

FDA Briefing Document

Active Substance: mRNA that encodes for the pre-fusion stabilized Spike protein of 2019-novel Coronavirus (SARS-CoV-2).

Intended Indication(s): mRNA-1273 is a vaccine indicated for the prevention of disease caused by SARS-CoV-2

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1. SUMMARY

1.1. Product Name(s)

mRNA-1273, a lipid-encapsulated mRNA-based prophylactic vaccine encoding the pre-fusion stabilized spike (S) glycoprotein of the SARS-CoV-2 virus.

1.2. Chemical Name, Established Name and/or Structure

mRNA-1273 Drug Product is a lipid nanoparticle (LNP) dispersion containing an mRNA (CX-024414) encoding the pre-fusion stabilized spike (S) protein of the SARS-CoV-2 virus and four lipids: SM-102 (a custom-manufactured, ionizable lipid); PEG2000-DMG; cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC).

1.3. Proposed Indication(s) or Context of Product Development

mRNA-1273 is a vaccine indicated for the prevention of disease caused by SARS-CoV-2.

1.4. Background

The Sponsor is collaborating with the Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Diseases (NIAID) to develop an mRNA-based vaccine, mRNA-1273, in response to the current COVID-19 declared Public Health Emergency (PHE). The Sponsor is working to expedite the development of the mRNA-1273 vaccine and believes that early and frequent engagement and guidance from the Agency will be critical to accomplish this goal.

1.5. Introduction

The Sponsor has commenced Process Performance Qualification (PPQ) activities for the mRNA-1273 vaccine (CX-024414 mRNA, (b) (4), mRNA-1273 LNP and mRNA-1273 Drug Product) with the aim to enable a commercial manufacturing process for mRNA-1273 vaccine while concurrently conducting the Phase 2 and Phase 3 human clinical trials. These activities are being performed to provide the necessary amendments to the existing regulatory filings to support the initial validated manufacturing process by September 2020 in anticipation of distribution of an mRNA-1273 vaccine once sufficient human clinical data become available. The Sponsor is requesting a teleconference to discuss critical activities related to its proposed commercial manufacturing strategy. This discussion would include:

- 1) The use of a multiple-dose vial that does not contain any preservative.
- 2) The fill volume for a multiple-dose vial.
- 3) Analytical comparability to support lot-to-lot consistency in lieu of a clinical lot consistency study.
- 4) Classification of materials for the CX-024414 mRNA.

2. LIST OF PROPOSED QUESTIONS

2.1. Question 1

mRNA-1273 Injection (Drug Product) is expected to be a vaccine that will be distributed widely and will be used for large-scale population (mass) vaccinations. mRNA-1273 Drug Product consists of a dispersion of mRNA-1273 Lipid Nanoparticles (LNP) in 20 mM Tris buffer, (b) (4) acetate and 87 mg/mL sucrose solution and is intended for long-term storage in the frozen state (-20°C) at the distribution sites and short-term storage in the refrigerator (2°C – 8°C) at the vaccine administration sites and will have an allowable shorter duration period prior to use (currently estimated at up to 2 weeks). The mRNA-1273 Drug Product is intended to be filled in a 10R glass vial with an appropriate 20 mm stopper (suitable for use with multiple-dose containers) and seal system.

The Sponsor plans to manufacture a preservative-free multiple-dose (maximum 10 doses) product for commercialization. This proposal is based (1) on the data generated to date and the knowledge and understanding of the biophysical, biochemical as well as microbiological growth-promoting characteristics of the lipid nanoparticle (LNP)-based product, and (2) the efficiencies offered by the multiple-dose vial in utilizing fill/finish, container/closure as well as supply chain resources in a pandemic response situation

Does the Agency agree with the proposal for a preservative-free multiple-dose vial with a label that allows a six-hour beyond-use period for the entered (needle-punctured) vial?

Sponsor's Position

The choice of a Drug Product presentation format rests between single-dose and multiple-dose (with or without preservative) vial. Note “preservative” in this context refers to antimicrobial preservative(s) that prevent microbial growth (for a certain period) after a sterile vial container/closure is entered for use, per USP <51>. The Sponsor's position for the proposed preservative-free multiple-dose vial is based on the following summary reasons, followed by a detailed discussion of each rationale.

- (1) Data generated by the Sponsor shows that the biochemical and biophysical nature of the LNP-based mRNA-1273 Drug Product does not readily support a preservative-based multiple-dose product. Even low levels of common preservatives (b) (4) cause changes in LNP particle size, polydispersity index and %RNA encapsulation levels.
- (2) Data generated by the Sponsor shows that the mRNA-1273 Drug Product does not support adventitious microbial growth for at least 24 hours at 20°C – 25°C, meeting the “No Increase” criteria defined in USP <51> and discussed in [Metcalf \(2009\)](#).
- (3) Data generated by the Sponsor shows that the mRNA-1273 Drug Product maintains its biochemical and biophysical quality within defined specifications, over a beyond-use period of six hours at 20°C – 25°C in the vial followed by up to eight hours in a syringe at both 2°C – 8°C or 20°C – 25°C.

Detailed discussion of these rationale is provided below.

(1) **Biophysical Impact of Preservatives:** The preservatives commonly used in parenteral products (including vaccines; [Table 1](#)) are expected to have a strong tendency to partition into the LNPs. This assessment is based on the mechanism by which of these compounds function which requires partitioning into membranes or cell walls of microbes ([Table 1](#)). However, once removed from the aqueous phase, these compounds lose their efficacy as antimicrobials, as only the fraction that remains in the aqueous phase is functional. As an example, a liposomal system studied by [Komatsu et al., 1986](#), (e.g. phosphatidylcholine / cholesterol / DPPC), showed that 90% of butylparaben was partitioned into the liposomes, i.e. 90% of the preservative was lost from the aqueous phase. Systems that can sequester preservatives therefore require significantly higher levels of preservatives to show antimicrobial properties, [(see e.g., in cyclodextrin systems reported by [Lehner et al., \(1994\)](#)].

Table 1: Common Antimicrobial Preservatives used in Parenteral Products (including Vaccines) [(based on [Elder and Crowley \(2012a, 2012b\)](#), [Meyer et al. \(2007\)](#)]

Preservative	Chemical Class	pH of Optimum Function	Typical In-Use Concentration	Site of Action ^(a)
Benzyl alcohol, Chlorbutanol, 2-ethoxyethanol	Alkyl / Aryl alcohols	< 5	1% w/v, 0.3 – 0.5% w/v	Cytoplasmic membrane, Cytoplasm
Methyl, Ethyl, Propyl, Butyl parabens and combinations	Amino aryl acid esters	4 – 8	0.2% w/v (Methyl, Propyl)	Cytoplasmic membranes
Benzoic acid, Sorbic acid	Alkyl / Aryl acids	< 5	No reference identified	Cell wall, Cytoplasmic membrane
Chlorhexidine	Biguanides	5 – 7	No reference identified	Cell wall, Cytoplasmic membrane, Cytoplasm (high concentrations)
Phenol, m-Cresol	Phenols	4 – 9	0.25 – 5% w/v, 0.3% w/v	Cell wall
Phenylmercurate salts	Organic mercurial	5 - 8	No reference identified	Cell wall, Cytoplasmic membrane
Thimerosal			0.002 – 0.01% w/v	Cell wall

a) Site of action can vary with concentration and preservatives may interfere with several different microbial mechanisms

(b) (4)

Figure 1: Impact of Preservatives (b) (4) on the Biophysical Quality Attributes (Particle Size, PDI, % RNA Encapsulation) of the 0.20 mg/mL mRNA-1273 Drug Product, when Stored at 2°C – 8°C (Left Panel) or -70°C (Right Panel)

(b) (4)



The left panel shows the data for higher preservative concentrations (b) (4) while the right panel shows data for lower preservative concentrations (b) (4). “Initial” implies data collected immediately after addition of preservative. In all cases, the results are compared against the mRNA-1273 Drug Product without added preservatives. Missing data implies precipitation was observed.

The Sponsor has also initiated antimicrobial efficacy (AET) studies (USP <51>) with (b) (4) to assess the impact of the partitioning effect, even though these levels of preservatives significantly disrupt the LNP structure as shown above.

(2) ***Growth Promotion Ability of mRNA-1273 Drug Product:*** In order to address the risk of microbiological contamination in improperly handled vials, the Sponsor has conducted “growth promotion tests” on the mRNA-1273 Drug Product vials by inoculating low levels of certain organisms (specified in USP <51> and an additional typical skin flora, (b) (4)) and examined the growth promotion abilities of the product. The Sponsor’s proposition for a 6 hour in vial beyond-use period is supported by the data which shows growth of the inoculated microorganism is hindered for up to 24 hours (= “No increase” as defined in USP <51>; [(Metcalf (2009))]. The data is summarized below in Table 2 and Table 3.

(b) (4)

- (3) **Stability of mRNA-1273 Drug Product:** The Sponsor has conducted stability studies to mimic the handling of mRNA-1273 Drug Product at the clinical sites, using representative materials, representative test articles and the appropriate dose preparation procedure for clinical use (Table 4). In support of Phase 3 dosing, two lots of mRNA-1273 Drug Product (representative multiple-dose vial lots with 6.5-mL fill volume; manufactured under cGMP conditions) were used for the stability study. A dose bracketing strategy was used (0.10 mg/mL mRNA and 0.5 mg/mL mRNA) to cover the intended clinical dose (0.20 mg/mL mRNA) to demonstrate compatibility of administration materials (b) (4) with mRNA-1273 Drug Product. mRNA-1273 Drug Product was not diluted for this study.

Table 4: Preparation Configurations for the In-use Stability Study

Lot No.	Dose, µg	Dose Concentration (mg/mL)	Dose volume (mL)
6006820001	(b) (4)	0.10	0.5
6006920001		0.5	0.5

The study was designed to enable direct removal of product solution from vial and holding it in syringes. The product solution was first held in the original vial at room temperature for either 1 hour or 6 hours after allowing 1 hour to thaw. Dosing syringes were prepared from the vial after 1 hour and then again after 6 hours. The syringes were then held for 0, 8, and 24 hours at room temperature and refrigerated conditions (2°C – 8°C) and assayed for RNA content by AEX-HPLC, % purity by RP-HPLC, lipid content by UPLC-CAD, % RNA encapsulation, and mean particle size and polydispersity by Dynamic Light Scattering as well as in vitro translation (Potency). The study design is schematically depicted below in Figure 2.

(b) (4)

Attributes of mRNA-1273 Drug Product remained within specification when held in a vial for 6 hours at room temperature, followed by storage in a syringe for 8 hours, at either 0.5 mg/mL mRNA or 0.10 mg/mL mRNA. Stability was demonstrated for the bracketing dosage strengths of 0.10 mg/mL mRNA to 0.5 mg/mL mRNA for up to 6 hours in the vial followed by 8 hours in the syringe at either room temperature or for storage between 2°C to 8°C, as % purity was not achieved at T = 24 hours at all conditions. The individual data sets are presented in [Table 21](#) to [Table 26](#) in the [Appendix](#) Section. An overall summary of the 6 hour post hold for the entered multi-dose vial at T = 24 hours is presented in the following tables.

Table 5: Clinical In-Use Compatibility Data for mRNA-1273 LS Injection, Lot 6006820001, 0.10 mg /mL, (b) (4) Post 6 Hour Hold of an Entered Multiple-Dose Vial at T = 24 Hours

Test	Acceptance Criteria		Initial*	T = 24h PC		T = 24h PP	
	Initial	T24 h		RT	5C	RT	5C
Appearance	Report result		White to off-white dispersion, essentially free of particulates				
RNA content by AEX-HPLC	(b) (4)						
Purity by RP-HPLC							
Product related impurities by RP-HPLC							
In Vitro Translation (Potency)							
% RNA encapsulation by (b) (4)							
Mean particle size by Dynamic Light Scattering							
Polydispersity by Dynamic Light Scattering							
Lipid content by UPLC-CAD							
SM-102	(b) (4)						
Cholesterol							
DSPC							
PEG2000-DMG							
Lipid impurities by UPLC-CAD							

* Initial (T = 0) results were from samples drawn up into a polycarbonate syringe and immediately pooled in a sample collection vial.
The impact of syringe material is expected to be negligible in the short timeframe involved.
Values reported in **bold**, denote a value below acceptance criteria

Table 6: Clinical In-Use Compatibility Data for mRNA-1273 LS Injection, Lot 6006920001, 0.5 mg /mL, (b) (4) Post 6 Hour Hold of an Entered Multiple-Dose Vial at T = 24 Hours

Test	Acceptance Criteria		Initial*	T = 24h PC		T = 24h PP	
	Initial	T24 h		RT	5C	RT	5C
Appearance	Report result		White to off-white dispersion, essentially free of particulates				
RNA content by AEX-HPLC	(b) (4)						
Purity by RP-HPLC							
Product related impurities by RP-HPLC							
In Vitro Translation (Potency)							
% RNA encapsulation by (b) (4)							
Mean particle size by Dynamic Light Scattering							
Polydispersity by Dynamic Light Scattering							
Lipid content by UPLC-CAD							
SM-102	(b) (4)						
Cholesterol							
DSPC							
PEG2000-DMG							
Lipid impurities by UPLC-CAD							

* Initial (T = 0) results were from samples drawn up into a polycarbonate syringe and immediately pooled in a sample collection vial. The impact of syringe material is expected to be negligible in the short timeframe involved.

The Sponsor plans to conduct additional and expanded in-use stability studies using planned commercial strength product (0.20 mg/mL) produced as part of mRNA-1273 Drug Product PPQ campaign to further demonstrate the stability and potency of mRNA-1273 Drug Product during the beyond-use period. These studies will assess impact of hold in an entered (needle-inserted) vials and impact of subsequent hold in syringe. Syringes from different manufacturers will be assessed including individual syringe variability.

Considerations in the Production, Distribution and Use of Single vs Multiple-Dose Product Presentations in COVID-19 Pandemic Response Scenario

The advantages and disadvantages of single and multiple-dose vaccine product presentations have been extensively studied due to their importance for global vaccine immunization programs. Some of these aspects are summarized below in [Table 7](#).

Table 7: Framework for Comparison of Production, Distribution and Use Aspects of Single and Multiple-dose Vaccine Vial Presentations [(Adapted from [Drain et al. \(2003\)](#); [Lee et al., \(2010\)](#)] and the Assessment of mRNA-1273 Drug Product

Factors	Formats		Assessment of Multiple-dose in Context of COVID-19 ^(a)
	Single-Dose	Multiple-Dose	
Production	Less efficient/dose <ul style="list-style-type: none"> • Slower fill rate/dose • Larger overfill of drug substance/dose • Higher fill/finish related material and capacity demand/dose 	More efficient/dose <ul style="list-style-type: none"> • Faster fill rate/dose • Less overfill of drug substance/dose • Lower fill/finish related material and capacity demand/dose 	Multiple <ul style="list-style-type: none"> • ++ • ++ • ++
Distribution	Simpler but overall less efficient <ul style="list-style-type: none"> • Greater cold chain volume and weight/dose (distribution and storage) • Less waste (in case of cold chain failures) • Simplified tracking and logistics • More medical waste (vials) but similar sharps waste 	More complex but overall more efficient <ul style="list-style-type: none"> • Lower cold chain volume and weight/dose (distribution and storage) • Risk for greater waste (in case of cold chain failures) • More complex tracking and logistics • Less medical waste (vials) but similar sharps waste 	Multiple <ul style="list-style-type: none"> • ++ • -- • 0 • 0
Use	Lower risk <ul style="list-style-type: none"> • Low wastage as vial only used when subject is present • Low risk of contamination • More accurate dose delivery (volume) 	Higher risk <ul style="list-style-type: none"> • Higher wastage if vial not fully utilized in designated time period • Higher risk of contamination with multiple entries into vial • Greater risk for inaccurate dose delivery (volume) 	Multiple <ul style="list-style-type: none"> • 0 • -- • -

a) + = Favorable; - = Unfavorable; 0 = Equivocal, when evaluating the multiple-dose presentation against single-dose version.

The mRNA-1273 Drug Product can be risk-assessed per the above factors. As a pandemic response, rapid production, lower material (container/closures and consumables etc.) and fill/-finish capacity demand, lower overfill (i.e. more efficient utilization of current LNP production capacity), and rapid distribution is of paramount importance. A multiple-dose product is more efficient in terms of number of doses produced per batch, and thus in utilization of fill/finish capacity. It also uses less glass vials/stoppers for the number of doses produced, helping to reduce the risk posed by potential glass vial shortage based on expected demand related to the COVID-19 response. [(1) <https://www.washingtonpost.com/business/2020/07/13/coronavirus-vaccine-corning-glass/>; (2) <https://www.businessinsider.com/coronavirus-vaccine-glass-shortage-operation-warp-speed-corning-sio2-2020-6>; (3) <http://www.pharmtech.com/industry-builds-fillfinish-capacity-pandemic-response?topic=354,358,364>].

Multiple-dose vials are also more efficient in terms of utilization of cold-chain distribution capacity. The risk for greater losses with multiple-dose vials in case of a failure in the cold-chain, is being mitigated by moving to a -20°C long-term storage and shipping conditions, for which the supply-chain capacity is higher, robust and well established. Furthermore, data will be generated to address impact of temperature excursions during shipping. It is expected that waste on use will not be as important a factor when mass vaccination is being considered, i.e. subject availability would not be limiting for the utilization of all the doses in the vial in the designated in-use period. The risk for contamination due to multiple entries into the vial is addressed by the microbial growth promotion study data provided above, and by limiting the beyond-use time to six (6) hours which is significantly less than the 24 hours for which no increase is seen. Furthermore, the stopper intended for use with the multiple-dose vial has been tested for functionality tests, including self-sealing capacity, per USP <381> Elastomeric Closure for Injections by the manufacturer. A product specific assessment will be conducted by the Sponsor. Clear instructions in the label text will require that an entered vial be discarded after this 6 hour period. The risk or inability to accurately extract the number of doses has been addressed by properly defining the overfill and is further discussed in the next question ([Question 2](#)).

A multiple-dose vial thus enables an efficient utilization of existing resources for COVID-19, (without the normal programmatic concerns of multiple-dose vaccines products where the Health-Care Practitioner may be reluctant to open a multiple-dose vial if there is doubt that the doses will be used before an entered vial expires).

In summary, the Sponsor's proposal to develop a preservative-free, multiple-dose vial for mRNA-1273 Drug Product is supported by the overall assessment of risks and benefits of single versus multiple-dose presentations. The biophysical attributes of the product do not support use of preservatives. The product solution does not support microbiological growth for at least 24 hours at 20°C - 25°C. Stability of the product has been demonstrated over the intended beyond-use time. Finally, the multiple-dose vial offers significant efficiencies in utilizing fill/finish, container/closure as well as supply chain resources in a pandemic response situation.

2.2. Question 2

The Sponsor has conducted a comprehensive laboratory study to define the fill-volume for the mRNA-1273 multiple-dose vaccine presentation. For a 0.5 mL dose and a ten (10)-dose vial, the Sponsor proposes an initial target fill of 6.3 mL for commercialization at (b) (4) scale at Catalent Biologics (Bloomington, IN). This proposal is based on examination of losses in the commonly used 1-mL dosing syringe, dead-volume in the vial, as well as process fill volume variability. Further refinement of the fill-volume towards lower excess volume will be made with more data and user/field experience prior to the PPQs for the scale-up to the (b) (4) scale at Catalent. However, it is also expected that due to variability in operator technique, skill, and

diligence, as well as practices such as use of devices for dose extraction, the intended ten (10) doses may not always be achieved.

- (1) Does the Agency agree with the proposal to target an initial target fill of 6.3 mL to enable ten (10) doses of 0.5 mL from the multiple-dose vial?*
- (2) Does the Agency agree with the proposal for a label that includes the statement “A maximum of ten (10) doses can be withdrawn from the multiple-dose vial”?*

Sponsor’s Position:

Allowable excess volume recommendations are provided in USP <1151> for mobile liquids but these recommendations apply to single-dose vials only. No specific guidance exists for multiple-dose vials other than not being more than 30 mL (USP <1>). The FDA Guidance on Allowable Excess Volume and Labelled Vial Fill Size in Injectable Drug and Biological Products (June 2015) recommends that a Drug Product’s vial fill size should be appropriate for the labeled use and dosing of the product. USP <697> states that each container of the injection contains sufficient excess to allow withdrawal of the labeled quantity of drug. For multi-dose containers, volume of injection in containers is tested with the same number of separate syringe assemblies as the number of doses specified. The volume is such that each syringe delivers no less than the stated dose.

(b) (4)

Combining the above data with typical fill volume variability seen in (b) (4) the Sponsor has conducted a (b) (4) of fill volumes and number of doses delivered from a large number of vials. Based on this analysis and a consideration of the FDA expectation of minimization of excess volume, the Sponsor has selected a fill volume of 6.3 mL for the initial launch and commercialization at (b) (4) scale at Catalent Biologics. The Sponsor intends to continue to gather data by benchmarking, obtaining user input, as well as incorporate field experience to the extent possible, to further refine this fill volume towards lower levels that meet the expectations of USP <697> and the Agency Guidance, while also maximizing utilization of drug substance.

It is understood that once in the field, the actual number of doses extracted from the vial may vary depending upon the technique, skill, as well as diligence applied by the Health Care Practitioner. Furthermore, use of non-optimal syringes as well as the aforementioned vial spike adapters or other such devices may lead to the intended 10 doses not being achieved in all circumstances. The Sponsor therefore proposes to apply for a label that includes the statement “A maximum of ten (10) doses can be withdrawn from the multiple-dose vial”. This is in alignment with the label for the Fluzone Quadrivalent vaccine (NDC 49281-631-78, carton 49281-631-15).

In summary, the Sponsor has collected laboratory data and developed a simulation model to define the total fill-volume for the mRNA-1273 multiple-dose vaccine. The Sponsor will refine the model and the excess fill-volume with more data and user/field experience to potentially update the fill volume prior to the expansion PPQs to (b) (4) scale at Catalent Biologics. Variability in practices and procedures applied by the Health Care Practitioner suggests that a label with the statement “A maximum of ten (10) doses can be withdrawn from the multiple-dose vial”, would be appropriate for the mRNA-1273 multiple-dose vaccine.

2.3. Question 3

Based on feedback received from the Agency on June 27, 2020, does the Agency agree that the summation of the analytical data generated for lots supporting the Phase 3 clinical trial (Phase 3 manufacturing campaign and the process and performance qualification (PPQ) lots demonstrates adequate manufacturing control such that a clinical lot consistency study is not necessary to support licensure of mRNA-1273

Sponsor's Position

The following feedback was received from the Agency on June 27, 2020:

“Please provide details on your plans to assess lot-to-lot consistency of your Drug Product. Clinical lot consistency studies are traditionally performed as a component of a Phase 3 clinical study. If you are not able to complete a lot consistency study in a clinical study, please propose an analytical comparability study to support the consistent manufacturing process and quality of the product batches used in your Phase 3 study.”

Given the urgency of the pandemic situation, the development timelines of mRNA-1273 are substantially compressed and the Phase 3 clinical study will be starting by the end of July. The mRNA-1273-P301 was not designed to include an assessment of lot-to-lot consistency. Assuming that early evidence of benefit would become available before the end of the 2020 and depending on the status of the pandemic at that point in time, it may be decided to expedite the availability of the vaccine to specific populations in the United States. Should that scenario become a reality, the vaccine could be administered to large numbers of individuals before the completion of a formal lot-to-lot clinical consistency study. In that situation, the later conclusion of a lot-to-lot consistency study would have limited value.

In lieu of a lot-to-lot clinical consistency, the Sponsor is proposing to provide an extensive analytical comparability plan to support the manufacturing process and quality of the mRNA-1273 Drug Product batches that will be used in the Phase 3 study. The Sponsor believes that the analytical comparability data will provide adequate assurance of the lot-to-lot consistency of the manufacturing of mRNA 1273 vaccine and will support the commercial production of the vaccine with the execution of PPQs for the mRNA-1273 Drug Product, release testing with statistical analysis and defined acceptance criteria for the mRNA-1273 Drug Product and extended characterization with statistical analysis and defined acceptance criteria for the mRNA-1273 Drug Product. As the mRNA-1273 Drug Product manufacturing process is a simple dilution of the mRNA-1273 LNP with 20 mM Tris and 87 mg/mL sucrose, pH 7.5 from (b) (4), execution of the analytical lot-to-lot consistency with the mRNA-1273 Drug Product will be informative for the lot-to-lot consistency with regard to the mRNA-1273 LNP. Although the Sponsor is also executing PPQs for CX-024414 and (b) (4) and will apply similar statistical analysis, the results for the consistency of these processes will be primarily out of scope for the analytical comparison for the lot-to-lot consistency of the mRNA-1273 Drug Product.

In alignment with the feedback provided by the Agency, the Sponsor agrees that the determination of manufacturing consistency for a defined molecular assembly such as an LNP encapsulated mRNA (LNP) can be achieved through a fundamental understanding of the biophysical and physicochemical properties of the product. The Sponsor has thorough technical knowledge of the LNP and the impact that processing conditions and manufacturing steps can have upon the product characteristics as detailed on the release specifications (Table 18 for mRNA-1273 LNP and Table 19 for mRNA-1273 Drug Product).

For the Phase 3 campaign, the Sponsor has initially manufactured three lots of mRNA-1273 Drug Product 6007520001, 6007520002, 6007520003. (Data in Table 12). These mRNA-1273 Drug Products lots were from the same mRNA-1273 LNP, Lot 5006820002. In addition, the Sponsor is conducting PPQ activities for the mRNA-1273 Drug Product. Three mRNA-1273 Drug Product lots (Lot 6007520004, Lot 6007520005 and Lot 6007520006) will be manufactured from different lots of mRNA-1273 LNP (Lot 5006820003, Lot 5006820004 and Lot 5006820003/Lot 5006820004). It is anticipated that these six lots of mRNA-1273 Drug Product will be utilized in the Phase 3 clinical study. Furthermore, data are available on four GMP lots (8520100101, 8520100102, 8520100103, 8520100104) and two development lots (AMPDP-200005, AMPDP-200022) that are supportive of the manufacturing capability of the mRNA-1273 Drug Product as well as providing information on analytical method performance.

Product Critical Quality Attributes

The Sponsor has established the Critical Quality Attributes (CQAs) for the mRNA-1273 Drug Product (Table 8), either based on risk assessment through platform knowledge of the (b) (4)

(b) (4) , previously reported information on similar products, or through process and product characterization knowledge gained for the mRNA-1273 Drug Product. All CQAs are monitored through release and stability testing as detailed in the specifications ([Table 8](#)).

Table 8: Critical Quality Attributes of mRNA-1273 Drug Product

Quality Attribute	Classification	Justification
Appearance	CQA	(b) (4)
Identity (mRNA)	CQA	
Identity (Lipids)	CQA	
pH	CQA	
Osmolality	CQA	
Particulate Matter	CQA	
Bacterial Endotoxins	CQA	
Sterility	CQA	
mRNA Content	CQA	
mRNA Purity	CQA	
mRNA Impurities (Product-related)	CQA	
% RNA Encapsulation	CQA	
Particle Size	CQA	
Polydispersity	CQA	
Lipids Content	CQA	
Impurities (Lipid-related)	CQA	
Potency	CQA	

Method Performance Attributes

The qualification parameters for mRNA-1273 Drug Product are provided in Table 9. The analytical methods, specification acceptance criteria, historical range criteria, and comparability acceptance criteria is provided in the CBER Type II Master File # 22940. The Sponsor is in the process of performing formal release method validation in accordance with the guidance detailed in ICH Q2(R1). In addition to method qualification data generated to support clinical development, method validation will comprise the addition of robustness assessments (for example, multiple reagent lots, instruments and operators) to the parameters assessed in Table 9.

Table 9: Qualification Parameters for mRNA-1273 Drug Product Analytical Methods

Method (Attribute)	Method Parameter
AEX-HPLC (RNA Content)	Specificity ^(a) , linearity, precision ^(a) , intermediate precision, accuracy, range, sample stability
RP-HPLC (Purity)	Specificity ^(a) , specificity by forced degradation ^(a) , accuracy, precision ^(a) , intermediate precision, linearity, range, Quantitation Limit (QL), sample stability
(b) (4) (% RNA Encapsulation)	Specificity ^(a) , linearity, precision ^(a) , intermediate precision, range, accuracy, QL
UPLC-CAD (Lipid Content, Identification and Impurities)	Specificity ^(a) , linearity, accuracy, precision ^(a) , range, intermediate precision, QL, Detection Limit (DL), sample stability

(a) Qualifications parameters specific for the mRNA-1273 product.

For the Dynamic Light Scattering (DLS) methodology, a series of particle size specific calibration standards (b) (4) are used, which are more appropriate for the qualification of an assay for the determination of particle size for this first principle's method. The methods for RNA content by AEX-HPLC, % purity by RP-HPLC, % RNA encapsulation (b) (4) and lipid content, identification and impurities by UPLC-CAD were qualified using representative mRNA of distinct nucleotide sequence complexity and size. Additional details are provided in CBER Type II Master File # 22940.

Impurities – Identification and Control

The sponsor has evaluated product-related impurities arising from the manufacture and/or through degradation to assess the impact on the quality of the product, and this has formed the basis for setting the acceptance criteria for individual and total impurities.

A high-level overview of the product-related impurities for CX-024414 mRNA, (b) (4) and mRNA-1273 LNP, which can all potentially be carried over to the mRNA-1273 Drug Product, are described in Table 10 along with the associated control strategy used to limit these product related impurities.

Table 10: Overview of Product-related Impurities

Product-Related Impurities	Description	Control Strategy
CX-024414 mRNA		
Short mRNAs resulting from either premature termination of transcription or in-process degradation	<p>Short mRNAs can be generated either by:</p> <ul style="list-style-type: none"> Premature termination of transcription during in vitro transcription Degradation of the mRNA during the manufacturing process <p>These short mRNA impurities will lack either the 5' cap or the 3' polyA tail and therefore cannot be translated.</p>	(b) (4)
High molecular weight impurities representing mRNAs longer than the CX-024414 generated via transcriptional read-through	mRNAs longer than the CX-024414 can be generated from read-through transcription. Read-through transcription can occur either in instances where the polymerase remains engaged with the linearized plasmid template following transcription of the polyA tail, resulting in continued transcription from the complementary strand of the template, or transcription from any closed circular plasmid impurities potentially present in the linearized plasmid template.	
Uncapped mRNA and other cap variants and degradants	Uncapped and other cap variants can be present in the CX-024414 if the capping reaction fails to go to completion or mRNA exposed to extreme conditions (heat and acidic).	
Point mutations, insertions/deletions	All polymerases have an intrinsic error rate that can lead to either incorporation of the wrong base (point mutation), or insertions/deletions where a base is erroneously added or skipped. Point mutations can lead to mis-incorporation of a single amino acid in the protein if the point mutation results in a codon that codes for a different amino acid. Insertions/deletions of 1 or 2 nucleotides within a protein coding region would lead to frame shifts that could produce truncated pre-fusion stabilized Spike protein of 2019-novel Coronavirus (SARS-CoV-2).	
Double stranded RNA (dsRNA)	Double stranded RNA (dsRNA) can potentially be formed during in vitro transcription. dsRNA can be recognized by receptors in the innate immune system, leading to production of immune-stimulatory cytokines.	

(b) (4)

Product-Related Impurities	Description	Control Strategy
mRNA-1273 Lipid Nanoparticle and/or mRNA-1273 Drug Product		
Lipid impurities and degradants	See above in (b) (4)	(b) (4)
Lipid mRNA adducts	Lipid mRNA adducts are covalent species formed by the reaction of electrophilic impurities in the lipid components of the formulation with the mRNA nucleobase. They can be formed during formulation and storage of the LNP and render the mRNA molecule biologically inactive.	(b) (4)
Particulate matter	Product-related particulate matter may be formed due to physical degradation of the lipid nanoparticle or incomplete formation of the lipid nanoparticle during the preparative process. Physical degradation of the lipid nanoparticle may be caused by exposure of the product to stresses such as interfaces, elevated temperature, freeze-thawing, and agitation. Particulate matter may manifest as subvisible and/or visible particles.	

Release Testing

Data from release testing of all lots of mRNA-1273 Drug Product are expected at a minimum to meet the release specifications established for the Drug Product. Release data and batch information are provided in [Table 11](#) for development lots and [Table 12](#) for GMP lots.

In order to determine comparability of the manufacturing process, additional statistically based acceptance criteria, based on the experience with development and GMP lots will be applied, these are discussed below.

Table 11: Analytical Testing Summary for mRNA-1273 Drug Product Development Lots

Test	Specification	Lot AMPDP-200005	Lot AMPDP-200022
MPI or Drug Substance Lot No.		AMPDS-200006	AMPDS-200022
mRNA-1273 LS LNP Lot No.		N/A	DHM-47516
Drug Product Vials Manufactured (vials)		(b) (4)	
Purpose		Development	Development
Manufacturing Location		ModernaTX, Inc. (Cambridge, MA)	ModernaTX, Inc. (Cambridge, MA)
Storage Condition (Long-term)		-60°C to -90°C	-60°C to -90°C
Storage Condition (Short-term)		N/A	2°C to 8°C
Appearance	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.
RNA content by AEX-HPLC	(b) (4)		
Identity by Reverse Transcription/Sanger Sequencing			
Purity by RP-HPLC			
Product-related impurities by RP-HPLC (Report % area for each impurity group)			
% RNA encapsulation by (b) (4)			
In vitro translation (Potency) by IVT/methionine labelling			
pH			
Osmolality			
Particle size by Dynamic Light Scattering			
Polydispersity by Dynamic Light Scattering	Report result	(b) (4)	
Lipid identification by UPLC-CAD	(b) (4)		
SM-102			
Cholesterol			
DSPC			
PEG2000-DMG			

Test	Specification	Lot AMPDP-200005	Lot AMPDP-200022
MPI or Drug Substance Lot No.		AMPDS-200006	AMPDS-200022
mRNA-1273 LS LNP Lot No.		N/A	DHM-47516
Drug Product Vials Manufactured (vials)		(b) (4)	
Purpose		Development	Development
Manufacturing Location		ModernaTX, Inc. (Cambridge, MA)	ModernaTX, Inc. (Cambridge, MA)
Storage Condition (Long-term)		-60°C to -90°C	-60°C to -90°C
Storage Condition (Short-term)		N/A	2°C to 8°C
Lipid content by UPLC-CAD	(b) (4)		
SM-102			
Cholesterol			
DSPC			
PEG2000-DMG			
Lipid impurities by UPLC-CAD			
Lipid impurities by UPLC-CAD			
Particulate matter			
Bacterial endotoxin			
Bioburden			

kDa = kilodalton;

ND = none detected;

RT= retention time;

(b) (4)

NT = not tested as the IVT was not part of the specification at the time of product release

a) Lower net yield as additional sampling was required for extended testing

Table 12: Analytical Testing Summary for mRNA-1273 Drug Product GMP lots

Test	Specification	Lot 8520100101	Lot 8520100102	Lot 8520100103	Lot 8520100104	Lot 6007520001	Lot 6007520002	Lot 6007520003
MPI or Drug Substance Lot No.		8410000101	8410000102	8410000103	8410000104	4007220002	4007220002	4007220002
mRNA-1273 LS LNP Lot No.		N/A	N/A	N/A	N/A	5006820002	5006820002	5006820002
Drug Product Vials Manufactured (vials)		(b) (4)						
Purpose		GMP	GMP	GMP	GMP	GMP	GMP	GMP
Manufacturing Location		ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)
Storage Condition (Long-term)		-60°C to -90°C	-60°C to -90°C	-60°C to -90°C	-60°C to -90°C	-60°C to -90°C	-60°C to -90°C	-60°C to -90°C
Storage Condition (Short-term)		N/A	N/A	N/A	N/A	2°C to 8°C	2°C to 8°C	2°C to 8°C
Appearance	White to off-white dispersion. May contain visible, white or translucent	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.	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.	White to off-white dispersion, essentially free of particulates.
RNA content by AEX-HPLC	(b) (4)	(b) (4)				N/A	N/A	N/A
RNA content by AEX-HPLC		N/A	N/A	N/A	N/A	(b) (4)		
Identity by RT/Sanger Sequencing	(b) (4)							
Purity by RP-HPLC								
Product-related impurities by RP-HPLC (Report % area for impurity group)								
% RNA encapsulation by (b) (4)								
In vitro translation (Potency) by IVT/methionine labelling								
pH								
Osmolality								
Particle size by DLS								
Polydispersity by DLS	Report result	(b) (4)				N/A	N/A	N/A
Polydispersity by DLS	≤ 0.5	N/A	N/A	N/A	N/A	(b) (4)		
Lipid identification by UPLC-CAD								
SM-102	(b) (4)							
Cholesterol								
DSPC								
PEG2000-DMG								
Lipid content by UPLC-CAD								
SM-102	(b) (4)					N/A	N/A	N/A
Cholesterol						N/A	N/A	N/A
DSPC						N/A	N/A	N/A
PEG2000-DMG						N/A	N/A	N/A

Test	Specification	Lot 8520100101	Lot 8520100102	Lot 8520100103	Lot 8520100104	Lot 6007520001	Lot 6007520002	Lot 6007520003
MPI or Drug Substance Lot No.		8410000101	8410000102	8410000103	8410000104	4007220002	4007220002	4007220002
mRNA-1273 LS LNP Lot No.		N/A	N/A	N/A	N/A	5006820002	5006820002	5006820002
Drug Product Vials Manufactured (vials)		(b) (4)						
Purpose		GMP	GMP	GMP	GMP	GMP	GMP	GMP
Manufacturing Location		ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)	ModernaTX, Inc. (Norwood, MA)
Storage Condition (Long-term)		-60°C to -90°C	-60°C to -90°C	-60°C to -90°C	-60°C to -90°C	-60°C to -90°C	-60°C to -90°C	-60°C to -90°C
Storage Condition (Short-term)		N/A	N/A	N/A	N/A	2°C to 8°C	2°C to 8°C	2°C to 8°C
Lipid content by UPLC-CAD	(b) (4)	N/A	N/A	N/A	N/A	(b) (4)	(b) (4)	(b) (4)
SM-102		N/A	N/A	N/A	N/A	(b) (4)	(b) (4)	(b) (4)
Cholesterol		N/A	N/A	N/A	N/A	(b) (4)	(b) (4)	(b) (4)
DSPC		N/A	N/A	N/A	N/A	(b) (4)	(b) (4)	(b) (4)
PEG2000-DMG		N/A	N/A	N/A	N/A	(b) (4)	(b) (4)	(b) (4)
Lipid impurities by UPLC-CAD		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Lipid impurities by UPLC-CAD		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Lipid impurities by UPLC-CAD		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Particulate matter		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Container content		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Bacterial endotoxin		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sterility		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

kDa = kilodalton;

ND = none detected;

RT= retention time;

(b) (4)

N/A = specification not associated with specific mRNA-1273 LS Injection

NT = not tested as the IVT was not part of the specification at the time of product release

a) Lower net yield as additional sampling was required for extended testing

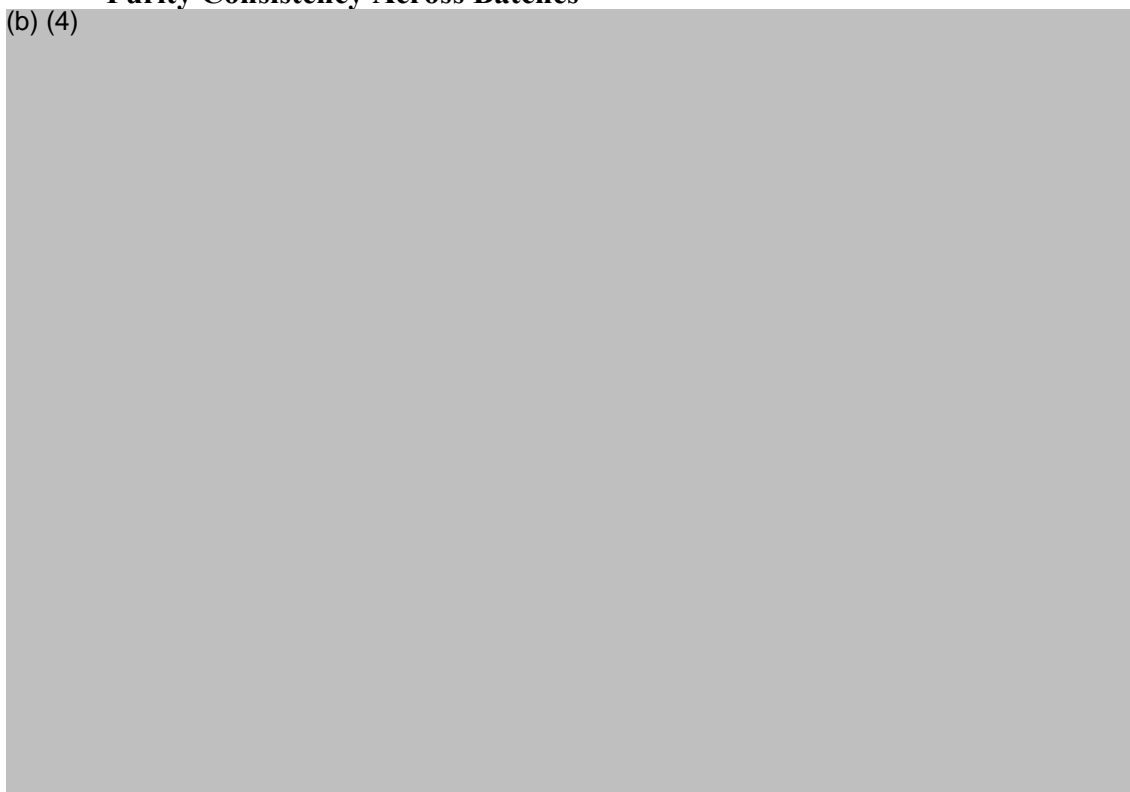
Statistical Assessment of Purity, %RNA Encapsulation and Particle Size

In order to assess the process and analytical capabilities and proposed acceptance criteria to be applied to the planned process performance qualification (PPQ) lots, a statistical analysis has been applied to the data generated from representative batches manufactured to date. Those parameters that are either stability-indicating or tied to product activity (purity, encapsulation and particle size) have been analyzed to ascertain the degree of control and hence prospective acceptance criteria for the lots to be used in consistency determination.

Each attribute is displayed within limits based on ± 3 standard deviations, using the test results from all representative lots available to estimate the lot-to-lot variation.

The control chart in [Figure 3](#) shows purity (main peak %) for the first six baseline lots (development and early phase) and the subsequent three Phase 3 lots. The lower specification limit is shown at (b) (4); all lots meet the specification. The lower specification at (b) (4) has been established to account for mRNA stability/degradation during refrigerated or ambient conditions. The red horizontal lines represent the average plus and minus three standard deviations for the first six baseline lots (development and early phase) and the subsequent three Phase 3 lots combined. Results for the three Phase 3 lots are represented with asterisks.

Figure 3: Control Chart of Nine Lots of mRNA-1273 Drug Product Demonstrating Purity Consistency Across Batches



Points represented by asterisks are batches to be used in Phase 3 pivotal studies.

The control chart in [Figure 4](#) shows encapsulation (%) for the first six baseline lots (development and early phase) and the subsequent three Phase 3 lots. The lower specification limit is shown at (b) (4) all nine lots meet the specification. The red horizontal lines represent the average plus and minus three standard deviations for the first six baseline lots (development and early phase) and the subsequent three Phase 3 lots combined. Results for the three Phase 3 lots are represented with asterisks. Encapsulation results reported as (b) (4) are replaced with the numeric value (b) (4)

Figure 4: Control Chart of Nine Lots of mRNA-1273 Drug Product Demonstrating %RNA Encapsulation Consistency Across Batches

(b) (4)



Points represented by asterisks are batches to be used in Phase 3 pivotal studies.

The control chart in [Figure 4](#) shows z-average particle size (nm) for the first six baseline lots (development and early phase) and the subsequent three Phase 3 clinical lots. The specification limits are shown at (b) (4) all nine lots meet the specification. The red horizontal lines represent the average plus and minus three standard deviations for the first six baseline lots (development and early phase) and the subsequent three Phase 3 lots combined. Results for the three Phase 3 lots are represented with asterisks.

Figure 5: Control Chart of Nine Lots of mRNA-1273 Drug Product Demonstrating Particle Size Consistency Across Batches



Points represented by asterisks are batches to be used in Phase 3 pivotal studies.

General Conclusions for Purity, %RNA Encapsulation and Particle Size

The average and standard deviation for these three attributes is shown below for the six baseline (development and early phase) and three Phase 3 clinical lots. The estimated standard deviation is smaller for the consistency lots than for the baseline lots for all three attributes. Based on the manufacturing history to date, the proposed acceptance criteria for these parameters are presented in [Table 13](#).

Table 13: Consistency Evaluation Across Lots for Purity, %RNA Encapsulation and Particle Size

(b) (4)



Extended Characterization

Extended characterization assays will include those which have a moderate or unproven impact to product quality and/or patient safety if there are deviations in results but have a high probability of detecting minor changes in product quality and are also mostly amenable to statistical evaluation. These assays may also include those with data reported in descriptive terms, such as an impurity limit < LOQ, or those which require a comparison of spectra or other non-numerical data sets. The analytical panel for extended characterization is shown in [Table 14](#), these methods are not validated and are not specifically identified to evaluate critical quality attributes, however they may be sensitive to variations in the product generated during manufacture and are therefore important as orthogonal measures of product quality and hence manufacturing consistency. The proposed acceptance criteria (where appropriate) to demonstrate consistency for the extended characterization panel for mRNA-1273 are also presented in [Table 14](#).

(b) (4)



(b) (4)



(b) (4)



Summary

The Sponsor proposes to demonstrate lot to lot manufacturing consistency through analytical comparability which will include release, stability and extended characterization data, in lieu of the completion of assessment in a clinical study. Historical data on both development and clinical lots will serve as supporting evidence for batch manufacturing consistency and aid in the establishment of acceptance criteria as presented in (Table 13 and Table 14). The Sponsor proposes to use the data from release and extended characterization testing of the process performance qualification (PPQ) Drug Product lots to confirm manufacturing consistency.

2.4. Question 4

(b) (4)



Does the Agency agree with the Sponsor's assessment?

Sponsor's Position

(b) (4)



Raw materials are received from qualified suppliers. The supplier qualification process demonstrates that the supplier has an effective and acceptable Quality Management System in place and that their supplied raw materials can meet the minimum quality requirements of the process. Qualified suppliers have been assessed using a supplier risk level review as well as audit requirements based on the materials to be sourced and 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.

(b) (4)



3. BACKGROUND INFORMATION

The following sections contains the overview of the Sponsor's manufacturing and analytical control strategy for PPQ of CX-024414, (b) (4), mRNA-1273 LNP and mRNA-1273 Drug Product. These PPQs will be based on a highly similar process to the one used to manufacture the Phase 3 clinical trial material. Final storage conditions have been developed and will continue to be evaluated through an extensive stability program. Data supporting the shelf life of the mRNA-1273 products will be submitted in the regulatory filings.

3.1. Overview of the mRNA-1273 Drug Product Manufacturing Processes

mRNA-1273 is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains an mRNA (CX-024414) that encodes for the pre-fusion stabilized Spike protein of 2019-novel Coronavirus (SARS-CoV-2) and four lipids which act as protectants and carriers of the mRNA. The four lipids are: SM-102 [(a custom-manufactured, ionizable lipid); PEG2000-DMG; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol].

mRNA-1273 Injection (Drug Product) has a total lipid content of 3.86 mg/mL and contains 20 mM trometamol (Tris), 87 mg/mL sucrose and (b) (4) acetate at a dosage strength of 0.20 mg/mL mRNA, pH 7.5. mRNA-1273 Drug Product is presented in 10R vials closed by a 20 mm stopper and has a 6.5 mL nominal fill volume. One vial of mRNA-1273 Drug Product contains 10 doses for intramuscular injection (0.5 mL each).

The quantitative composition of the components in mRNA-1273 Drug Product is presented in [Table 15](#).

(b) (4)



An overview of the process flow diagram for mRNA-1273 Drug Product manufacturing process is provided in [Figure 6](#).

(b) (4)



(b) (4)



(b) (4)



Figure 7: CX-024414 mRNA Manufacturing Scheme

(b) (4)



3.1.1.2 Specification for CX-024414 (mRNA)

Testing of CX-024414 is performed in accordance with the specification listed in [Table 16](#).

Table 16: Specification for CX-024414

Test	Analytical Method	Specification
Appearance	Visual	(b) (4)
Identity	Reverse Transcription/Sanger Sequencing	
Total RNA content	UV	
Purity	RP-HPLC	
Product-related impurities	RP-HPLC	
% 5' Capped	RP-UPLC-UV	
% PolyA tailed RNA (% Tailless RNA)	RP-HPLC	
Residual DNA template	qPCR	
pH	USP <791>	
Bacterial endotoxin	USP <85>, EP 2.6.14	
Bioburden	USP <61>, EP 2.6.12	

(b) (4)

(b) (4)



(b) (4)



(b) (4)



An overview of the process flow diagram for mRNA-1273 LNP manufacturing process is provided in [Figure 9](#).

(b) (4)



3.1.3.2 Specification for mRNA-1273 Lipid Nanoparticle (LNP)

The specification for mRNA-1273 Lipid Nanoparticle (LNP) are described in [Table 18](#).

Table 18: mRNA-1273 LNP Specification

Test	Analytical Method	Specification
Appearance	Visual	(b) (4)
Identity	Reverse Transcription/ Sanger Sequencing	
Total RNA content	Anion Exchange HPLC	
Purity	RP- HPLC	
Product-related impurities		
% RNA encapsulation	(b) (4)	
Mean particle size	Dynamic Light Scattering	
Polydispersity		
Lipid identification		
SM-102	UPLC-CAD	
Cholesterol		
DSPC		
PEG2000-DMG		
Lipid content		
SM-102	UPLC-CAD	
Cholesterol		
DSPC		
PEG2000-DMG		
Lipid impurities	UPLC-CAD	
pH	USP <791>	
Osmolality	USP <785>	
Bacterial endotoxin	USP <85>, EP 2.6.14	
Bioburden	USP <61>, EP 2.6.12	

RT= retention time

(b) (4)

3.1.4 Manufacture and Control of mRNA-1273 Drug Product

mRNA-1273 Drug Product has a total lipid content of 3.86 mg/mL and contains 20 mM trometamol (Tris), 87 mg/mL sucrose and (b) (4) acetate at a dosage strength of 0.20 mg/mL mRNA, pH 7.5. mRNA-1273 Drug Product is presented in 10R vials closed with a 20 mm stopper and has a 6.5 mL nominal fill volume. Details of the container-closure system are provided in [Section 3.1.4.2.1](#). The stopper closure material has been tested by the manufacturer to comply with requirements for functionality tests including self-sealing capacity per USP <381> Elastomeric Closures for Injections.

3.1.4.1 Manufacture of mRNA-1273 Drug Product

The frozen mRNA-1273 LNP, as described in [Section 3.1.3](#), is thawed and pooled as required and filtered through a (b) (4). The concentration of the mRNA-1273 LNP is adjusted with a dilution buffer comprising 20 mM Tris and 87 mg/mL sucrose, pH 7.5, to achieve the target mRNA content of 0.20 mg/mL mRNA. The resultant bulk product solution is sampled for pre-filtration bioburden and tested with a specification of (b) (4) and (b) (4). The bulk product solution is then filtered through (b) (4) and (b) (4) and aseptically filled into sterile 10R vials. The sterilizing-grade filters are pre sterilized and are ready to-use. The sterilizing-grade filters are integrity tested by the filter manufacturer (pre filtration) and are integrity tested (post-use) after the filtration step. Due to the disposable assemblies utilized, post-use filter integrity testing is conducted offline. The filled vials are stoppered, capped, inspected. Vials for sterility testing are sampled prior to freezing and stored at 2°C to 8°C prior to testing.

The process flow diagram for mRNA-1273 Drug Product manufacturing process is provided in [Figure 10](#).

(b) (4)



3.1.4.2 Specification for mRNA-1273 Drug Product

The specification for the mRNA-1273 Drug Product are provided in [Table 19](#).

Table 19: mRNA-1273 Drug Product Specification

Test	Method	Acceptance Criteria	
Appearance	Visual	White to off-white dispersion. May contain visible, white or translucent product-related particulates.	
RNA content	Anion Exchange HPLC	(b) (4)	
Identity	Reverse Transcription/ Sanger Sequencing		
Purity	RP-HPLC		
Product-related impurities			
% RNA encapsulation	(b) (4)		
IVRP (Potency)	HeLa Cells		
Particle size	Dynamic Light Scattering		
Polydispersity			
Lipid identification			
SM-102	UPLC-CAD	(b) (4)	
Cholesterol			
DSPC			
PEG2000-DMG			
Lipid content			
SM-102	UPLC-CAD		
Cholesterol			
DSPC			
PEG2000-DMG			
Lipid impurities	UPLC-CAD		
Particulate matter			
≥ 25 µm	USP <788> Method 2	(b) (4)	
≥ 10 µm			
pH	USP <791>		
Osmolality	USP <785> Freezing Point Depression		
Container content	USP <697>	≥ 5.0 mL (10 doses of 0.5 mL from 1 vial)	
Bacterial endotoxin	USP <85>, EP 2.6.14	(b) (4)	
Sterility	USP <71>, EP 2.6.1		

RT = retention time

(b) (4)

3.1.4.2.1 Container Closures for mRNA-1273 Drug Product

The components of the container closure system for the mRNA-1273 Drug Product manufactured at either ModernaTX, Inc. (Norwood, MA) or Catalent Biologics (Bloomington, IN) are described in [Table 20](#).

Table 20: Container Closures for mRNA-1273 Drug Product

Vial	
General Description	(b) (4)
Moderna NWD, Catalent: 10R Borosilicate Type 1 clear glass vial (Ompi, Italy)	
Stopper	
General Description	Specific Item
(b) (4)	(b) (4)
Catalent: 20 mm West 4432-50/Grey, (b) (4)	Catalent: Stopper 20 mm WPS S10-F451 4432/50 GY (b) (4) Westar RU/SP ST
Cap	
General Description	(b) (4)
Catalent: Aluminum Flip-off Seal, West	

(b) (4)

(b) (4)



4. APPENDIX

Stability studies were performed to mimic the handling of mRNA-1273 Drug Product at the clinical sites, using representative materials, representative test articles and the appropriate dose preparation procedure for clinical use. Two lots of mRNA-1273 Drug Product [(representative multi-dose vials with 6.5-mL fill volume, 0.10 mg/mL mRNA (Lot 6006820001) and 0.5 mg/mL mRNA (Lot 6006920001)] were used for the study and were used for bracketing an intended clinical dose concentration to demonstrate compatibility of administration materials (b) (4) with mRNA-1273 Drug Product. mRNA-1273 Drug Product was not diluted for this study.

The study was designed to enable direct removal of one dose from the vial followed by a hold in the syringe. Dosing syringes were removed from the vial after a one hour thaw. The remaining product solution in the vial was then held at room temperature for an additional six hours. Additional dosing syringes were then removed from the vial after six hours after the room temperature hold. All syringes were then held for 0, 8, and 24 hours at room temperature and refrigerated conditions, and assayed for RNA content by AEX-HPLC, % purity by RP-HPLC, lipid content by UPLC-CAD, % RNA encapsulation, mean particle size and polydispersity by Dynamic Light Scattering and in vitro translation (potency). Attributes of mRNA-1273 LS Injection stayed within specification when held in a vial for 6 hours at room temperature, followed by storage in a syringe for 8 hours, at either 0.5 mg/mL or 0.1 mg/mL. In-use stability was demonstrated for bracketing dosage strengths of 0.1 mg/mL to 0.5 mg/mL mRNA for up to 6 hours in the vial followed by 8 hours in the syringe at either ambient temperature or at storage between 2°C to 8°C. The clinical in-use stability results for mRNA-1273 LS Injection, Lot 6006820001 (0.1 mg/mL) is provided in [Table 21](#) to [Table 23](#).

The clinical in-use stability results for mRNA-1273 LS Injection, Lot 6006920001 (0.5 mg/mL) is provided in [Table 24](#) to [Table 27](#).

Table 21: Clinical In-Use Compatibility Data for mRNA-1273 LS Injection, Lot 6006820001, 0.1 mg /mL, (b) (4) Unopened Multiple-Dose Vial

Test	Acceptance Criteria		Initial*	T = 8h		T = 24h	
	Initial	T8h and T24h		RT	5C	RT	5C
Appearance	Report result		White to off-white dispersion, essentially free of particulates				
RNA content by AEX-HPLC	(b) (4)						
Purity by RP-HPLC							
Product related impurities by RP-HPLC							
In Vitro Translation (Potency)							
% RNA encapsulation by (b) (4)							
Mean particle size by Dynamic light scattering	(b) (4)						
Polydispersity by Dynamic light scattering							
Lipid content by UPLC-CAD	Report result		(b) (4)				
SM-102	(b) (4)						
Cholesterol							
DSPC							
PEG2000-DMG							
Lipid impurities by UPLC-CAD (Report RRT and % Area)							
pH	(b) (4)			N/A			
Osmolality				N/A			

* Initial (T = 0) results were from samples drawn up into a polycarbonate syringe and immediately pooled in a sample collection vial.

The impact of syringe material is expected to be negligible in the short timeframe involved.

kDa = kilodalton

ND = not detected

N/A = not required per the stability protocol

(b) (4)

**Table 22: Clinical In-Use Compatibility Data for mRNA-1273 LS Injection,
Lot 6006820001, 0.1 mg /mL, (b) (4)
Post 6 Hour Hold of an Entered Multiple-Dose Vial**

Test	Acceptance Criteria		Initial*	T = 8h		T = 24h		
	Initial	T8h and T24h		RT	5C	RT	5C	
Appearance	Report result		White to off-white dispersion, essentially free of particulates					
RNA content by AEX-HPLC	(b) (4)							
Purity by RP-HPLC								
Product related impurities by RP-HPLC								
In Vitro Translation (Potency)								
% RNA encapsulation by (b) (4)								
Mean particle size by Dynamic light scattering								
Polydispersity by Dynamic light scattering	Report result		(b) (4)					
Lipid content by UPLC-CAD	(b) (4)							
SM-102								
Cholesterol								
DSPC								
PEG2000-DMG								
Lipid impurities by UPLC-CAD (Report RRT and % Area)								
pH	(b) (4)			N/A				
Osmolality				N/A				

* Initial (T = 0) results were from samples drawn up into a polycarbonate syringe and immediately pooled in a sample collection vial.

The impact of syringe material is expected to be negligible in the short timeframe involved.

Values reported in **bold**, denote a value below acceptance criteria

kDa = kilodalton

ND = not detected

N/A = not required per the stability protocol

(b) (4)

**Table 23: Clinical In-Use Compatibility Data for mRNA-1273 LS Injection,
Lot 6006820001, 0.1 mg /mL, (b) (4)
Post 6 Hour Hold of an Entered Multiple-Dose Vial**

Test	Acceptance Criteria		Initial*	T = 8h		T = 24h			
	Initial	T8h and T24h		RT	5C	RT	5C		
Appearance	Report result		White to off-white dispersion, essentially free of particulates						
RNA content by AEX-HPLC	(b) (4)								
Purity by RP-HPLC									
Product related impurities by RP-HPLC									
In Vitro Translation (Potency)									
% RNA encapsulation by (b) (4)									
Mean particle size by Dynamic light scattering	(b) (4)								
Polydispersity by Dynamic light scattering						Report result			
Lipid content by UPLC-CAD									
SM-102						(b) (4)			
Cholesterol									
DSPC									
PEG2000-DMG									
Lipid impurities by UPLC-CAD (Report RRT and % Area)	(b) (4)								
pH								N/A	
Osmolality								N/A	

* Initial (T = 0) results were from samples drawn up into a polycarbonate syringe and immediately pooled in a sample collection vial.

The impact of syringe material is expected to be negligible in the short timeframe involved.

kDa = kilodalton

ND = not detected

N/A = not required per the stability protocol

(b) (4)

Table 24: Clinical In-Use Compatibility Data for mRNA-1273 LS Injection
Lot 6006920001, 0.5 mg /mL, (b) (4)
Unopened Multiple-Dose Vial

Test	Acceptance Criteria		Initial*	T = 8h		T = 24h		
	Initial	T8h and T24h		RT	5C	RT	5C	
Appearance	Report result		White to off-white dispersion, essentially free of particulates					
RNA content by AEX-HPLC	(b) (4)							
Purity by RP-HPLC								
Product related impurities by RP-HPLC								
In Vitro Translation (Potency)								
% RNA encapsulation by (b) (4)								
Mean particle size by Dynamic light scattering								
Polydispersity by Dynamic light scattering	Report result		(b) (4)					
Lipid content by UPLC-CAD								
SM-102	(b) (4)							
Cholesterol								
DSPC								
PEG2000-DMG								
Lipid impurities by UPLC-CAD (Report RRT and % Area)								
pH	(b) (4)		N/A					
Osmolality			N/A					

* Initial (T = 0) results were from samples drawn up into a polycarbonate syringe and immediately pooled in a sample collection vial.

The impact of syringe material is expected to be negligible in the short timeframe involved.

kDa = kilodalton

ND = not detected

N/A = not required per the stability protocol

(b) (4)

**Table 25: Clinical In-Use Compatibility Data for mRNA-1273 LS Injection,
Lot 6006920001, 0.5 mg /mL, (b) (4)
Post 6 Hour Hold of an Entered Multiple-Dose Vial**

Test	Acceptance Criteria		Initial*	T = 8h		T = 24h		
	Initial	T8h and T24h		RT	5C	RT	5C	
Appearance	Report result		White to off-white dispersion, essentially free of particulates					
RNA content by AEX-HPLC	(b) (4)							
Purity by RP-HPLC								
Product related impurities by RP-HPLC								
In Vitro Translation (Potency)								
% RNA encapsulation by (b) (4)								
Mean particle size by Dynamic light scattering								
Polydispersity by Dynamic light scattering	Report result		(b) (4)					
Lipid content by UPLC-CAD								
SM-102	(b) (4)							
Cholesterol								
DSPC								
PEG2000-DMG								
Lipid impurities by UPLC-CAD (Report RRT and % Area)								
pH	(b) (4)			N/A				
Osmolality				N/A				

* Initial (T = 0) results were from samples drawn up into a polycarbonate syringe and immediately pooled in a sample collection vial.

The impact of syringe material is expected to be negligible in the short timeframe involved.

kDa = kilodalton

ND = not detected

N/A = not required per the stability protocol

(b) (4)

**Table 26: Clinical In-Use Compatibility Data for mRNA-1273 LS Injection,
Lot 6006920001, 0.5 mg /mL, (b) (4)
Post 6 Hour Hold of an Entered Multiple-Dose Vial**

Test	Acceptance Criteria		Initial*	T = 8h		T = 24h	
	Initial	T8h and T24h		RT	5C	RT	5C
Appearance	Report result		White to off-white dispersion, essentially free of particulates				
RNA content by AEX-HPLC	(b) (4)						
Purity by RP-HPLC							
Product related impurities by RP-HPLC							
In Vitro Translation (Potency)	(b) (4)						
% RNA encapsulation by (b) (4)							
Mean particle size by Dynamic light scattering							
Polydispersity by Dynamic light scattering							
Lipid content by UPLC-CAD	Report result		(b) (4)				
SM-102	(b) (4)						
Cholesterol							
DSPC							
PEG2000-DMG							
Lipid impurities by UPLC-CAD (Report RRT and % Area)	(b) (4)						
pH	(b) (4)		N/A				
Osmolality	(b) (4)		N/A				

* Initial (T = 0) results were from samples drawn up into a polycarbonate syringe and immediately pooled in a sample collection vial.

The impact of syringe material is expected to be negligible in the short timeframe involved.

kDa = kilodalton

ND = not detected

N/A = not required per the stability protocol

(b) (4)

(b) (4)



(b) (4)



(b) (4)



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