



CMC Review Memorandum

Date: December 23, 2020

To: The Emergency Use Authorization (EUA) File STN 27073

From: (b) (6), (b) (6)
CMC Product Reviewer

Through: (b) (6) (b) (6)

cc: (b) (6) (b) (6)

Applicant: ModernaTX, Inc.

Product name: Moderna COVID-19 Vaccine (mRNA-1273)

Subject: CMC Review of Original EUA STN 27034.0;
Human Coronavirus mRNA Vaccine for the Prevention of
Coronavirus Disease 2019 (COVID-19)

Action Due Date: December 23, 2020

Abbreviations Used in the Memorandum

CoA	Certificate of Analysis
CIPC	Critical In-process Control
CCS	Container Closure System
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
(b) (4)	(b) (4)
DS	Drug Substance
DP	Drug Product
EUA	Emergency Use Authorization

GMP	Good Manufacturing Practice
IPC	In-process Control
(b) (4)	(b) (4)
LNP	Lipid Nanoparticle
(b) (4)	(b) (4)
(b) (4)	(b) (4)
PAR	Proven Acceptable Ranges
PDI	Polydispersity Index
PPQ	Process Performance Qualification
PVU	Personal Vaccine Unit
RP-HPLC	Reverse Phase Liquid Chromatography
TAR	Target Acceptable Range
(b) (4)	(b) (4)
TOR	Time Out of Refrigeration
(b) (4)	(b) (4)

Contents

1. Product Name/Proprietary Name/Product Type.....	4
2. General Description	4
3. Executive Summary and Recommendations.....	4
4. Drug Substance (DS) and Drug Product (DP) Manufacturers	6
5. DS and DP Manufacturing Process Development and Comparability Approach	7
6. DS and DP Analytical Assays	9
7. DS and DP Raw Materials	9
8. Drug Substance.....	9
8.1 CX-024414 mRNA - Description of manufacturing process and controls	10
8.1.1 (b) (4)	13
8.1.2 CX-024414 mRNA manufacturing process validation and evaluation.....	15
8.1.3 Major process changes in CX-024414 mRNA manufacture - Process comparability assessment	15
8.1.4 Characterization - Elucidation of structure and other characteristics	16
8.1.5 Characterization - Impurities	17
8.1.6 Analytical procedures	17
8.1.7 Container Closure System.....	18
8.1.8 Stability	18
8.2 (b) (4) - Description of manufacturing process and controls	19
8.2.1 (b) (4) manufacturing process validation and evaluation	21

8.2.2 Major process changes in (b) (4) manufacture - Process comparability assessment.....	21
8.2.3 Characterization - Elucidation of structure and other characteristics	23
8.2.4 Characterization - Impurities	23
8.2.5 Analytical procedures	23
8.2.6 Container closure system	24
8.2.7 Stability	24
8.3 mRNA-1273 LNP - Description of manufacturing process and controls	25
8.3.1 mRNA-1273 LNP manufacturing process validation and evaluation	26
8.3.2 Major process changes in mRNA-1273 LNP manufacture - Process comparability assessment	27
8.3.3 Characterization - Elucidation of structure and other characteristics	28
8.3.4 Characterization - Impurities	28
8.3.5 Analytical procedures	29
8.3.6 Container-closure system	30
8.3.7 Stability	30
9. Drug Product	30
9.1 mRNA-1273 DP - Description of manufacturing process and controls	30
9.2 mRNA-1273 DP manufacturing process validation and evaluation	32
9.3 Major changes in mRNA-1273 DP manufacture – Process comparability assessment.....	32
9.4 Characterization - Elucidation of structure and other characteristics	35
9.5 Characterization - Impurities	35
9.5.1 Analytical procedures	36
9.6 Container closure systems	36
9.7 Stability	37
10. Reviewer's Conclusion and Recommendation	38

1. Product Name/Proprietary Name/Product Type

Product name: Moderna COVID-19 Vaccine

Proprietary name: SPYKEVAX

Product Type: Human Coronavirus mRNA vaccine expressing SARS-CoV-2 spike glycoprotein (Moderna code number mRNA 1273) formulated with lipids SM-102, PEG2000-DMG, DSPC, and cholesterol to form RNA encapsulated lipid nanoparticles (LNPs).

2. General Description

The mRNA-1273 vaccine is an mRNA-based vaccine indicated for active immunization for prevention of coronavirus disease 2019 (COVID-19). The mRNA encodes the full-length spike (S) glycoprotein of SARS-CoV-2, modified to replace uridine nucleosides with N1-methyl-pseudouridine and to introduce two proline residues shown to stabilize the S glycoprotein into the prefusion conformation. The in vitro transcribed single-stranded RNA is encapsulated in a lipid nanoparticle (LNP) composed of four lipids: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC).

mRNA-1273 vaccine is provided as a sterile, clear colorless suspension for intramuscular injection. Each 0.5 mL vaccine dose is targeted to contain 0.1 mg mRNA in 20 mM trometamol (Tris) buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate. The vaccine does not contain preservatives, antibiotics, adjuvants, human-derived or animal-derived materials.

The vaccine is presented as a frozen suspension in multi-dose vials containing ten 0.5 mL doses (≥ 5.0 mL per vial). The vaccine is stored frozen between -25° to -15°C but can be stored refrigerated between 2° to 8°C for up to 30 days prior to first use.

mRNA-1273 vaccine is administered intramuscularly as a series of two doses (0.5 mL each). The second dose is administered 28 days after the first dose. Prior to administration, the vaccine should be thawed in refrigerated conditions between 2° to 8°C for 2.5 hours and kept at room temperature for 15 minutes before administering. Alternatively, it can be thawed at room temperature between 15° to 25°C for 1 hour.

The vaccine is authorized for use in individuals 18 years of age and older.

3. Executive Summary and Recommendations

This review encompasses all CMC-related information in Module 3 of IND 19745 and additional information submitted in multiple IND amendments. The results of nonclinical studies relevant to evaluating effectiveness and risk for enhanced respiratory disease (Module 4) and validation of clinical diagnostic assays supporting clinical efficacy endpoints (Module 5) are provided in a separate memorandum.

Chemistry, Manufacturing, and Controls

The Moderna COVID-19 vaccine (Code number mRNA-1273) is a nucleoside-modified messenger RNA (mRNA)-based vaccine indicated for active immunization for the prevention of coronavirus disease 2019.

The manufacturing process for the drug substance (DS) consists of (b) (4)

The mRNA-1273 drug product (DP) is manufactured by (b) (4)

(b) (4), filling of final containers and labeling/packaging. To support the EUA application, process performance qualification (PPQ) data and in-process, release, and characterization data for DS and DP lots were provided for each manufacturing facility. Once authorized, the Sponsor will submit the Certificates of Analysis (CoAs) of DS and DP lots to be distributed under EUA for FDA review at least 48 hours prior to lot distribution.

The DS manufacturing process underwent scale-related changes during vaccine development to increase production capacity. DS and DP Scale A was used for the manufacture of Phase 3 clinical-trial material, while DS and DP Scale B will be used in the manufacture of vaccine intended for emergency use. An in-depth analytical comparability assessment based on a minimum of 3 DS PPQ lots and 3 DP PPQ lots at each Scale A and Scale B was performed. The submitted data show that the DS and DP lots manufactured at Scale A and Scale B are highly comparable, and the DS lots manufactured at Scale B in different facilities are also comparable. The manufacturing process and controls have been well characterized and qualified. A more comprehensive comparability assessment encompassing additional lots is ongoing and the results will be provided to the EUA upon completion of the study.

Stability studies have been designed to support the use of vaccine under the EUA. All available stability data generated using the mRNA-1273 DS and DP lots support the emergency deployment of the Moderna COVID-19 vaccine. All stability studies of the DS and DP lots are ongoing and will continue to be monitored. Stability data will be submitted to the EUA as they become available.

The analytical procedures developed and used for the release and stability monitoring of mRNA1273 DS and DP include tests to ensure vaccine safety, identity, purity, quality, and potency. All non-compendial analytical procedures have been adequately validated. The validation results demonstrate acceptable precision, accuracy, sensitivity, specificity, and reproducibility of the analytical assays, indicating that they are suitable for the quality control of DS and DP.

Diagnostic Assays for Clinical Efficacy Endpoint Assessment

Two diagnostic assays were used for the assessment of the Phase 3 clinical study efficacy endpoints. The Roche Elecsys Anti-SARS-CoV-2 assay was used for the evaluation of SARS-CoV-2 serostatus of study participants before vaccination. The Viracor Eurofins Clinical Diagnostics RT-qPCR was used to determine the virus infection status of study participants before vaccination and to confirm COVID-19 cases for the evaluation of clinical-study endpoints. Both assays have received FDA emergency use authorization. Additional data were submitted to support the suitability of both assays for their intended use in the Phase 3 clinical study for mRNA1273. The Roche Elecsys Anti-SARS-CoV-2 assay is done under contract to PPD Global Central

Laboratories, and the RT-qPCR assay is done by Viracor Eurofins Clinical Diagnostics. Both contracting laboratories are CAP-accredited and CLIA certified. The review of the clinical diagnostic assays is provided in separate memorandum.

Nonclinical Data

Several nonclinical studies in mice, hamsters, and rhesus macaques were conducted to support the safety and efficacy of the mRNA-1273 COVID-19 vaccine. mRNA-1273 was assessed for immunogenicity and for protection against SARS-CoV-2 challenge in mice, hamsters, and rhesus macaques. mRNA-1273 was highly immunogenic in all species tested with strong antigen-binding IgG and high titer neutralizing antibody responses together with a Th1-phenotype CD4+ response, as well as an IFN γ +, IL-2+, CD8+ T-cell response, after a single immunization. Animals immunized intramuscularly had readily detectable S-binding IgG and SARS-CoV-2 neutralizing titers (NT50) as early as one week after a single immunization, and these titers were boosted substantially with a second immunization. Immunized mice were challenged with a mouse-adapted SARS-CoV-2, and hamsters and macaques were challenged with wild-type SARS-CoV-2. The mRNA-1273 vaccine was protective in all three species as indicated by a substantial decrease in viral RNA in bronchoalveolar lavage fluid and the nasal turbinates in the immunized animals as compared with the controls. In addition, there was no histopathologic or radiographic evidence of vaccine-elicited enhanced disease in immunized animals. Based on current hypotheses regarding the etiology of vaccine-associated enhanced respiratory disease, the data are reassuring due to: (1) the robust induction of functional (i.e., neutralizing) antibodies in mice, hamsters, and rhesus macaques; (2) the Th1 bias in T-cell responses; and (3) the reduced viral load and lack of disease markers in vaccinated animals challenged with SARS-CoV-2. The review of nonclinical data is provided in separate memorandum.

4. Drug Substance (DS) and Drug Product (DP) Manufacturers

The facilities for manufacture and testing of DS and DP under EUA for use in the US are listed in Table 1. All sites are cGMP compliant and have US FDA establishment licenses.

Table 1. Facilities and responsibilities for manufacture, release and stability testing of mRNA-1273 Vaccine

Facility	Manufacturing step	Responsibility
ModernaTX, Inc. (Norwood, MA)	CX-024414 mRNA	Manufacture of CX-024414 (b) (4) scale) Release and stability testing of CX-024414 Lot release of CX-024414
	(b) (4)	Manufacture of (b) (4) scale) Release testing of (b) (4) (excludes bacterial endotoxin testing and residual solvents) Stability testing of (b) (4) (excludes bacterial endotoxin testing) Lot release of (b) (4)
	mRNA-1273 LNP	Manufacture of mRNA-1273 LNP (b) (4) scale) Release and stability testing of mRNA-1273 LNP (excludes bacterial endotoxin testing) Lot release of mRNA-1273 LNP
	mRNA-1273 DP	Release and stability testing of mRNA-1273 Drug Product (excludes bacterial endotoxin and sterility) Lot release of mRNA-1273 Drug Product
Aldevron (Fargo, ND)	CX-024414 mRNA	Manufacture of (b) (4) Release testing of (b) (4) template
Lonza Biologics, Inc.	CX-024414 mRNA	Manufacture of CX-024414 (b) (4) scale) (b) (4) release testing of CX-024414

(Portsmouth, NH)	(b) (4)	Manufacture of (b) (4) scale)
	mRNA-1273 LNP	(b) (4) release testing of (b) (4)
	mRNA-1273 DP	Manufacture of mRNA-1273 LNP (b) (4) g scale) (b) (4) release testing of mRNA-1273 LNP
Associates of Cape Cod, Inc (East Falmouth, MA)	(b) (4)	Manufacture of mRNA-1273 LNP (b) (4) scale)
	mRNA-1273 LNP	Bioburden release testing of mRNA-1273 LNP
	mRNA-1273 DP	(b) (4) release and stability testing of (b) (4) (b) (4) release and stability testing of mRNA-1273 LNP
Eurofins Advantar Laboratories, Inc. (San Diego, CA)	(b) (4)	Bacterial endotoxins release and stability testing of mRNA-1273 DP
	(b) (4)	(b) (4) release testing of (b) (4)
Catalent Indiana, LLC (Bloomington, IN)	mRNA-1273 DP	Fill/Finish of mRNA-1273 Drug Product Packaging of mRNA-1273 Drug Product Labelling of mRNA-1273 Drug Product Sterility release and stability testing of mRNA- 1273 Drug Product

5. DS and DP Manufacturing Process Development and Comparability Approach

The manufacturing process for mRNA-1273 vaccine consists of the manufacture of (b) (4) (b) (4) DS mRNA-1273 LNP, and DP mRNA-1273.

The initial process for mRNA-1273 was conducted in Moderna's Personal Vaccine Unit (PVU) facility. To support increases in manufacturing capacity, the process underwent scale-related changes, denoted as Scale A, Scale B Initial and Scale B Final, for increasingly larger scales which included adjustment of hold times, (b) (4) of intermediates and changes in equipment.

Phase 1/2 clinical lots were manufactured in the PVU. Phase 3 clinical lots were manufactured with Scale A materials and processes, which are similar to those used for Scale B production except for (b) (4) differences. Characterization studies were performed to support critical and non-critical process parameters and proven acceptable ranges (PARs) for the manufacturing steps.

Moderna developed a robust manufacturing process and analytical comparability assessment strategy to support site and scale changes involving four phases of comparability shown in Table 2 and included the following 3 elements in the comparability studies:

1. Description and justification of process changes including sites, scales, raw materials, process equipment and evaluation of process performance with respect to critical process parameters (CPPs) and in-process controls (IPCs)
2. Statistical evaluation of comparability of release testing results
3. Statistical evaluation of selected extended characterization results.

Table 2. Phases of comparability

Comparability Phase	DS or DP	Manufacturing Site
Phase 1 – Initial (PVU) and Scale A	DS (b) (4) mRNA	Moderna
	DP (b) (4) vials)	Moderna
Phase 2-Preliminary Scale B	DS (b) (4) mRNA)	Moderna
	DP (b) (4) vials)	Catalent

Phase 3 – Scale B Comparability	DS (b) (4) mRNA)	Moderna, Lonza
	DP (b) (4) vials)	Catalent
Phase 4 – Formal Comparability	Develop post-licensure comparability protocols	Moderna, Lonza and Catalent

Detailed descriptions of manufacturing and testing changes, analysis of their impact and justification were provided. To date, only Phase 1 and Phase 2 comparability, including elements 1 to 3 listed above, are completed and reported. Partial Phase 3 comparability based on results of critical-quality attributes (CQA) were also provided. Process comparability of Scale A (3 PPQ lots at a minimum) and Scale B (multiple GMP and PPQ lots) was demonstrated as presented in Table 3 below.

The DS and DP lots in support of this EUA application, and their scales and manufacturing sites are presented in Table 3.

Table 3. Summary of mRNA-1273 manufacturing scales and sites to support EUA

Product	Scale B process				
	Site	Initial scale		Final Scale	
		GMP	PPQ	GMP	PPQ
CX-024414 mRNA	Lonza	(b) (4) mRNA PN 40075	(b) (4) mRNA PN 40074		
		(b) (4) b)	(b) (4) b) (b) (4) b) (b) (4) b)	(b) (4) a)	N/A Full PPQ data – 11-Jan-2021 ^{c)}
	Moderna	N/A	N/A	(b) (4) b) (b) (4) b)	(b) (4) b) (b) (4) b) Full PPQ data - Dec-2020 ^{c)}
	(b) (4)	Lonza	(b) (4) (b) (4) PN 50063	(b) (4) PN 50074	
		N/A	N/A	(b) (4) a)	N/A Full PPQ data – 11-Jan-2021 ^{c)}
	Moderna	(b) (4) b) (b) (4) b)	(b) (4) b) (b) (4) b) (b) (4) b)	(b) (4)	(b) (4)
mRNA-1273 LNP	Lonza	(b) (4) mRNA PN 50073	(b) (4) mRNA PN 50075		
		N/A	N/A	(b) (4) a)	N/A Full PPQ data – 11-Jan-2021 ^{c)}
	Moderna	(b) (4) b) (b) (4) b)	(b) (4) b) (b) (4) b) (b) (4) b)	(b) (4)	(b) (4)
		Catalent Scale A (b) (4) doses)	(b) (4) b)	(b) (4) b) (b) (4) b) (b) (4) b)	N/A
	Catalent Scale B (b) (4) doses)	N/A	N/A	N/A	(b) (4) a) (b) (4) a) full PPQ data - Dec 2020 ^{e)}

N/A – not available yet; PN – process numbers established to distinguish between the process scales; a) - batch release data only; b) - CoA; c) - expected submission date; d) - release data for quantitative tests only.

The control strategy developed to ensure the consistent process performance and product quality includes the following attributes established for each DS and DP:

- Critical Quality Attributes (CQAs) for release testing with established acceptance criteria, numerical limits and ranges
- Critical Process Parameters (CPP), which may significantly impact CQAs and fail release specifications, with their proven acceptable ranges (PAR)

- Critical In-process Parameters Control (CIPC) to ensure the quality of in-process intermediates and monitor in-process parameters that may impact the product quality
- In-Process Control (IPC) performed for routine testing of process intermediate quality to ensure that the product conforms to its specifications
- Critical in-process hold limits and process duration determined for each manufacturing step.

6. DS and DP Analytical Assays

All analytical procedures, including compendial and non-compendial methods used to assess identity, purity, safety, potency, and stability of DS and DP, are described and supported with the correspondent SOPs. All reference standards and reference materials used in the analytical procedures were qualified and supported with qualification documentation. The precision, accuracy, sensitivity, specificity, linearity, range, and robustness were established for each testing method under actual conditions of use. All assays are validated, and analytical summaries with qualification results provided in Method Validation Reports are included in IND sections 3.2.S.4.3 and 3.2.P.4.3 *Validation of Analytical Procedures* for the DS and DP, respectively. All non-compendial testing of DS and DP lots for release and stability are performed at the Moderna facility.

The analytical assay methods used for DS and DP controls are listed in the relevant sections of this memo (e.g., Analytical procedures, Description of manufacturing process and controls, Assessment of process comparability, Characterization, Stability).

7. DS and DP Raw Materials

All raw materials used in the mRNA-1273 manufacturing process are obtained from qualified accredited suppliers and quality tested prior to release. No human- or animal-derived materials are used in the preparation of DS. All non-compendial materials are supported with representative Certificates of Analysis (CoAs) or Certificates of Compliance, which include BSE/TSE certificates. Non-compendial and custom raw materials used in the of (b) (4) production, e.g., (b) (4) (b) (4), are additionally tested for identification or other material attributes in accordance with individual specifications.

Information on the source and control of raw materials are provided in the IND (sections 3.2.S.2.3 *Control of Materials* for the DS and 3.2.P.4 *Control of Excipients* for the DP).

8. Drug Substance

The DS manufacture at the ModernaTX (Norwood, MA) and Lonza Biologics, Inc. (Portsmouth, NH) sites are very similar and involve the manufacture of (b) (4) (b) (4), and final DS, mRNA-1273 LNP. The process development was initially completed at Moderna using small-scale PVU lots, scaled up to the initial Scale A process at the Moderna site and extended to the Initial and Final Scale B processes. The final scales are (b) (4) (b) (4).

8.1 CX-024414 mRNA - Description of manufacturing process and controls

(b) (4)



19 pages determined to be not releasable: (b)(4)

(b) (4)

9. Drug Product

9.1 mRNA-1273 DP - Description of manufacturing process and controls

The DP manufacture is an aseptic process that includes (b) (4) of mRNA-1273 LNP, (b) (4)

, followed by filling, visual inspection, freezing and storage. Inspection, labeling and packaging activities occur with the validated duration (b) (4) (b) (4) at (b) (4). Inspected vials are labeled and packaged 10 per carton with an insert and transferred for conditioning freezing at (b) (4). (b) (4) (b) (4), the vials are transferred to -20°C for the final storage. The unit operations, IPC, and materials used are presented in flow diagram (Figure 4).

(b) (4)

Figure 4. mRNA-1273 DP process flow diagram.

The quantitative composition of the final mRNA-1273 DP, including DS intermediates, buffers, and cryoprotectant, is listed in Table 8. There are no novel excipients used for the DP formulation.

(b) (4)

(b) (4)



9.2 mRNA-1273 DP manufacturing process validation and evaluation

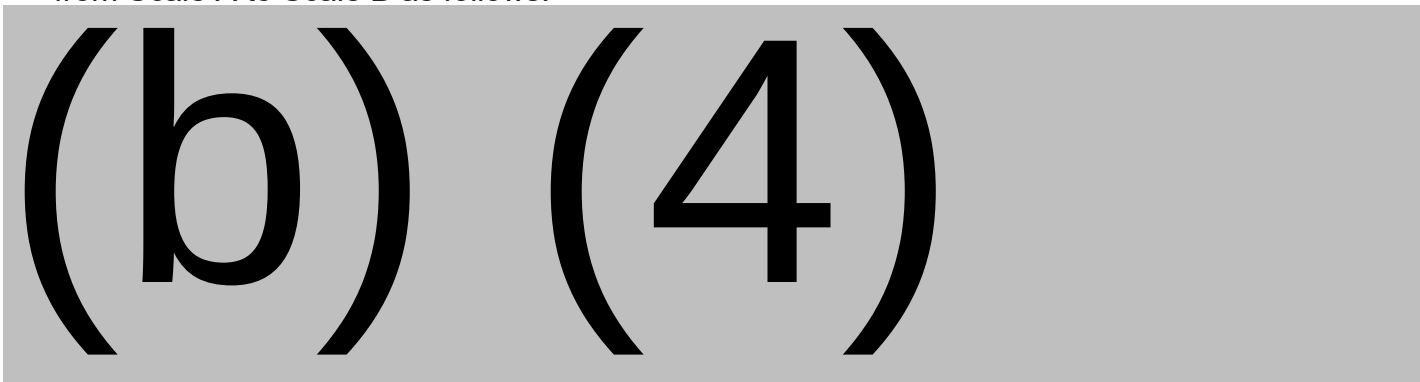
The key quality attributes CPP, IPC and CIPC defined for the mRNA-1273 LNP are presented from Table 9 through Table 11 below.

Cumulative process duration time from thawing start to freeze for out of refrigeration at 15 -30 °C is (b) (4) and for refrigeration at 2 -8 °C is (b) (4)

9.3 Major changes in mRNA-1273 DP manufacture – Process comparability assessment

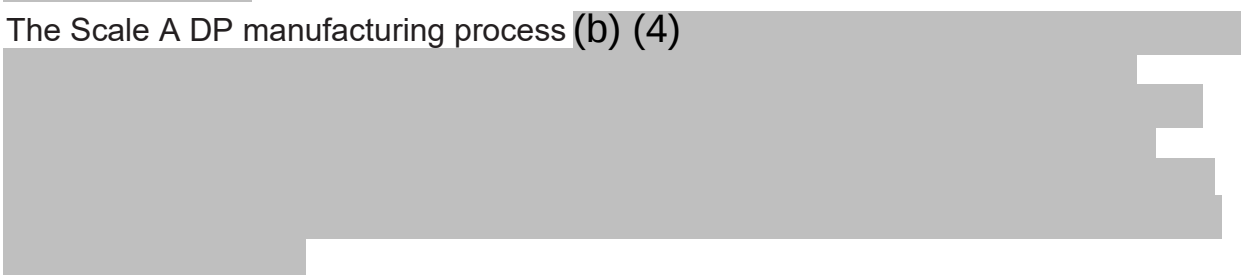
The majority of DP manufacturing changes were introduced during the process transfer from Scale A to Scale B as follows:

(b) (4)



The specification changes implemented during the process transfer from Scale A to Scale B include tightening of acceptance criterion for RNA content from (b) (4) (b) (4), establishment of purity release acceptance criterion of (b) (4) (b) (4) with a shelf life criterion of (b) (4), and extension of upper limit on particle size from (b) (4).

The Scale A DP manufacturing process (b) (4)



The CPP results for the final Scale B DP batches for EUA distribution were provided in the Interim Comparability Report submitted in IND 19745.86 on 11-Dec-20. Data presented in Table 9 demonstrate that all batches were manufactured with CPPs

controlled within the established PARs with the exception of cumulative process duration at 2°-8°C.

Table 9. Critical process parameters (CPP) for the final Scale B DP lots under EUA distribution

(b) (4)

Reviewer's comment 5:

Although the cumulative process duration during the filling of DP lots (b) (4) (b) (4) exceeded the PAR for time out of refrigeration, the testing results met the acceptance criteria on release for both lots and support their EUA distribution.

The CIPC and IPC results for the DP EUA lots, which are provided in Table 10 below, met the expected ranges and support the final Scale B process consistency and comparability.

Table 10. In-process control (IPC) data for the final Scale B DP lots under EUA distribution

(b) (4)

(b) (4)

Validation activities for Scale B DP process are still ongoing. The release testing results were submitted for 3 GMP lots filled in Flexi line (b) (4) lot 6007320005 (filled in Ompi vials) and lots #6007920001 and lot 6007920002 (both filled in SIOPlas vials). The release data for lot 6007320005, including the RNA purity conformed to both, the release specification and comparability acceptance criteria. The purity results for lot 6007920001 was (b) (4) and for lot 6007920002 was (b) (4), both conformed to release acceptance criterion of (b) (4) however, they were slightly out of the comparability acceptance criterion of (b) (4). In response to our information request from 11-Dec-20, the sponsor clarified that lot 6007920002 is a sublot of 6007920001 and was created due to the finding of particulates during the filling session as documented in Catalent deviation report REC 270793. Since additional time out of refrigeration occurred, the mRNA purity declined but it still complied with the release-acceptance criterion.

The consistency of DP Scale B process is supported with release data from additional lot 6008620001 filled at Vial line (system (b) (4)) in Corning Valor vials. The RNA purity of lot 6008620001 is (b) (4), however results of the other CQAs are still pending. The most recent comparability data from release testing of DP lots under EUA distribution were provided in an Interim Comparability Report and summarized in Table 11 below. All available results conformed to both the specification and comparability acceptance criteria.

Table 11. Summary for release testing of the DP lots under EUA distribution (Final Scale B)

Test	Analytical Method	Specification Acceptance Criteria	Comparability Acceptance Criteria	6007320005	6007920001	6007920002	6008620001
Appearance	Visual	White to off-white dispersion. May contain visible, white or translucent product-related particulates.	White to off-white dispersion. May contain visible, white or translucent product-related particulates.	White to off-white dispersion. Essentially Free of particulates.	White to off-white dispersion. Essentially Free of particulates.	White to off-white dispersion. Essentially Free of particulates.	Pending
RNA content	Anion Exchange HPLC	(b) (4)					
Identity	Reverse Transcription/						
Purity							

Product-related

RP-HPLC

(b) (4)

% RNA encapsulation	(b) (4)	(b) (4)	N/A	N/A	N/A	(b) (4)	
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Pending
Particle size	Dynamic Light Scattering	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Polydispersity		Report result	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)		(b) (4)	(b) (4)	Conforms	Conforms	Conforms	Pending
Cholesterol		(b) (4)	(b) (4)	Conforms	Conforms	Conforms	Pending
DSPC	UPLC-CAD	(b) (4)	(b) (4)	Conforms	Conforms	Conforms	Pending
PEG2000-DMG		(b) (4)	(b) (4)	Conforms	Conforms	Conforms	Pending
SM-102	UPLC-CAD	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Pending

All release testing results available to date for EUA DP lots produced at initial Scale B and final Scale B conformed with the established specifications and comparability acceptance criteria except the noted above deviation with RNA purity results, which are slightly outside the comparability criteria for two lots. Overall, the results from the final Scale B ((b) (4) vial) mRNA-1273 DP manufactured at Catalent demonstrated that the pre-change (Scale A lots used in the Phase 3 study) and post-change (Scale B EUA lots) manufacturing processes and quality attributes were comparable.

Reviewer's comment 6:

Although validation of the DP final Scale B process is not completed and PPQ activities are ongoing, the available quality release data are adequate and sufficient to support the mRNA-1273 DP manufacture for emergency use. Based on the absence of complete PPQ data for DS and DP manufacture, we requested that the CoAs for all lots be submitted to the EUA at least 48 hours before lots are released for distribution by Moderna. The DS and DP manufacturing sites should be included in the CoA.

9.4 Characterization - Elucidation of structure and other characteristics

The physico-chemical and biological properties of mRNA-1273 DP were studied with the same techniques that have been used for mRNA-1273 LNP characterization (described in section 8.3.3). These techniques were also applied to the extended characterization of clinical and EUA/commercial Scale A and Initial Scale B lots to support their comparability. The obtained results were highly similar for all lots tested.

9.5 Characterization - Impurities

No process-related impurities are anticipated to form or be introduced during mRNA-1273 DP manufacturing. The impurity profile of mRNA-1273 DP is similar to mRNA-1273 LNP, with the exception of potential degradation or potential extractables/leachables from the container closure system (CCS). Extractables summary for CCS is provided in section 9.6 below.

9.5.1 Analytical procedures

Many of the analytical assays performed for the mRNA-1273 DP are the same as those described for mRNA-1273 LNP DS in section 8.3.5.

Moderna utilizes the measurement of mRNA content by AEX-HPLC in conjunction with the measurement of mRNA purity by RP-HPLC for potency testing of the mRNA-1273 DP.

The potency of mRNA-1273 DP is assessed by a qualitative *in vitro* translation test performed on release. (b) (4)

(b) (4) test is included in the DP stability program. Of note, this potency release test is different from the quantitative (b) (4)-based test used for characterization of the mRNA-1273 LNP (please see description in 8.3.3).

9.6 Container closure systems

The EUA supply of mRNA-1273 DP is dispensed into Ompi® 10R clear Type 1 borosilicate glass vials (b) (4), SIOPlas™ 10-mL Cyclic Olefin Polymer (COP) vials (b) (4) or Valor® (Corning) 10R clear Type 1 equivalent alkali-aluminosilicate glass vials (b) (4). All vials are closed with a 20-mm (b) (4) Gray (b) (4) (b) (4) stopper and 20 mm flip-off red matte aluminum seal in (b) (4). The mRNA-1273 DP container closure systems (CCS) used at Catalent are listed in Table 12.

Table 12. Primary container closure systems used for EUA supply of mRNA-1273 DP

Presentation	Fill Line	Container Closure Component	Material of Construction ^(a)
mRNA-1273 DP PN 60073	Flexible Filling Line (System (b) (4))	Vial, Ompi® 10R, sterile, for human use (b) (4)	Type 1 borosilicate glass, clear
		Stopper, (b) (4), 20 mm (b) (4)	(b) (4) Gray (b) (4)
		Seal, (b) (4) 20 mm, Red Matte flip-off	Aluminum seal with flip-off plastic cap; color Red
mRNA-1273 DP PN 60079	Flexible Filling Line (System (b) (4))	Vial, SIOPlas™ 10-mL, sterile (b) (4)	Cyclic Olefin Polymer (COP)
		Stopper, (b) (4) 20 mm (b) (4)	(b) (4) Gray (b) (4)
		Seal, (b) (4) 20 mm, Red Matte flip-off	Aluminum seal with flip-off plastic cap; color Red
mRNA-1273 DP PN 60086	Vial Line (System (b) (4))	Vial, Corning Valor® 10R (b) (4)	Type 1 equivalent alkali aluminosilicate glass, clear
		Stopper, (b) (4), 20 mm (b) (4)	(b) (4) Gray (b) (4) (b) (4)
		Seal, (b) (4) 20 mm, Red Matte flip-off	Aluminum seal with flip-off plastic cap; color Red
mRNA-1273 DP PN 60085	Vial Line (System (b) (4))	Vial, Ompi® 10R (b) (4)	Type 1 borosilicate glass, clear
		Stopper, (b) (4), 20 mm (b) (4)	(b) (4) Gray (b) (4)
		Seal, (b) (4) 20 mm, Red Matte flip-off	Aluminum seal with flip-off plastic cap; color Red

a - The (b) (4) designation indicates the presence of a (b) (4) coating; (b) (4) - (b) (4).

The vials and stoppers meet the compendial requirements for glass and elastomeric components. The results of functionality tests performed for mRNA-1273 DP vial/stopper seal system for penetrability, fragmentation and self-sealing capacity in accordance with USP requirements demonstrated full compliance with release specifications and met acceptance criteria. Vials (Ompi, SIOPlas, Valor Corning), (b) (4) stoppers and (b) (4) seals are provided in Technical Development Memorandum PD-MEM-0258 and supported with CoA, Certificate of Processing, Certificate of Compliance, and BSE/TSE statement.

Extractables summary

The safety-risk assessment utilized material characterization studies performed as worst-case extraction profiles. Extractions were carried out with (b) (4) solvents and screening methods to create an extractables profile for each container-closure material. These studies identified potential compounds and elements with susceptibility to migrate into mRNA-1273 DP and served as a guide to the risk assessment. Results of an analysis of elemental impurities based on extractable studies performed by the respective vendors of the Ompi glass vials, Valor Corning glass vials, SIOPlas vials and (b) (4) stoppers were provided. Based on their risk assessment Moderna concluded that the presence of the extractables associated with these container components pose a negligible safety risk to humans at the levels currently assessed for the mRNA-1273 DP. This conclusion is based on the very low estimated worst-case total daily intake (TDIs) of the elemental analytes identified in vendor-supplied extractable studies and the results of literature-based toxicological assessment.

9.7 Stability

The overall mRNA-1273 DP stability plan, including the stability lot numbers, description and storage conditions, is presented in Table 13.

Table 13. mRNA-1273 DP stability testing overview

Lot Number	Usage	Concentration Fill Volume	mRNA-1273 LNP Lot Number	Site of Manufacture	Stability Storage Condition
6007520001	Clinical Supplies and Stability	0.20 mg/mL 5.0 mL	(b) (4)	ModernaTX, Inc.	-60°C to -90°C -20±5°C (Intended Long-term) 5±3°C (Intended Short-term) 25±2°C
6007520002					
6007520003					
6007520004	(b) (4)				
6007520005	Moderna PPQ		(b) (4)		-60°C to -90°C -60°C to -90°C followed by storage at 5±3°C (Intended Short-term)
6007520006			(b) (4) (b) (4)		
(b) (4)			(b) (4) (b) (4)		-20±5°C (Intended Long-term) -20±5°C followed by storage at 5±3°C (Intended Short-term)
6007320001	Catalent PPQ	0.20 mg/mL 6.3 mL	(b) (4)	Catalent Pharma Solutions	-20±5°C (Intended Long-term) -20±5°C followed by storage at 5±3°C (Intended Short-term) 25±2°C
6007320002			(b) (4)		
6007320003			(b) (4)		

The CQAs being tested in the stability studies include appearance, RNA content, RNA identity, RNA encapsulation, individual lipids (SM-102, cholesterol, DSPC, and PEG2000-DMG) content and purity, LNP size and polydispersity, and *in vitro* translation. In addition, particulate matter testing was included for stability testing of the DP. The stability results available to date pertain to Scale A GMP lots produced at Moderna site and are as follows:

- For lots 6007520001, 6007520002, 6007520003, and 6007520004: 3 months of storage at -60°C to -90°C; at -20±5°C; at 5±3°C; and 72 hours of storage at 25±2°C
- For lots 6007520005 and 6007520006: 2 months of storage at -60°C to -90°C; 1 month of storage at -60°C to -90°C, then stored at 5±3°C.

All generated data are within the DP-stability specifications for 3 months for long-term storage at -20±5°C and 3 months for short-term storage at 5±3°C. Based on accelerated stability results, the DP was found to be stable up to 72 hours of storage at 25±2°C. Additional Scale B GMP lot (b) (4) was placed on a new stability protocol to monitor samples stored at -20±5°C (b) (4) with specified intervals for up to (b) (4) (b) (4)

Freeze-thaw cycling data for the DP stored at -60°C to -90°C and thawed at room temperature support five freeze/thaw cycles. Clinical in-use stability data demonstrated DP stability was maintained for bracketing dosage strengths of 0.10 mg/mL to 0.5 mg/mL mRNA for up to (b) (4) hours in the vial followed by (b) (4) hours in the syringe at either ambient temperature or at storage at 5±3°C.

Based on available stability data, mRNA-1273 DP stored in the commercial CCS will be assigned to an initial shelf life of 7 months when stored at the recommended long-term storage condition of -15°C to -25°C (-20°C), which can include up to 30 days of storage at 5±3°C at the point of care site. On the day of dose administration, the product is allowed an additional in-use time of up to 12 hours at 8 to 25°C.

10. Reviewer's Conclusion and Recommendation

The CMC information submitted in IND 19745 and multiple IND amendments includes data indicating that the DS and DP manufacturing process and controls are well characterized and qualified, and the lots manufactured on different scales and in different facilities are comparable.

Although validation of the final Scale B process is not completed and PPQ activities are ongoing, the available quality-release data are adequate and sufficient to support the mRNA-1273 DP manufacture for emergency use. Based on the absence of complete PPQ data for DS and DP, we requested that the CoAs for all lots be submitted to the EUA at least 48 hours before lots are released for distribution by Moderna.

We recommend approval of the EUA request.