CX-04414} for a discussion of each of these impurities and provision of data demonstrating the ability of the process to clear them down to acceptable levels in the final filtered bulk mRNA.

CCI [redacted]

An overview of the process-related impurities is presented in Table 6.

Table 6: Overview of Process-related Impurities

Impurity	Test Method	Release (Acceptance Criteria)	Characterization (Expected Range)
CCI [redacted]			

CCI [redacted]

2.3.S.4 Control of the Drug Substance

2.3.S.4.1 Specification

Testing of CX-031302 is performed in accordance with the specification listed in Table 7.

Table 7: Specification for CX-031302

Test	Analytical Method	Acceptance Criteria
Appearance	Visual Ph. Eur. 2.2.1, 2.2.2	Clear, colorless solution, essentially free of visible particulates
Identity	Reverse Transcription/Sanger Sequencing	Sequence matches 100% description of coding region
Total RNA content	UV	CCI
Purity	RP-IP-HPLC	
Product-related impurities	RP-IP-HPLC	
% 5' Capped	RP-HPLC	
% PolyA tailed RNA (% Tailless RNA)	RP-HPLC	
pH	USP <791>, Ph. Eur. 2.2.3	
Bacterial endotoxin	USP <85>, Ph. Eur.2.6.14	
Bioburden	USP <61>, Ph. Eur. 2.6.12	

Abbreviations: UV= Ultraviolet; RP-IP-HPLC= Reverse-phase ion-pair high-performance liquid chromatography; RP-HPLC= Reversed Phase High Performance Liquid Chromatography; CFU=Colony forming unit; TAMC = Total aerobic microbial count; TYMC = Total combined yeasts/molds count

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, mRNA content, purity, impurities and microbiological quality were established based on compliance with regulations, guidances and compendial methods, and are justified based on characterization studies, the manufacturing process, available batch analyses data, and stability results using validated analytical methods.

The analytical methods used for release testing of CX-031302 and prototype CX-024414 are identical with the exception of the identity method, since this is the only method that is sequence-specific. For descriptions of the common methods please refer to Section 3.2.S.4.2 {CX-024414}. A full description of the identity method is provided in Section 3.2.S.4.2 {CX-031302}.

2.3.S.4.3 Validation of Analytical Procedures

The analytical procedures used for testing CX-031302 and the prototype CX-024414 are identical with the exception of the identity method, since this is the only method that is sequence specific. For information on validation of common methods please refer to Section 3.2.S.4.3 {CX-024414}. For a validation summary of the CX-031302 identity testing method, please refer to Section 3.2.S.4.3 {CX-031302}.

2.3.S.4.4 Batch Analyses

CX-031302 mRNA GMP lots are intended for further manufacturing into mRNA-1273.529 LNP Drug Substance GMP lots. Batch analysis data generated for CX-031302 according to specifications approved at time of release are presented in Section 3.2.S.4.4 {CX-031302}.

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 drug substance (DS) or drug product (DP) rather than to establish full characterization and should focus on those characteristics found to be of utility in ensuring the safety and efficacy of DS and DP (ICH Q6B and Q11).

A Critical Quality Attribute (CQA) 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*.

This justification of specifications relates to critical quality attributes for all prototype and associated variant RNA for the mRNA-1273 program. During development of the mRNA-1273 vaccine program, new variant mRNA sequences have been introduced in addition to the prototype CX-024414 mRNA. Different mRNA-1273 LNPs and drug products are manufactured from these prototype and variant RNA. The CX-031302 covered within the scope of this justification of specifications is summarized in Section 3.2.S.4.5 {CX-024414}.

Table 8 summarizes the CQAs and the corresponding justifications for CX-031302 (prototype CX-024414 mRNA and associated variant RNAs) based on a risk assessment performed and process and product characterization knowledge gained for mRNA-1273.

Table 8: Critical Quality Attributes Assessment for CX-031302

Quality Attribute	Test Method	Justification
Appearance	Visual	CCI
pH	USP <791>	
Identity	Reverse Transcription Sanger Sequencing	
Bacterial Endotoxins	USP <85>, Ph. Eur. 2.6.14	
Bioburden	USP <61>, Ph. Eur. 2.6.12	
Total RNA Content	NaOH Digest by UV	
RNA Purity	RP-IP-HPLC	
RNA Impurities	RP-IP-HPLC	
%Cap1	RP-IP HPLC	
%PolyA Tailed RNA	RP-HPLC	
%Tailless RNA	RP-HPLC	

Abbreviations: CQA = critical quality attribute; IG = impurity group; RP-HPLC = reverse-phase high-performance liquid chromatography; RP-IP-HPLC = reverse-phase ion-pair high-performance liquid chromatography; UV = ultraviolet

The specification for release of CX-031302 is presented in Section 2.3.S.4.1. The specification includes the attributes, test methods, and acceptance criteria that together confirm the quality of the RNA lots and ensure each lot is acceptable for use in DP manufacturing. Acceptance criteria were established according to ICH Q6B guidelines and reflect historical product quality data from preclinical and clinical lots, release results for manufactured CX-024414 mRNA, stability study results, relevant development data, and analytical method performance data.

The rationale for the establishment and justification of the release specification is provided in Section 3.2.S.4.5 {CX-024414}.

2.3.S.5 Reference Standards or Materials

The reference material as described in Section 3.2.S.5 {CX- 024414} will serve as the reference material for CX-031302

2.3.S.6 Container Closure System

For information regarding the container closure system, please refer to Section 3.2.S.6 {CX-024414}.

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

The CX-031302 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*.

The approved shelf life for CX-024414 utilized in the manufacture of prototype mRNA-1273 DP is currently set at 9 months when stored at -15°C to -25°C in the commercial container closure system (defined in Section 3.2.S.6 {CX-024414}).

An initial shelf-life of 36 months is proposed for CX-024414 and CX-031302 materials stored in the commercial container closure system, defined in Section 3.2.S.6 {CX-031302}, when stored at the recommended long-term storage condition of -60°C to -90°C. Moving forward, Moderna will utilize the long term storage temperature range of -60°C to -90°C for CX-031302 to ensure higher starting levels of purity in the mRNA-1273 drug product and to increase manufacturability.

The properties of CX-031302 with respect to the attributes that affect product potency have been systematically and thoroughly assessed. These attributes include fidelity of the mRNA sequence, including cap, tail, and open reading frame; and the integrity of the RNA. Direct measurements of those attributes have been established and are included in the routine release panel for CX-031302 mRNA. The stability of CX-031302 mRNA will be evaluated against a broad set of stability data and modeling encompassing both CX-024414 registration lots and additional variant RNAs associated with the mRNA-1273 program.

The product quality attribute expected to change most during the manufacturing and distribution of the product is mRNA purity, which represents the fraction of intact mRNA. The degradation of RNA in the product has been extensively studied by applying a sensitive chromatographic assay to assess the formation of RNA degradants. The principal route of degradation for the RNA is hydrolytic chain scission to species that elute prior to the main peak (RNA fragments). mRNA purity correlates with protein levels measured in the in vitro relative protein expression assay. Direct measurement of RNA degradation utilizing the RNA purity assay by RP-HPLC is precise, accurate, and the most stability-indicating measure of product activity.

The degradation rates can be determined from the purity analysis over different stability timepoints. Based on the stochastic nature of the degradation mechanism, there is a dependence on the rate of degradation on RNA size (length). Since CX-024414 and CX-031302 mRNAs have approximately the same overall length (~4,000 nt), a similar rate of degradation is expected across these different sequences.

The stability profiles for all the stability-indicating attributes are being evaluated and monitored, but purity is the primary determinant of shelf-life, since it is the most stability-indicating attribute. Degradation rates for purity at each temperature of interest are reported in Section 3.2.S.7.1.1 {CX-031302}.

The shelf-life is justified from the purity statistical model. The lots used in the purity modeling analysis were manufactured using a development process, PVU scale process, and the Scale B process. Process details are included in Section 3.2.S.2.6{CX-024414} Manufacturing History and Section 3.2.S.2.2 {CX-031302}. The modeling results are provided in Section 3.2.S.7.1.1 {CX-031302}and the purity data from these studies are presented in Section 3.2.S.7.3 {CX-031302}.

Registration lots, Scale B Process Performance Qualification (PPQ) lots manufactured using the process described in Section 3.2.S.2.2 {CX-031302}, were also placed on stability studies. Available data from these studies are presented in Section 3.2.S.7.3 {CX-031302} and protocols are provided in Section 3.2.S.7.1.2 {CX-031302}.

An overview of the CX-031302 stability program is outlined in Table 9, Table 10, Table 11 and Table 12..

Table 9: Summary of CX-024414 Batch Information

Lot Number	Usage	Manufacturing Site	Date of Manufacture	Container Closure System	Conditions	
					Temperature	Duration
MTDS20002	Toxicology, Development	ModernaTX, Inc. Cambridge, MA	March 26, 2020	30 mL PETG Bottle	-20 ± 5°C	12 months
					5 ± 3°C	1 month
4007220001	Phase 3 Clinical Supplies (10 L IVT)	ModernaTX, Inc. Norwood, MA	April 03, 2020	5 mL PETG Bottle	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007220002	Phase 3 Clinical Supplies (10 L IVT)	ModernaTX, Inc. Norwood, MA	May 04, 2020	5 mL PETG Bottle	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007220003	Phase 3 Clinical Supplies (10 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	May 20, 2020	5 mL PETG Bottle	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007220004	Phase 3 Clinical Supplies (10 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	June 04, 2020	5 mL PETG Bottle	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007220005	Phase 3 Clinical Supplies (10 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	June 18, 2020	5 mL PETG Bottle	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007520001	GMP (20 L IVT)	Lonza Biologics, Inc. Portsmouth, NH	July 28, 2020	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007520004	GMP (20 L IVT PPQ)	Lonza Biologics, Inc. Portsmouth, NH	August 31, 2020	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007420003	GMP (60 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	October 19, 2020	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	3 months
4007420004	GMP (60 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	October 31, 2020	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	3 months
4007420006	GMP (60 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	November 10, 2020	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	3 months
4007420007	GMP	ModernaTX, Inc.	November 12,	50 mL Mobius Bag	-20 ± 5°C	48 months

Lot Number	Usage	Manufacturing Site	Date of Manufacture	Container Closure System	Conditions	
					Temperature	Duration
	(60 L IVT PPQ)	Norwood, MA	2020		5 ± 3°C	3 months
4007421017	GMP (60 L IVT PPQ)	Lonza Biologics, Inc. Portsmouth, NH	January 21, 2021	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	3 months
4007420021	GMP (60 L IVT PPQ)	ModernaTX, Inc. Norwood, MA	January 06, 2021	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	3 months
4007421013	GMP (60 L IVT PPQ)	Lonza Biologics, Inc. Portsmouth, NH	January 21, 2021	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	3 months
CCI Lot 1002 (4007520803)	GMP (20 L IVT PPQ)	Lonza AG (Visp, Switzerland)	16 Dec 2020	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
CCI Lot 1003 (4007520804	GMP (20 L IVT PPQ)	Lonza AG (Visp, Switzerland)	23 Dec 2020	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
(CCI lot 1014)	GMP (20 L IVT PPQ)	Lonza AG (Visp, Switzerland)	21 Mar 2021	50 mL Mobius Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007421005 (CCI lot 41001)	GMP (60 L IVT Pre-PPQ)	Lonza AG (Visp, Switzerland)	23 Jan 2021	50 mL CC [redacted] Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007421006 (CCI lot 41002)	GMP (60 L IVT PPQ)	Lonza AG (Visp, Switzerland)	12 Feb 2021	50 mL CC [redacted] Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007421008 (CCI lot 41003)	GMP (60 L IVT PPQ)	Lonza AG (Visp, Switzerland)	24 Feb 2021	50 mL CC [redacted] Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007421009 CCI lot 41004)	GMP (60 L IVT PPQ)	Lonza AG (Visp, Switzerland)	11 Mar 2021	50 mL CC [redacted] Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4007421067 CCI lot 51001)	GMP (60 L IVT PPQ)	Lonza AG (Visp, Switzerland)	13 Mar 2021	50 mL CC [redacted] Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months

Lot Number	Usage	Manufacturing Site	Date of Manufacture	Container Closure System	Conditions	
					Temperature	Duration
4007421092 CCI lot 61001)	GMP (60 L IVT PPQ)	Lonza AG (Visp, Switzerland)	11 May 2021	50 mL CC [redacted] Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months
4010221001 CCI lot 54001)	GMP (75 L IVT PPQ)	Lonza Visp, Switzerland	06 Oct t2021	50 mL CC [redacted] Bag	-20 ± 5°C	48 months
					5 ± 3°C	6 months

Abbreviation: IVT = in vitro transcription; PPQ = process performance qualification; mo = months

Table 10: CX-031302 mRNA Registration Stability Lots

Lot	Usage	Manufacturing Site	Lot Size	Fill Volume	Process Train	Container Closure System	Conditions	
							Temperature	Duration
4011422002	PPQ, Comparability	CCI [redacted]	CCI IVT	10 mL	8	50-mL CCI s bag	-20 ± 5°C	24 months
							5 ± 3°C	3 month
4011822001	PPQ, Comparability		CCI IVT	30 mL	5	50-mL CCI [redacted] bag	-20 ± 5°C	48 months
							5 ± 3°C	3 month

Abbreviation: IVT = in vitro transcription; N/A: Analysis was not applicable

Table 11: Additional Stability Modeling Lots

Lot	Product	Purpose	Manufacturing Site	Lot Size	Fill Volume	Container Closure System	Conditions	
							Temperature	Duration
DH-06126	CX-027367 mRNA	Development	Moderna	CCI IVT	0.3 mL	1 mL CCI Tubes	-60°C to -90°C	12 months
							-20 ± 5°C	12 months
							5 ± 3°C	1 month
DH-09963	CX-029444 mRNA	Development	Moderna	CCI IVT	6 mL	50 mL CCI [redacted] bag	-60°C to -90°C	N/A
							-20 ± 5°C	6 months
							5 ± 3°C	1 month

Lot	Product	Purpose	Manufacturing Site	Lot Size	Fill Volume	Container Closure System	Conditions	
							Temperature	Duration
MTDS20002	CX-024414 mRNA	Development	Moderna	CCI IVT	6 mL	30 mL PETG Bottle	-60°C to -90°C	24 months
							-20 ± 5°C	12 months
							5 ± 3°C	N/A
MTDS21003	CX-027367 mRNA	Development	Moderna	CCI IVT	6 mL	50-mL CCI bag	-60°C to -90°C	N/A
							-20 ± 5°C	12 months
							5 ± 3°C	N/A

Abbreviation: IVT = in vitro transcription

Table 12: Stability Lots at -60°C to -90°C

Lot	Product	Manufacturing Site	Lot Size	Fill Volume	Container Closure System	Conditions	
						Temperature	Duration
4007922058	CX-024414 mRNA	ModernaTX	CCI IVT	15 mL	50-mL Mobius bag	-60°C to -90°C	48 months
4007922061	CX-024414 mRNA	ModernaTX	CCI IVT	15 mL	50-mL Mobius bag	-60°C to -90°C	48 months
4007922064	CX-024414 mRNA	ModernaTX	CCI IVT	15 mL	50-mL Mobius bag	-60°C to -90°C	48 months
4011422007	CX-031302 mRNA (Omicron)	CCI	CCI IVT	15 mL	50-mL CCI bag	-60°C to -90°C	60 months
						-20 ± 5°C	60 months
4008022002	CX-027367 mRNA (Beta)		CCI IVT	15 mL	50-mL CCI bag	-60°C to -90°C	48 months
						-20 ± 5°C	48 months
4011822002	CX-031302 mRNA (Omicron)		CCI IVT	30 mL	50-mL CCI bag	-70°C to -90°C	48 months
						-20 ± 5°C	48 months
						5 ± 3°C	3 months

The stability protocols are described in Section 3.2.S.7.1 {CX-031302}.

Stability conclusion and stability data are provided in Section 3.2.S.7.1 {CX-031302} and Section 3.2.S.7.3 {CX-031302}, respectively.

Freeze-Thaw Cycling Stability Study

A freeze-thaw stability study was performed using Development CX-024414 Lot MTDS20002. CX-024414 samples were subjected to a series of CCI freezing and thawing cycles at room temperature and assessed for purity by RP-HPLC. No notable changes in the CX-024414 purity were observed after CCI freeze-thaw cycles. The data are presented in Section 3.2.S.7.3 {CX- 024414}.

Stability Conclusions

Based on all the available stability data, combining dataset obtained on the CX-024414 and CX-031302, the use period for GMP CX-031302 stored at -60°C to -90°C is 36 months. Use period extensions will be evaluated as additional stability data is obtained.

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

For information regarding the post-approval stability, please refer to Section 3.2.S.7.2 Post-Approval Stability Protocol and Commitment {CX-031302}.

2.3.S.7.3 Stability Data

Stability data are provided in Section 3.2.S.7.3 {CX-031302}.