1 INTRODUCTION

mRNA-1273 Drug Product (DP) is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains an mRNA (CX-024414) encoding for the Spike glycoprotein of 2019-novel Coronavirus (SARS-CoV-2) and four lipids that act as protectants and carriers of the mRNA. The S protein is stabilized in the pre-fusion conformation by two amino acid mutations, K986P and V987P. The four lipids of the LNP are: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and cholesterol. The mode of action (MoA) is based on delivery of the mRNA-LNPs to the tissues, release of the mRNA and *in vivo* expression of the pre-fusion stabilized Spike glycoprotein of the Coronavirus (SARS-CoV-2).

The DP is supplied as a multiple-dose liquid, ready-to-use solution at 0.20 mg/mL for intramuscular administration in 10-mL (10R) vials, are closed with a rubber stopper and aluminum crimp flip-off seal.

mRNA-1273 DP is provided in two vial presentations:

Labeled Fill volume 5.5 mL (0.5 mL per dose) vial: Each vial contains (b) (4) mg of CX-024414 mRNA and (b) (4) mg of SM-102 LNP as a white to off-white dispersion in a preservative-free buffer containing 20 mM Tromethamine (Tris), (b) (4) acetate, 87 g/L sucrose at pH 7.5. The target fill volume is 6.3 mL, which allows removal of a maximum of 11 doses (0.5 mL per dose) per vial.

Labeled Fill volume 7.5 mL (0.5 mL per dose) vial: Each vial contains (b) (4) mg of CX-024414 mRNA and (b) (4) mg of SM-102 LNP as a white to off-white dispersion in a preservative-free buffer containing 20 mM Tromethamine (Tris), (b) (4) acetate, 87 g/L sucrose at pH 7.5. The target fill volume is 8.0 mL, which allows removal of a maximum of 15 doses (0.5 mL per dose) per vial.

Composition of the DP is described in Table 1.

(b) (4)

The starting materials of the mRNA-1273 LNP Drug Substance are the CX-024414 mRNA that encodes for the pre-fusion stabilized Spike protein of 2019 Coronavirus (SARS-CoV-2) and the (b) (4) The starting material for DP manufacture is the mRNA-1273 LNP Drug Substance (encapsulated mRNA). The reporting of starting materials in Module 3 Body of Data are indexed in Table 2.

Table 2: Location of Starting Material Data within Module 3

Starting Material	Module 3 Location
CX-024414 mRNA	3.2.S {CX-024414}
(b) (4)	(b) (4)

Figure 1 provides an overview of the manufacturing process illustrating how the starting materials are used to manufacture mRNA-1273 drug substance and drug product. All production processes are controlled and the three starting materials are release tested before used for subsequent production steps.

Figure 1: Overview of the mRNA-1273 Manufacturing Processes and the Use of Starting Materials

(b) (4)

CX-024414 mRNA

CX-024414 mRNA is manufactured in a series of unit operations including an In Vitro Transcription (IVT) Reaction and Cap Reaction, (b) (4)

(b) (4)

(b) (4)

mRNA-1273 LNP Drug Substance

(b) (4)

Drug Product

DP is formulated to contain 20 mM Tris, (b) (4) sodium acetate, 87 g/L sucrose at pH 7.5. Dilution of the mRNA-1273 LNP with dilution buffer (20 mM Tris, 87 g/L sucrose, pH 7.5) during DP formulation reduces the concentration of mRNA, lipids, and sodium acetate relative to the mRNA-1273 LNP. No novel excipients or excipients derived from human or animal sources are used in the DP.

(b) (4)

Representative batch size and formula for the manufacture of DP are provided in Table 3 and Table 4, respectively. Number of vials and component amounts per batch are adjusted based on actual mRNA input.

Table 3: Drug Product Target Batch Size

Product (Strength)	Site Fill Volume	Nominal Batch Size	Theoretical Number of Vials
0.20 mg/mL mRNA	Baxter	(b) (4) mRNA (b) (4) DP	(b) (4) (8.0 mL fill volume)
	Catalent	(b) (4) mRNA (b) (4) DP	(b) (4) (6.3 mL fill volume) (b) (4) (8.0 mL fill volume)

Abbreviation: DP = drug product

Table 4: Drug Product Batch Formula

Component	Nominal Amount per Batch
mRNA-1273 LNP	(b) (4)
Dilution Buffer [a]	

Abbreviations: LNP = lipid nanoparticle; WFI = water for injection

[a] Dilution Buffer composition in WFI ((b) (4) Tris, (b) (4) Tris-HCl, 87 g/L Sucrose, pH 7.5), (b) (4)

[b] (b) (4)

The DP does not include a preservative, due to the lipid nanoparticle-based product being incompatible with common preservatives; however, it is presented as a multiple-dose vial. The ability of the product to be used as an unpreserved multiple-dose product was demonstrated in a microbial challenge hold study that examined the ability of the product to support or hinder microbial growth. This study was designed to support the proposed "In-Use Time" of 12 (in US) hours from initial needle puncture/vial entry. The study involved

inoculating low levels of selected microorganisms (b) (4) (b) (4) and evaluating the product's ability to promote or hinder growth of the microorganisms over a timeframe corresponding to the proposed "In-Use Time" of the entered vial.

Process Validation

Moderna has successfully completed process performance qualifications (PPQs) of the CX-024414 mRNA, (b) (4) mRNA-1273 Drug Substance, and the DP manufacturing processes as a means of demonstrating that the commercial-scale manufacturing processes are capable of consistently delivering quality product. The PPQ studies have generated data at commercial scale to support and complement concurrent laboratory-scale studies. The proposed commercial control strategies were defined based on the state of control demonstrated during PPQ.