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2.3.S DRUG SUBSTANCE {CX-034476}

2.3.S.1 General Information

CX-034476 is the mRNA that encodes for the pre-fusion stabilized Spike protein of 2019-novel Coronavirus (SARS-CoV-2) BA.4/BA.5 Omicron sub-variants.

2.3.S.1.1 Nomenclature

International Non-proprietary Name (INN):	davesomeran
Proprietary name:	N/A
Company product codes:	CX-034476
Drug Product name:	mRNA-1273
Synonymous name:	N/A

2.3.S.1.2 Structure

The BA.4 and BA.5 variants are sub-variants of the Omicron variant and were first detected in South Africa in February of 2022. As of July 2022, the BA.4 and BA.5 sub-lineages make up the majority of cases in the US according to the CDC. BA.4 and BA.5 have 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 BA.4/BA.5 sub-variants share a number of the same mutations as the Omicron B.1.1.529 variant with several unique mutations as follows:

T19I L24- P25- P26- A27S H69- V70- G142D **V213G** G339D **S371F*** S373P S375F **T376A D405N R408S** K417N N440K **L452R** S477N T478K E484A *R493Q* **F486V** Q498R N501Y Y505H D614G H655Y N679K P681H N764K D796Y Q954H N969K

- **bold text** indicates mutations unique to BA.4/BA.5
- normal text indicates mutations shared with Omicron BA.1
- *italicized* text indicates mutation only relative to BA.1, not to Wuhan. BA.1 had Q493R relative to Wuhan.
  In BA.4/BA.5, this site has reverted back to the Wuhan sequence (R493Q),
- asterisk (*) denotes same mutation as BA.1 but involves different amino acids

CX-034476 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 N1-methylpseudouridine, a naturally occurring pyrimidine base present in mammalian tRNAs. This nucleoside is included in the CX-034476 mRNA in place of the normal uridine base to minimize the indiscriminate recognition of CX-034476 mRNA by pathogen associated molecular pattern (PAMP) receptors (e.g., Toll-like receptors). The molecular sequence of CX-034476, including the 5′ cap, the 5′ untranslated region (UTR), the Open Reading Frame (ORF), the

3′ UTR, and the 3′ polyA tail, is provided in Figure 1, with the structural overview and sequence features in Table 1 and Table 2 respectively. The cap structure to be used in the mRNA is identical to the natural mammalian Cap 1 structure consisting of a guanosine residue methylated in the 7-position linked through a 5'-5' triphosphate linkage to the first residue of the mRNA at the 5' end, and methylation of the 2'-position of the ribose sugar of the penultimate nucleotide. Both the cap structure at the 5' end and the polyA tail at the 3' end are required for the CX-034476 mRNA to be translated by the cellular translational machinery.

For the amino acid sequence alignments for BA.4/BA.5 and prototype S-2P refer to Section 3.2.S.1.2 {CX-034476}.

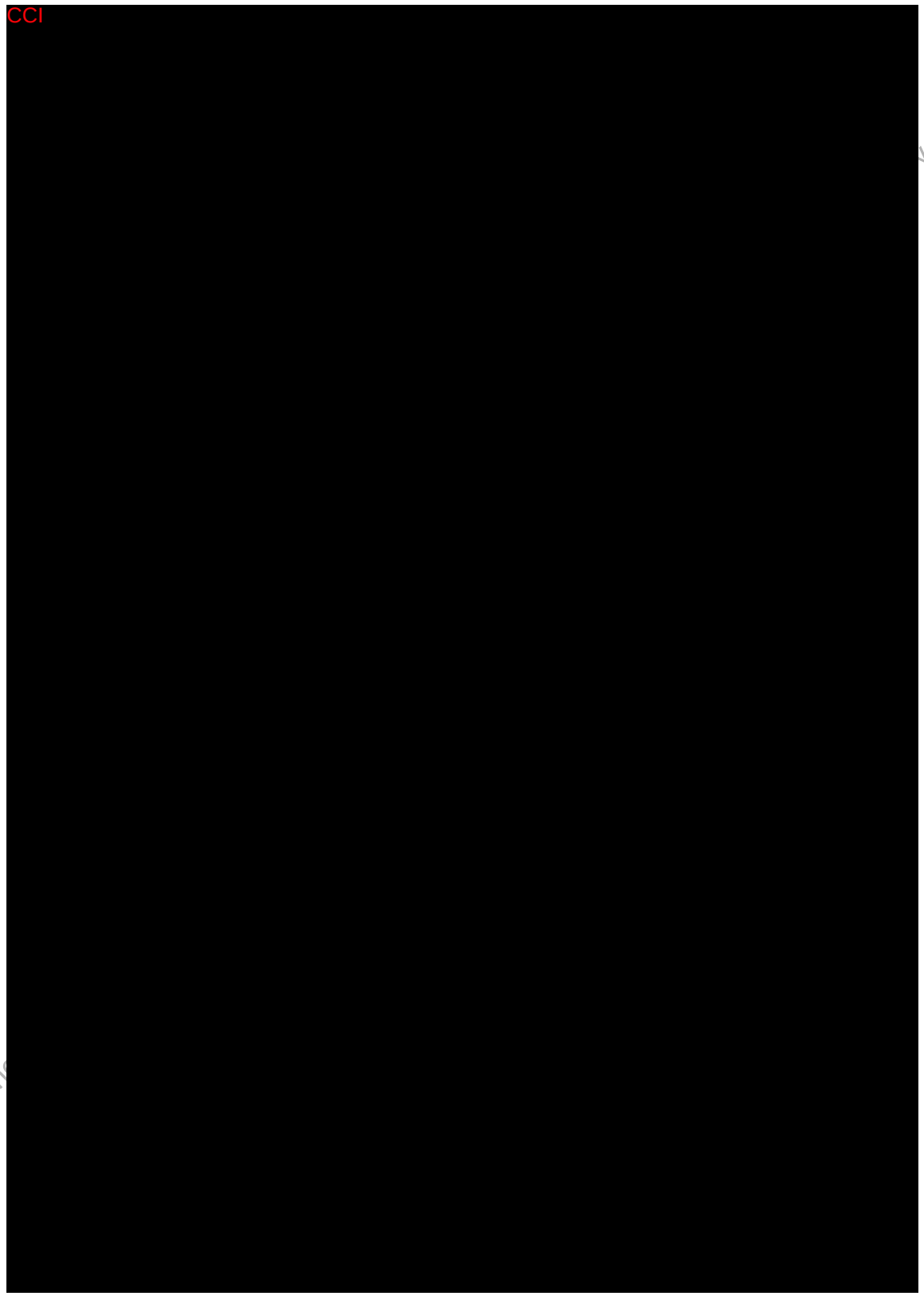
Table 1: Structural Overview of CX-034476

mRNA Sequence Molecular Weight (free acid)	CCI [redacted]
mRNA Sequence Molecule Length	
mRNA Sequence Elements	ORF: CCI [redacted]
	5′ UTR:
	3′ UTR:
	PolyA tail:

Abbreviations: ORF = open reading frame; UTR = untranslated region

Figure 1: Full mRNA Sequence of CX-034476

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



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

Table 2: Features of CX-034476 Molecular Sequence

Element	Description	Position
Cap	CCI [redacted]	
5′ UTR		
ORF		
3′ UTR		
polyA tail		

Abbreviations: ORF = open reading frame; UTR = untranslated region

2.3.S.1.3 General Properties

CX-034476 mRNA is intended for further processing into mRNA-1273.045 LNP-B Drug Substance, an mRNA/lipid-based product. The general properties of CX-034476 mRNA are summarized in Table 3.

Table 3: General Properties of CX-034476 mRNA

Attribute	Summary
Appearance	Clear, colorless solution, essentially free of visible particulates
pH	Formulated at a target CCI [redacted]
Partition coefficient	Due to the high aqueous solubility and charge density, the partition coefficient is negligible for mRNAs like CX-034476
Aqueous solubility	Readily soluble in water and salts, demonstrated solubility up to at least CCI [redacted], solution
Extinction coefficient	A sequence specific coefficient is calculated using the formula as described in Section 3.2.S.3.1 {CX-034476}. The SSC for mRNA-1273.222 is CCI [redacted]

Abbreviations: SSC = sequence specific coefficient

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer(s)

The facilities and responsibilities for the manufacture and quality control testing of CX-034476 are summarized in Table 4 and Table 5.

Table 4: European Facilities and Responsibilities for Manufacture and Testing of CX-034476

Facility	Address	Responsibility
CCI [redacted]		

Table 5: US Facilities and Responsibilities for Manufacture and Testing of CX-034476

Manufacturers	Location	Responsibility
ModernaTX, Inc.	One Moderna Way Norwood, MA, 02062 USA	Manufacturer of CX-034476
CCI [redacted]		

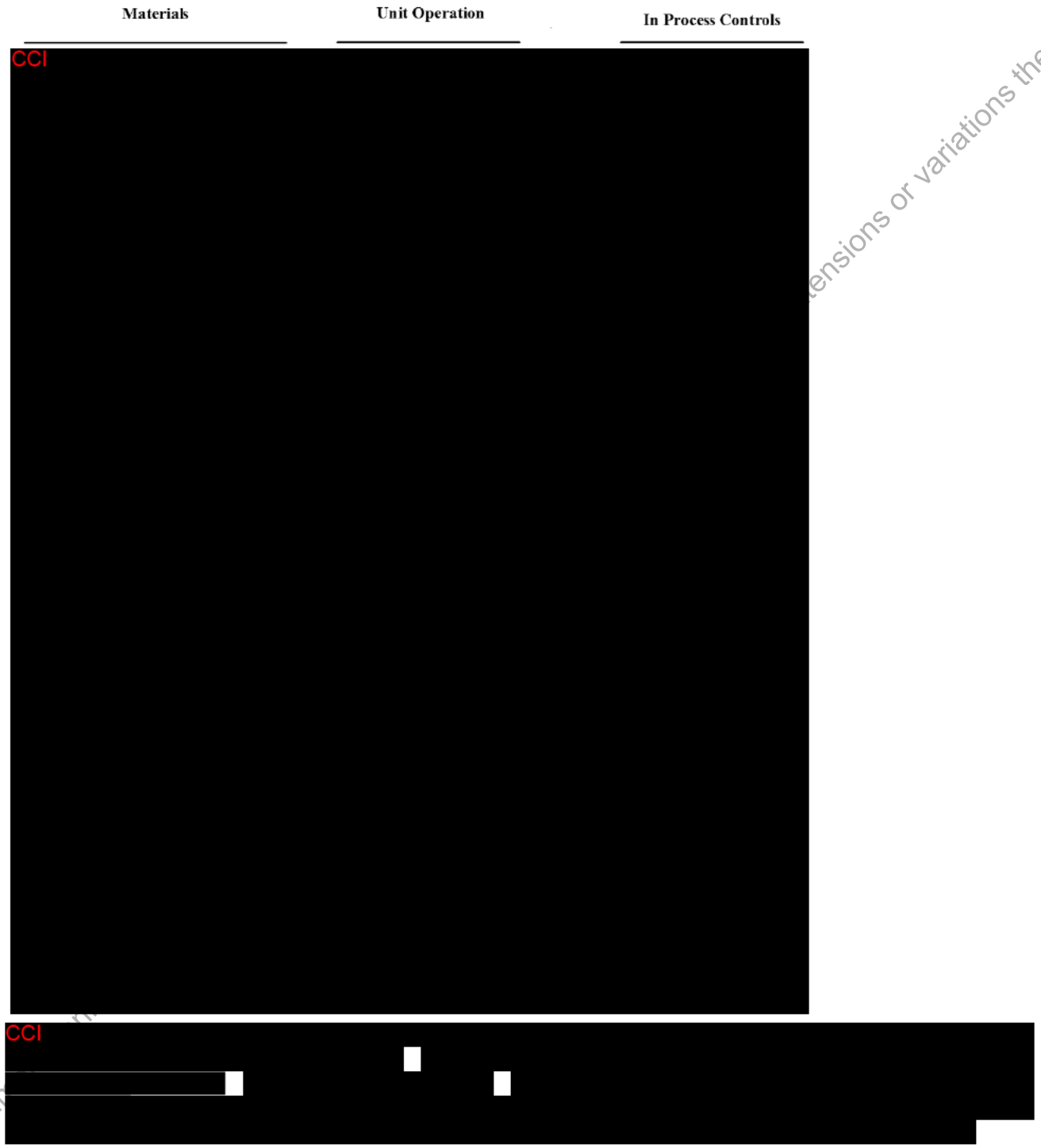
2.3.S.2.2 Description of Manufacturing Process and Process Controls

The nominal manufacturing batch size for CX-034476 mRNA CCI [redacted] ModernaTX (Norwood, United States) is 75 L (Scale B) in vitro transcription (IVT) reaction volume. The manufacturing process for CX-034476 is identical to the manufacturing process presented for CX-024414 at the 75 L scale CCI [redacted] ModernaTX Norwood.

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

CCI [redacted]

Detailed description of the manufacturing process is provided in Section 3.2.S.2.2 {CX-034476}.

2.3.S.2.3 Control of Materials

The raw materials used in the manufacture of CX-034476 manufactured at the US manufacturing site (ModernaTX, Norwood) CCI [redacted] are identical to the raw materials used for manufacture of CX-024414.

Raw Materials

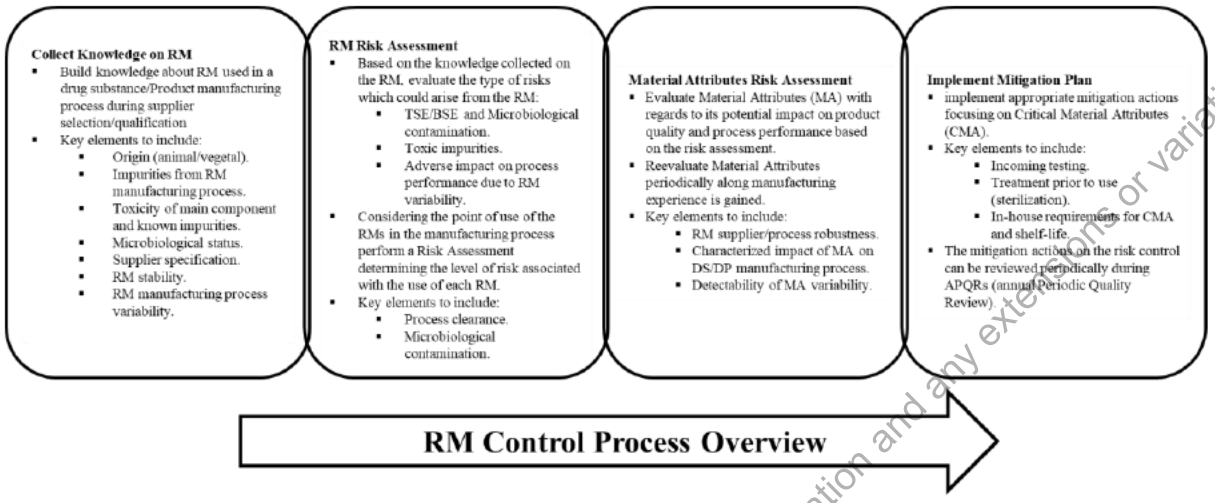
Quality of materials is assured through a rigorous system consisting of supplier evaluation, supplier qualification, audits, quality agreements, incoming goods testing, internal release procedure, package selection, shipping, storage conditions, expiry dates, and/or sterility requirements, based on the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

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-034476.

Starting Materials

The starting materials in the manufacture of CX-034476 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 mRNA. For more information refer to Section 3.2.S.2.3 {CX-024414 – Starting Materials – CCI } and Section 3.2.S.2.3 {CX-024414 - Starting Materials - US}. This Section will focus on the plasmid and its cell banking system.

Linearized Plasmid Template

A unique linearized DNA plasmid template specific for CX-034476 mRNA was manufactured at CCI . The features of the plasmid template specific for CX-034476 mRNA are consistent with CX-024414 mRNA described in Section 3.2.S.2.3 {CX-024414 – Starting Materials – CCI } and Section 3.2.S.2.3 {CX-024414 – Starting Materials – US}, with the exception of the specific sequence of the coding region and the 3'UTR. In addition to the elements described for the 3'UTR of CX-024414, the 3'UTR for CX-034476 also includes a substitution in an 11 nucleotide region of the prototype 3'UTR for up to 25 nucleotides in length as an Identification and Ratio (IDR) sequence, to enable identification and relative ratio determination of individual RNA components in the bivalent Drug Product. Introduction of the

IDR in the 3'UTR enables analytical control CCI [redacted] targeting the IDR for each RNA and offers the flexibility and efficiency for analytical control of future variant vaccines. These proposed sequences are non-coding and would therefore not be translated into peptides.

The full plasmid DNA sequence and the plasmid map are provided in Section 3.2.S.2.3 {CX-034476} – Starting Materials.

Generation of Host Cell Line

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

Figure 4: Lineage of CX-034476 PL-030872 Host Cell Line

CCI [redacted]

The host strain used for manufacture of PL-030872 for CX-034476 mRNA is the same as described for CX-024414 mRNA in Section 3.2.S.2.3 {CX-024414 – Starting Materials – Lonza Visp} and Section 3.2.S.2.3 {CX-024414 – Starting Materials – US}.

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-034476} – Starting Materials.

2.3.S.2.4 Controls of Critical Steps and Intermediates

The process control strategy and methods for critical in-process controls testing for the CX-034476 mRNA manufacturing process are identical to the ones in place for the CX-024414.

Critical Process Parameters

Critical process parameters (CPPs) and their proven acceptable range (PARs) for the CX-034476 manufacturing process are provided in Table 6. Excursions outside of these established ranges are reported, investigated, and assessed by the Quality Unit per established standard operating procedures.

Table 6: Critical Process Parameters

Step	CPP	PAR	Rationale
CCI [redacted]			

CCI [redacted]

Microbial Control

The CX-034476 manufacturing process is carried out in a controlled manufacturing area. Raw materials are tested as described in Section 3.2.S.2.3 {CX-024414 – Raw Materials– Lonza Visp} Section 3.2.S.2.3 (Raw Materials) {CX-024414}-US. Manufacturing operations utilize single-use, disposable materials for product contact equipment whenever possible. CCI [redacted]

The operations and manufacturing controls specifically intended for microbial control of the CX-034476 manufacturing process are provided in Section 3.2.S.2.4 {CX-024414- Lonza Visp} and Section 3.2.S.2.4 {CX-024414}-US. 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 200 cycles. CCI [redacted]

Critical In-Process Controls

The critical in-process testing and associated method references for the CX-034476 manufacturing process are summarized in Table 7. In-process sample matrices were qualified and/or validated for the appropriate criteria as described in ICH Q2.

Table 7: 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-034476 mRNA 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-034476}. PPQ (Phase 2) and CPV (Phase 3) are discussed in Section 3.2.S.2.5 {CX-024414}.

Section 3.2.S.2.5 {CX-034476} discusses the process verification used to support the introduction of CX-034476 mRNA.

Moderna has successfully completed process verification of the CX-034476 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-034476}. 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 PPQ verification lot was performed to demonstrate process consistency per site per the requirements specified in the Process Validation Master Plan. Moderna has successfully completed PPQ verification of the CX-034476 mRNA manufacturing process as a means of demonstrating that the commercial-scale manufacturing process is capable of consistently delivering quality product. The PPQ verification has generated data at commercial scale to support and complement laboratory-scale studies.

Based on the outcome of the PPQ exercise, the CX-034476 mRNA manufacturing process has been successfully verified at CCI and ModernaTX Norwood.

More complete information on process validation is provided in Section 3.2.S.2.5 {CX-034476}.

2.3.S.2.6 Manufacturing Process Development

The development of additional mRNA-1273 vaccines was initiated in response to the emergence of SARS-CoV-2 variants of concern. Sequences for mRNA-1273 vaccines are designed based

upon the S-2P encoding sequence for CX-024414 mRNA. Changes relative to this sequence are made only to incorporate the specific mutations of the variant S protein sequence encoded by the sequence of the specific mRNA-1273 RNA. The manufacturing process and process and analytical control strategies established for the CX-024414 mRNA are applied directly to CX-034476 mRNA (Omicron BA.4/BA.5).

Manufacturing process development for the prototype CX-024414 is described in Section 3.2.S.2.6{CX-024414}. An overview of the process development of Omicron BA.4/BA.5 variant CX-034476 is provided in Section 3.2.S.2.6 {CX-034476}. 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-034476}.

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and Other Characteristics

The structure, physicochemical properties of CX-034476 mRNA, were studied using a variety of techniques applicable to mRNAs. Unless otherwise indicated, data were generated from development lot DH-38293.1. The data generated from these analyses confirm the physico-chemical structure of CX-034476 mRNA, as described in more detail in Section 3.2.S.3.1 {CX-034476}.

2.3.S.3.2 Impurities

The CX-034476 mRNA is comprised of the same nucleotide components as the original prototype CX-024414 mRNA, including the 5' Cap and polyA tail and the nucleotide components used to manufacture the mRNA. In addition, the manufacturing process for CX-034476 mRNA is consistent with the manufacturing process for the original prototype, CX-024414 at the 75 L scale. The product- and process-related impurities for CX-034476 are therefore consistent with what is described in Section 3.2.S.3.2 Impurities {CX-024414}, as the changes made to the mRNA sequence to target Omicron BA.4/BA.5 would not result in any changes in the types of impurities present in the final product.

Product-Related Impurities

Product-related impurities (Table 8) 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-034476 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 8.

Table 8: Overview of CX-034476 Product-related Impurities

Product-Related Impurities	Description	Control Strategy
	CX-034476	
CCI		

Process-Related Impurities

Process-related impurities (Table 9) that may be present in CX-034476 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-024414} 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 9.

Table 9: 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-034476 is performed in accordance with the specification listed in Table 10.

Table 10: Specification for CX-034476

Test	Analytical Method (SOP Reference)	Acceptance Criteria
Appearance	CCI	
Identity		
Total RNA content		
Purity		
Product-related impurities		
% 5' Capped		
% PolyA tailed RNA (% Tailless RNA)		
pH		
Bacterial endotoxin		
Bioburden		

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-034476 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-034476}.

2.3.S.4.3 Validation of Analytical Procedures

The analytical procedures used for testing CX-034476 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-034476 identity testing method, please refer to Section 3.2.S.4.3 {CX-034476}.

2.3.S.4.4 Batch Analyses

CX-034476 GMP lots are intended for further manufacturing into mRNA-1273.222 Drug Product GMP lots. Batch analysis data generated for CX-034476 according to specifications approved at time of release are presented in Section 3.2.S.4.4 {CX-034476}.

2.3.S.4.5 Justification of Specification

The specifications for CX-034476 and CX-024414 are identical, except for the specification for identity by reverse transcription / Sanger sequencing.

For justification of specifications, please refer to Section 3.2.S.4.5 {CX-024414}. For identity more details are provided in Section 3.2.S.4.5 {CX-034476}.

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-034476.

The CX-024414 reference material is used as a system suitability standard for several release tests and as a reference standard for measurement of total RNA content of CX-034476, and related variant mRNA-1273 LNP and DP materials.

Sanger sequencing test methods are used to confirm identity for both mRNA-1273 RNA and LNP. These test methods can experimentally measure the nucleotide sequence of specific regions of the RNA. Test results are compared against the theoretical mRNA sequence to confirm identity of the test sample. CCI [redacted]

CCI

[redacted]

Therefore, the use of the CX-024414 mRNA established reference material, is justified for use for testing of CX-034476 mRNA samples.

2.3.S.6 Container Closure System

The container closure system for CX-034476 mRNA is the same as for the original prototype, CX-024414 mRNA.

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-034476 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 CX-034476 mRNA is stored at -60 to -90°C, after an optional interim storage at -15 to -25°C of maximum 3 months. An initial shelf-life of 36 months is proposed as from the time of freezing for CX-034476 mRNA material stored in the commercial container closure system, defined in Section 3.2.S.6 {CX-034476}, when stored at the recommended long-term storage condition of -60°C to -90°C.

The properties of CX-034476 mRNA with respect to the attributes that affect product potency have been systematically and thoroughly assessed. These attributes include fidelity of the RNA sequence, including cap, tail, and open reading frame; and integrity of the RNA. Direct measurements of those attributes have been established and are included in the routine release panel for CX-034476 mRNA.

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-034476 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 described in Section 3.2.S.7.1.1 {CX-031302}. The lots used in the purity modeling analysis were manufactured using a development process, PVU scale process, the initial Scale B process and the Scale B process. Modeling included data from development lots from additional variant RNAs to incorporate sequence differences in the statistical model. 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}.

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 as the commercial closure system.

Size-based RNA purity and polyA tailed RNA, as determined by reverse-phase high-performance liquid chromatography (RP-HPLC), were demonstrated to be stability indicating (refer to Section 3.2.S.4.2 {CX-034476} for analytical procedures).

A stability study was also initiated for CX-034476 mRNA (Table 11) manufacturing at ModernaTX, Inc. (Norwood, MA). Additionally, stability studies for the proposed long term storage condition for CX-034476 mRNAs at -60°C to -90°C are included (Table 12). These studies are currently ongoing and the data from these studies will be presented in Section 3.2.S.7.3 {CX-034476}.

Table 11: CX-034476 Supporting Stability Study (CCI [redacted])

Lot	Purpose	Manufacturing Site	Lot Size	Fill Volume (mL)	Container Closure	Conditions	
						Temperature	Duration
DH-38293.1	Development lot	ModernaTX, Inc. (Norwood, MA, USA)	CCI [redacted] IVT	1.0 mL (PETG) 0.5 mL CCI [redacted]	10 mL PETG Bottle with HDPE Cap 1.0 mL CCI [redacted] Tube	-70 ± 10°C-	48 months
						-20 ± 5°C	24 months
						5 ± 3°C	3 months
						25 ± 5°C	1 months

Table 12: CX-034476 mRNA -60°C to -90°C Stability Lots

Lot	Product	Manufacturing Site	Lot Size	Fill Volume	Container Closure	Conditions	
						Temperature[a]	Duration
4013422002	CX-034476 mRNA (Omicron)	ModernaTX	75 L IVT	15 mL	50-mL CCI [redacted] bag	-60°C to -90°C	60 months
						-20°C ± 5°C	3 months
						5°C ± 3°C	3 months

Abbreviation: IVT = in vitro transcription
[a] Stability chamber temperature set point chosen based on site capabilities; study for 4013422002 is ongoing at -70±10°C

The stability protocols are described in Section 3.2.S.7.1 {CX-034476}.

Stability conclusion and stability data are provided in Section 3.2.S.7.1 {CX-034476} and Section 3.2.S.7.3 {CX-034476}, respectively.

Freeze-Thaw Cycling Stability Study

Freeze-thaw cycling studies were performed on CX-024414 material and are applicable to CX-034476.

Stability studies in support of CX-024414 freeze-thaw cycling were performed using CX-024414, Development Lot MTDS20002. Sample vials are frozen at -60°C to -90°C held in frozen state for 24 hours, thawed at ambient temperature, and held ambient for at least 4 hours. The freeze-thaw cycling was repeated CCI [redacted]. Samples were tested for %purity by RP-HPLC, after samples were subjected to CCI [redacted] freeze-thaw cycles CCI [redacted]

Stability Conclusions

Based on all the available stability data, combining datasets obtained on the CX-024414 and CX-034476, the use period for GMP CX-034476 stored at -60°C to -90°C is 36 months, as from the time of freezing. Use period extensions will be evaluated as additional stability data is obtained. The use period cannot exceed the duration of the stability protocol.

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-034476}.

2.3.S.7.3 Stability Data

Stability data are provided in Section 3.2.S.7.3 {CX-034476}.