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CBER CMC BLA Review Memorandum

BLA STN 125869

mRNA-1010, an LNP-encapsulated mRNA prophylactic vaccine for prevention of diseases associated with the seasonal influenza viruses represented in the vaccine in persons 50 years of age and older.

(b) (6)

CBER/OVRR/(b) (6)

BLA# STN 125869

APPLICANT NAME AND LICENSE NUMBER

Moderna TX

PRODUCT NAME/PRODUCT TYPE

mRNA-1010. An Influenza Virus (Hemagglutinin; A/H1, A/H3, B/Victoria-lineage) Vaccine in Lipid Nanoparticles.

GENERAL DESCRIPTION OF THE FINAL PRODUCT

The drug product (DP) is an RNA-lipid complex suspension that contains monovalent lipid nanoparticles (LNPs). The RNA in each monovalent LNP encodes the hemagglutinin (HA) glycoprotein of the seasonal influenza virus strain. Each LNP consists of the following four lipids: SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octanoate), cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), and PEG2000-DMG (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000). The DP is supplied as a sterile single dose, ready-to-use suspension for intramuscular (IM) administration in a 1-mL prefilled syringe (PFS). Each PFS delivers 12.5 µg of each seasonal influenza HA surface glycoprotein encoding RNA (37.5 µg of total RNA) and 759 µg of total lipids as a suspension in preservative-free buffer containing (b) (4) mM Tris, and (b) (4) g/L sucrose at (b) (4)

MAJOR MILESTONES

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BLA Action Due Date: 8/5/2026

CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
(b) (6), OVRR/(b) (6)	Modules 3 (except for facilities and equipment information), 4 (except for toxicology studies), and 5 (assays used to assess clinical endpoints)
(b) (6)	Release assays

SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
12/5/25	STN 125869/0 (original submission)	Reviewed
3/4/26	STN 125869/10 (response to IR8, issued 2/25/26)	Reviewed
3/13/26	STN 125869/13 (response to IR8, cont.)	Reviewed
3/20/26	STN 125869/18 (strain update, “first wave”)	Reviewed
3/20/26	STN 125869/21 (response to IR8 cont.)	Reviewed
4/2/26	STN 125869/30 (response to IR13, issued 3/12/26)	Reviewed
5/4/26	STN 125869/44 (response to IR25, issued 4/14/26)	Reviewed
5/18/26	STN 125869/56 (response to IR30, issued by the clinical team 4/23/26)	Reviewed
5/19/26	STN 125869/57 (response to IR35, issued 4/30/26)	Reviewed
5/22/26	STN 125869/59 (strain update, “second wave”)	Reviewed
6/1/26	STN 125869/65 (responses to IR8, 25, and 35, cont.)	Reviewed
6/4/26	STN 125869/70 (response to IR50, issued 5/29/26)	Reviewed
6/16/26	STN 125869/78 (response to IR62, late cycle meeting, issued 6/15/26)	Reviewed
6/18/26	STN 125869/79 (response to IR59, Monte Carlo Simulation, issued 6/11/26)	Reviewed
6/22/26	STN 125869/81 (response to IR57, non-clinical studies, issued 6/8/26)	Reviewed
7/1/26	STN 125869/88 (strain update, “third wave”)	Reviewed
7/15/26	STN 125869/93 (strain update, “third wave”, cont.)	Reviewed
7/17/26	STN 125869/98 (response to IR70, raw materials and DP specs, issued 7/10/26)	Reviewed
7/21/26	STN 125869/101 (response to IR74, reference materials and CP, issued 7/17/26)	Reviewed
7/22/26	STN 125869/102 (response to IR76, DP spec issued 7/21/26)	Reviewed
7/23/26	STN 125869/103 (response to IR79, stability commitment 7/22/26)	Reviewed
7/28/26	STN 125869/107 (response to IR82, DP composition issued 7/27/26)	Reviewed
7/30/26	STN 125869/111 (response to IR57, cont., non-clinical studies, issued 6/8/26)	Reviewed
7/31/26	STN 125869/115 (response to IR83, PMC, issued 7/27/26)	Reviewed
8/4/26	STN 125869/117 (response to IR90, PMC, issued 8/3/26)	Reviewed

REFERENCED REGULATORY SUBMISSIONS (e.g., IND, BLA, 510K, MASTER FILE, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 027460	Modern TX	The IND for this vaccine	no	Information was reviewed

EXECUTIVE SUMMARY

Moderna submitted a BLA seeking approval of mRNA-1010 on December 5, 2025. I reviewed the CMC section and non-clinical studies.

mRNA-1010 is a multi-component, LNP-encapsulated mRNA prophylactic vaccine intended for active immunization for prevention of disease associated with the seasonal influenza viruses represented in the vaccine in persons 50 years of age and older. The firm uses its RNA-LNP based delivery platform which relies on the principle and observations that cells can take up LNPs and express the protein viral antigen(s) from the encapsulated mRNAs. The mRNA is chemically similar to mammalian mRNA with the exception that the uridine nucleoside is fully replaced with N1-methyl-pseudouridine. This nucleoside is included in place of uridine to minimize the indiscriminate recognition of the mRNA by pathogen-associated molecular pattern receptors. The cap structure used in the mRNA is (b) (4). The following four lipids are (b) (4): SM-102 (b) (4); cholesterol (b) (4); DSPC (b) (4); and PEG2000-DMG (b) (4). The (b) (4) is combined with the mRNA to form the RNA-LNP complex.

mRNA-1010 DP is a suspension of multiple monovalent RNA-LNP complexes. Each monovalent LNP in mRNA-1010 DP corresponds to a specific RNA. Each RNA in mRNA-1010 DP contains mRNA encoding the

full-length, membrane-bound, HA glycoprotein of each of the seasonal influenza strains recommended by the WHO for influenza vaccines (subtypes A and type B).

The DP is supplied as a sterile single dose, ready-to-use suspension for intramuscular administration in a 1-mL cyclic olefin copolymer PFS. Each PFS delivers 12.5 µg of each seasonal influenza HA surface glycoprotein encoding RNA (37.5 µg of total RNA at 0.10 mg/mL) and 759 µg of total lipids as a suspension in preservative-free buffer containing (b) (4) mM Tris, and (b) (4) mg/mL sucrose at (b) (4)

The vaccine manufacturing process is robust and consistent. The firm performs testing at different stages of production to ensure that the product meets specifications. There are no excipients of human or animal origin in the DP. No antibiotics are used in the manufacturing process of mRNA-1010.

The non-clinical evaluation of this vaccine included studies in different animal models to demonstrate the vaccine is safe and immunogenic.

While the commercial DP process to be licensed is formulated with LNP-102 inputs (see below), the clinical trials were conducted with DP formulated with LNP-100 inputs. The LNP-102 manufacturing process incorporates (b) (4). Comparability of DP formulated with LNP-102 and LNP-100 inputs was demonstrated using a combination of release and extended characterization testing against pre-defined acceptance criteria, stability monitoring, and non-clinical immunogenicity. DP formulated with LNP-102 inputs will be evaluated in Phase 4 clinical studies to generate additional safety and efficacy data.

In the original submission, the following deficiencies were observed and subsequently resolved:

No quantitative test was included to monitor expression of each influenza mRNA in the DP. The (b) (4) test was added for DP release and DP stability monitoring.

Inadequate justification was provided for the initially proposed minimum effective delivered dose of (b) (4) (EDD; (b) (4)) at end of shelf life. The firm provided additional clinical data to support that an EDD of (b) (4) elicited comparable immune response as the EDD used in the pivotal clinical study.

While the release acceptance criteria for RNA content and (b) (4), and the EoSL stability acceptance criteria for RNA purity are individually justified, lots released at lower limit specification of RNA content and (b) (4) may not meet the minimum EDD at the EoSL. Therefore, a new specification of (b) (4) was added to ensure that all released lots will maintain its effectiveness at EoSL.

Insufficient data was provided to qualify the two amino acid substitutions included in the mRNA from the influenza B strain. The firm provided additional data, including analytical, non-clinical, clinical studies. Analytical data show enhanced expression of the mRNA containing the two substitutions using a panel of (b) (4) mRNAs from (b) (4) different influenza B strains. Non-clinical and clinical data showed enhanced immunogenicity of DP containing the two mutations.

Among other studies, non-clinical studies to assess immunogenicity were proposed for the qualification of new strain for vaccine updates. However, the analysis of the results from these initial studies was not satisfactory. The firm provided a comprehensive package for the assessment of the immunogenicity of new strains, that included (b) (4) analyses to demonstrate comparable HA expression levels relative to previously qualified reference and clinical materials; quantitative (b) (4) using (b) (4) to confirm

expression of each HA in the multivalent vaccine context; (b) (4) analysis to confirm correct HA (b) (4); and non-clinical studies to assess side-by-side mouse immunogenicity of the prior and new vaccine compositions by HAI against the new vaccine strains (in addition to the (b) (4) testing for the prior season's composition).

No stability data was provided for DP manufactured with LNP-102 inputs in the original submission. Per FDA request, the firm provided up to 9 months of DP stability data (formulated with LNP-102 lots) at real-time storage conditions and accelerated stability data.

The Date of Manufacture for the mRNA-1010 final vaccine is defined as the start date of the assembly, label, and pack operations for the labeled DP.

RECOMMENDATION

Approval of the submission.

SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Primary Level Review including all CMC reviewers	Concur	
Secondary Level Review (e.g., Branch/Lab Chief)	Concur	
Tertiary Level Review (e.g., Division Director)	Concur	

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REVIEW OF CTD

MODULE 3

3.2.S DRUG SUBSTANCE

In this BLA there are (b) (4) 3.2.S DRUG SUBSTANCE (DS) sections: one for RNA, (b) (4) [REDACTED], and one for LNP. The DS section for (b) (4) [REDACTED] was previously reviewed under BLA125835. This review memo will cover DS RNA and DS LNP sections.

3.2.S DRUG SUBSTANCE. RNA.

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Proper Name

(b) (4) [REDACTED]

[REDACTED]

(b) (4) [REDACTED]

[REDACTED]

(b) (4)

(b) (4) [REDACTED]

[REDACTED]

[REDACTED]

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the drug product (DP)

The DP is an RNA-lipid complex dispersion that contains three monovalent LNPs. The buffer components and composition of the DP are listed in the table below.

Table 1: mRNA-1010 PFS DP Composition

Component	Grade	Function	Unit Formula (mg/mL)	Unit Formula (µg/dose) ^(a)
Total RNA			0.10	37.5

RNA for Influenza A/H1N1		Custom	Contains mRNA encoding glycoprotein hemagglutinin (HA) of the seasonal influenza virus strains	0.033	12.5
RNA for Influenza A/H3N2				0.033	12.5
RNA for Influenza B/Victoria				0.033	12.5
Total Lipids*	SM-102	Custom, (b) (4)	Individual lipids make up the lipid components of the LNP	2.0	(b) (4)
	Cholesterol	(b) (4)			759
	DSPC	(b) (4)			(b) (4)
	PEG2000-DMG	Custom, (b) (4)			
Tris		(b) (4)	Buffer components in Tris buffer	(b) (4)	189
Tris-HCl		(b) (4)		(b) (4)	934
Sucrose		(b) (4)	Cryoprotection	(b) (4)	32.6 mg
Water for injection		(b) (4)	Diluent	q.s. to volume	q.s. to volume

Abbreviations: NF = National Formulary; (b) (4) ;

RNA = ribonucleic acid; LNP = lipid nanoparticle; SM-102 = heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octanoate; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG = 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000; q.s = quantum sufficit.

a The calculation is performed with (b) (4) mL dose volume.

* while all intermediate calculations are performed using unrounded values, the final values reported in the table are rounded (for both, individual and total lipids) which can result in minor discrepancies. The firm provides (amendment 107) the unrounded values of each lipid component and shows that that the Total Lipid value reported is consistent with the sum of the individual lipid components when calculated using the underlying unrounded values.

The DP is supplied as a sterile single dose, ready-to-use liquid for intramuscular (IM) administration in a 1-mL prefilled syringe (PFS). The DP manufacturing process and controls are designed on the basis of a 37.5 µg dose at 0.10 mg/mL. Each PFS delivers 12.5 µg of each seasonal influenza HA surface glycoprotein (HA) encoding RNA and 759 µg of total lipids as a white to off-white dispersion in preservative-free buffer containing (b) (4) mM Tris, and (b) (4) g/L sucrose at (b) (4). The PFS presentation is detailed in the table below.

DP in Prefilled Syringes

RNA Dose	37.5 µg
Administration Route	Intramuscular (IM)
Syringe	1-mL long COC with halobutyl rubber tip-cap in rigid plastic cover
Plunger Rod	Polypropylene
Plunger	1-mL long halobutyl rubber plunger with fluoropolymer coating on product contact surface
Nominal doses/syringe	Single dose

Abbreviations: COC = cyclic olefin copolymer

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the DP

3.2.P.2.1.1 DS

The DP includes three DSs. Each of the three DSs contains mRNA encoding the HA glycoprotein of one of the seasonal influenza viruses.

3.2.P.2.1.2 Excipients

No novel excipients or excipients derived from human or animal sources are used in the DP. SM-102 is the ionizable lipid component of the (b) (4). The selection of SM-102 is based on prior knowledge and experience with lipid systems at Moderna. Cholesterol is (b) (4). DSPC is (b) (4). PEG2000-DMG (b) (4). Tris buffer is used to (b) (4). The selection of 10 mM Tris buffer at (b) (4) was based on prior knowledge and experience with lipid systems at Moderna. Sucrose is included as a cryoprotectant.

3.2.P.2.2 DP

3.2.P.2.2.1 Formulation Development

The selection of lipid excipients and their molar composition is based on prior knowledge and experience with lipid systems at Moderna (including Spikevax, mRESVIA, and mNEXSPIKE). The Tris buffer has been found to provide optimum product stability at (b) (4). Sucrose is included as a cryoprotectant. The commercial and clinical formulations are summarized below.

Comparison of Clinical and Commercial Formulations

(b) (4)

(b) (4)

Impact of Change in Valency of Influenza Strain (stability): a development study was performed to assess the impact of change in valency (3 vs. 4) of seasonal influenza strain on the stability profile of the DP while keeping the RNA concentration fixed at 0.10 mg/mL. The DP was filled in 1-mL COC PFS at 0.10 mg/mL and subjected to accelerated stability conditions at 2°C to 8°C and 23°C to (b) (4) C. Key stability-indicating attributes were assessed. The statistical assessment, summarized in below table, shows the differences in slopes of trivalent (TIV) and quadrivalent (QIV) are statistically comparable at both temperature conditions, except in (b) (4) at 25°C. However, this result for (b) (4) is not considered significant since the lower limit of the 95% CI is very close to 0. Overall, the stability trends at both storage conditions are consistent between TIV and QIV, supporting the conclusion of comparable stability profiles in DP for 3 or 4 influenza strains.

Summary of Valency Impact on Stability

DP Quality Attribute	Statistical assessment between TIV and QIV Seasonal Influenza DP ^(a)	
	2°C to 8°C (5°C)	23°C to (b) (4) C (25°C)
mRNA Purity	Comparable	Comparable
(b) (4)	Comparable	Comparable
	Comparable	Comparable
	Comparable	Comparable
Total Lipid Impurities	Comparable	Comparable
(b) (4)	Comparable	(b) (4)

^(a) Stability is deemed statistically comparable if the 95% confidence interval (CI) on the estimated difference in average slopes contain zero. If the 95% CI does not contain zero, the estimated difference in average slopes (Quadrivalent – Trivalent) and 95% CI are reported.

Data for RNA Purity and (b) (4), as examples, are shown in the figure below.

(b) (4)

(b) (4)

(b)

(b) (4)

3.2.P.2.2.2 Overages

No overages are applied for the production of DP. An overfill is applied to ensure delivery of the labeled dose of the product with a needle attached.

3.2.P.2.2.3 Physicochemical and Biological Properties

The density of the DP is (b) (4) at room temperature. The (b) (4) and the (b) (4)

3.2.P.2.3 Manufacturing Process Development

Manufacturing process development for the mRNA-1010 DP progressed to support clinical development and commercial registration.

Process Versions A and B were developed to supply early-phase clinical studies. Process Versions D to F were developed as a conventional aseptic process, aligned with the intended commercial process, to supply clinical studies. Specifically, Process Version A-2 was used to manufacture the DP material for mRNA-1010-P303 Part A (previously referred to as mRNA-1010.6), while Process Versions E/F were used to manufacture the DP for mRNA-1010-P303 Parts B&C and mRNA-1010-P304 (previously referred to as mRNA-1010.4; mRNA-1010.4

contained updated (b) (4), and the RNA manufacturing process contained the introduction of (b) (4). The intended commercial process was developed as a conventional aseptic process to achieve the target strength, safety, and product quality attributes that are comparable to the previously manufactured clinical DP.

Batch Genealogy and Lot History: the firm utilizes product IDs and part numbers to distinguish processes and mRNA sequences. The product ID is made up of three parts: material code, process code, and content code. The material code denotes the end product manufactured. The process code denotes the high-level process type used to generate the material, and the content code denotes which mRNA sequence was used. The product ID is in the format: XXX-###-ZZZZ where XXX is the material code, ### is the process code, and ZZZZ is the content code.

An overview of DP process development from clinical supply to registration for mRNA-1010 is shown in the table below.

DP Manufacturing Overview for mRNA-1010

Process Version	Manufacturing Site	Clinical Study Supply	Nominal Batch Size (b) (4)	DP Concentration (mg/mL)	LDP Product ID ^(a)	UDP Product ID ^(a)
A	ModernaTX (b) (4)	mRNA-1010-P101-Ph1/2	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		mRNA-1010-P303 Part A		0.10		
B	ModernaTX (b) (4)	mRNA-1010-P101 Ph2		(b) (4)		
D	ModernaTX (b) (4)	mRNA-1010-P301 and P302		0.10		
E	ModernaTX (b) (4)	mRNA-1010-P303 Part B&C		0.10		
F	(b) (4)	mRNA-1010-P304		(b) (4)		
Commercial Scale	(b) (4)	(b) (4)		0.10		
Commercial Scale ^(a)	(b) (4)	(b) (4)		0.10		

Abbreviation: DP = drug product; LDP = labeled drug product; N/A = not applicable; UDP = unlabeled drug product

^a For the unnoted products ID, all DPs have LNP-100 input.

The major changes implemented from Version A to commercial are summarized below. The process Version A, used to manufacture clinical supply for mRNA-1010-P101-Ph1/2 and mRNA-1010-P303 Part A, is part of a sequential, integrated batch process for DP manufacturing. The RNA is processed into an (b) (4) and is subsequently used to fill the DP. The process Version B, used to manufacture clinical supply for mRNA-1010-P101-Ph2, is similar to process Version A, with the introduction of (b) (4) steps. The process Version D to F are used to manufacture clinical supply for mRNA-1010-P301 and

P302, mRNA-1010-P303 Part B and Part C, and mRNA-1010-P304. These process is similar to Version B, with the change of (b) (4) [REDACTED]. The commercial scale DP process intended for registration is a conventional aseptic process and is implemented at (b) (4) [REDACTED]. This process is similar to process Version D to F, with the change of container closure to PFS and (b) (4) [REDACTED]. Detailed process changes are summarized in the table below.

Comparison of DP Process and Presentation Changes

(b) (4)

(b) (4)

3.2.P.2.3 Comparability

A comparability assessment has been performed to ensure that DP quality attributes of materials used in mRNA-1010 clinical studies through PPQ are comparable. Comparability was assessed using a combination of release, extended characterization testing, and stability monitoring. A set of (b) (4) -agnostic quality attributes has been identified for which comparability limits were tightened compared to release specifications, using DP comparability limits of Spikevax. The DP comparability criteria for Spikevax were implemented based on extensive manufacturing experience and include n = (b) (4) lots. The DP PPQ release specifications and comparability criteria are shown in the table below.

DP PPQ Release Specifications and Comparability Criteria

Test Method	Comparability Criteria	Comparability Criteria Basis
Appearance by Visual Inspection	White to off-white dispersion. May contain visible, white or translucent product-related particulates	DP Specifications for mRNA-1010
Identity by (b) (4)	(b) (4)	
(b) (4)		
Total RNA Content by (b) (4)		
mRNA Purity by (b) (4)		
Product-related Impurities by (b) (4)		
(b) (4)		
(b) (4)		mRNA-1273 Historical Data
(b) (4)		
(b) (4)		
Lipid Identity: SM-102		DP Specifications for mRNA-1010
Cholesterol		
DSPC		
PEG2000-DMG		
Lipid Content: SM-102		
Cholesterol		
DSPC		

PEG2000-DMG	(b) (4)	
Lipid Impurities		
(b) (4)		
(b) (4)		
(b) (4)		mRNA-1273 Historical Data
(b) (4)		DP Specifications for mRNA-1010
Bacterial Endotoxins by (b) (4)		
Abbreviations: (b) (4); DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; (b) (4)		

Comparability of (b) (4) was assessed by (b) (4), as indicated in the table below.

DP Extended Characterization Comparability Expected Range

(b) (4)

The results from release met the acceptance criteria. Regarding the increase in (b) (4) in LNP-102 lots relative to LNP-100 lots Please see Overall Reviewer’s Assessment of Section 3.2.S.2.6 (LNP). Extended characterization testing results are summarized below. All results met the comparability expected ranges.

(b) (4) Results for Development & Supportive, Clinical, Commercial Scale mRNA-1010 DP Lots with LNP-100 and LNP-102 Inputs

(b) (4)

(b) (4)

(b) (4)

Stability comparability between LNP-100 and LNP-102 lots was performed using mRNA-1010 DP lots stored at 23°C to (b) (4) °C with at least (b) (4) timepoints. mRNA-1010 DP with LNP-100 input included (b) (4) PPQ and (b) (4) PSB lots and mRNA-1010 DP with LNP-102 input included (b) (4) PSB lots. This assessment

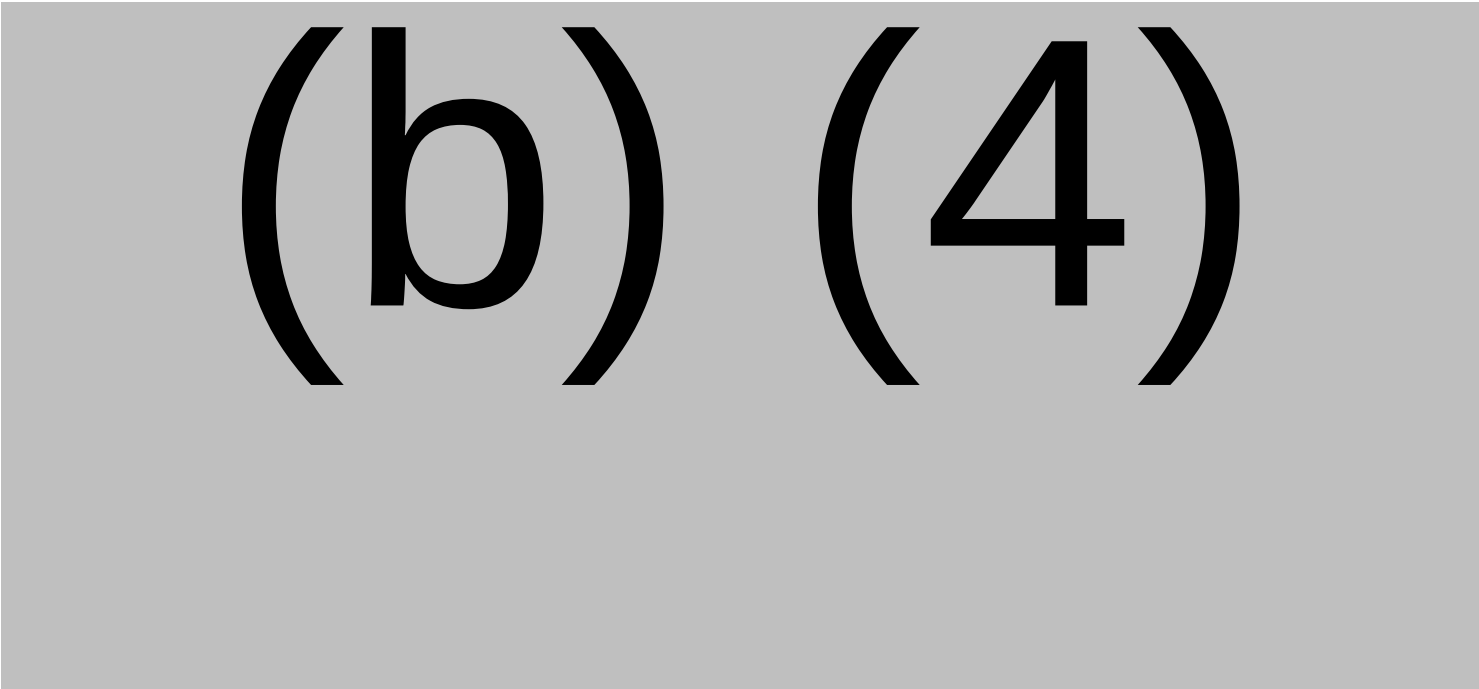
focused on quantitative CQAs that show meaningful change over time at 23°C to (b) (4) C: mRNA Purity, (b) (4) Total Lipid Impurities. To assess comparability between LNP-102 and LNP-100 lots, an equivalency test was performed Results show that the degradation rates for (b) (4) Total Lipid Impurities are equivalent between groups. For mRNA Purity, (b) (4) statistically significant differences are observed in the degradation rates. However, the DP prepared with LNP-102 input demonstrate improved performance over the course of accelerated stability (Table below).

Estimated Differences in Slope for mRNA-1010 DP Lots Stored at 23°C to (b) (4) C

Attribute (Units)	Contrast	Estimated Difference in Slopes (Units/month)	Standard Error of Estimated Difference	(b) (4) Lower Bound on Estimated Difference	(b) (4) Upper Bound on Estimated Difference	±EAC	EAC Contains (b) (4) CI (Y/N)
Ln(mRNA Purity) (%) (b) (4)	LNP-102 – LNP-100	(b) (4)					
Total Lipid Impurities (%)							

Abbreviations: CI = confidence interval; EAC = equivalence acceptance criteria.
a Equivalence analysis inconclusive: 90% CI on estimated difference in slopes falls partially outside EAC interval. LNP-102 lots show superior stability profiles compared to LNP-100 lots.

As an example, a graph showing stability plots of mRNA-1010 DP for RNA purity is shown below.



Comparability of LNP-102 and LNP-100 in a non-clinical mouse immunogenicity study: to assess the comparability of DP materials manufactured with LNP-100 and LNP-102 inputs in eliciting immune responses post-vaccination, a mouse immunogenicity study was conducted using one LNP-102 DP lot and one LNP-100 DP lot. Independent of the LNP process, mRNA-1010 induced robust HA binding antibodies against the 3

influenza strains encoded by the vaccine. A dose response was observed at both timepoints (Day 21 and Day 36) between the highest dose (2 µg) and the lowest dose (0.5 µg); titers were boosted at D36 compared to Day 21. See details in Module 4, influenza binding antibody responses (LNP-102 vs LNP-100).

3.2.P.2.4 Container Closure System

The DP of mRNA-1010 is supplied as a sterile, single-dose, ready-to-use liquid solution in a 1-mL long PFS. The PFS system consists of a 1-mL long syringe, 1-mL long plunger, and a 1-mL long plunger rod. The suitability of the selected primary container closure system for the DP has been demonstrated through functionality, compatibility, as well as container closure integrity and plunger placement characterization.

3.2.P.2.5 Microbiological Attributes

DP is manufactured by a conventional aseptic process using (b) (4) is monitored as part of the manufacturing process and (b) (4). Microbiological quality attributes are controlled by testing for sterility and bacterial endotoxins at release. The microbiological suitability of the selected primary container closure system has been demonstrated through container closure integrity (CCI) characterization and (b) (4) testing. CCI is also monitored as part of the manufacturing process and (b) (4) as part of the stability testing program.

3.2.P.2.6 Compatibility

In-use stability studies were performed to mimic handling of DP at administration sites using representative mRNA-1010 DP. The study was designed to assess the DP physicochemical stability in syringes. DP was prepared per the proposed administration instructions, including thawing PFS and equilibrating to room temperature, removing the tip cap, attaching a needle appropriate for intramuscular administration, and holding at room temperature while exposed to ambient light conditions. Samples were collected after varying hold durations. The quality attributes of DP remained within acceptance criteria when held at room temperature and ambient light conditions for up to (b) (4) hours. Data is presented below.

In-Use Stability Data for DP for mRNA-1010 Held at 25°C for at Least (b) (4)

Attribute	Target Criteria ^(a)	Control ^(b)	8 hours ^(c)	(b) (4) hours ^(c)
Appearance	White to off-white dispersion. May contain visible, white or translucent product-related particulates.	Conforms ^(d)	Conforms ^(d)	Conforms ^(d)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
mRNA Purity	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Lipid Content	SM-102	(b) (4)	(b) (4)	(b) (4)
	Cholesterol			
	DSPC			

	PEG2000-DMG	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Lipid Impurities	Individual impurities: (b) (4)	(b) (4)			
	Total impurities: (b) (4)				
(b) (4)	(b) (4)				
RNA Content	(b) (4)				

^a Target criteria aligned with specification effect

^b Samples in (b) (4) without a hold.

^c Samples kept in 1-mL syringes. 7 h: Samples in syringes held for 7 hours. (b) (4) Samples in syringes held for (b) (4) hours.

^d Sample results “White to off white dispersion essentially free of visible particles” aligns with target criteria.

Overall Reviewer’s Assessment of Section 3.2.P.2

In this BLA, the firm and the FDA consider that the four lipids that constitute the LNP are not classified as DP excipients, but as raw materials. This is in agreement with section 3.2.P.4 Control of Excipients, where the four lipids are not listed. However, in section 3.2.P.2.1.3 Excipients, the firm states “The function of each excipient in the DP is also described below...” and then the 4 lipids are listed, indicating that the four lipids are DP excipients. I think that the statement in section 3.2.P.2.1.3 Excipients is an error, and I don’t think that this error is critical.

Overall, the mRNA-1010 DP comparability data conform to the comparability acceptance criteria for release, extended characterization testing, and stability. Non-clinical studies further indicated equivalent immunogenicity between LNP-102 and LNP-100-formulated DPs. Taken together these results demonstrate that mRNA-1010 DP lots derived from the LNP-102 process have product quality and stability profiles consistent with or superior to mRNA-1010 DP lots derived from the LNP-100 process.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

DP manufacturing, storage, and testing operations are performed according to current GMP at the sites listed in the table below (as updated in amendment 65, submitted on 6.1.26).

DP Manufacturers

Facility	Responsibility
(b) (4)	Manufacturing of unlabeled drug product (UDP) In-process testing
(b) (4)	(b) (4) UDP (b) (4) Assembly, label, and packaging of drug product In-process testing Release and stability testing

(b) (4)	Release and stability testing
(b) (4)	Batch certification Release and stability testing
ModernaTX, Inc. (ModernaTX (b) (4)	Release testing (b) (4)
(b) (4)	(b) (4) Storage (interim and long-term)
(b) (4)	Distribution
(b) (4)	Distribution

^a Subcontracted by (b) (4)

3.2.P.3.2 Batch Formula

Representative batch size, and formula for the manufacture of DP are provided in the table below. DP is qualified across a batch size range of (b) (4)

DP Batch Composition

Component	Amount per Batch ^(a)	
	(b) (4) DP (b) (4)	(b) (4) DP (b) (4)
Total LNP ^(b)	(b)	(4)
LNP for Influenza A/H1N1		
LNP for Influenza A/H3N2		
LNP for Influenza B/Victoria		
Tromethamine (Tris) ^(c)		
Tromethamine-HCl (Tris-HCl) ^(c)		
Sucrose		
Water for Injection (WFI)		

Abbreviation: RNA = ribonucleic acid; DP = drug product

^a Representative quantities shown are based on target LNP input and a nominal RNA content of (b) (4) since quantities used in the manufacturing process are based on actual RNA content and dispensed weight of LNP input.

^b Total LNP comprises of three LNP components: LNP for influenza A/H1N1, LNP for influenza A/H3N2, and LNP for influenza B/Victoria. Weights of LNP are controlled in the manufacturing process as described in Section 3.2.P.3.3 {DP, 37.5 PFS} to achieve target individual RNA dose level described in Section 3.2.P.1 {DP, 37.5 PFS}

^c Tris is referred to as Tromethamine in the (b) (4) and as Trometamol in the (b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2

The information provided is acceptable. In response to IR#13 (amendment 31) the firm indicates that that the date of manufacture for the mRNA-1010 final vaccine is defined as the start date of the assembly, label, and pack operations for the labeled DP.

3.2.P.3.3 Description of Manufacturing Process

Two manufacturing process flows have been designed: Process Flow 1 and Process Flow 2. Process Flow 1 will be the primary process flow used for manufacture of mRNA-1010 DP. In Process Flow 1 (see figure below, main diagram), following (b) (4)

In Process Flow 2 (see figure below, dotted arrow), following (b) (4)

The DP is filled and closed with ready-to-use (RTU) syringes and plungers. Release and stability samples are (b) (4) testing.

DP Process Flow Diagram

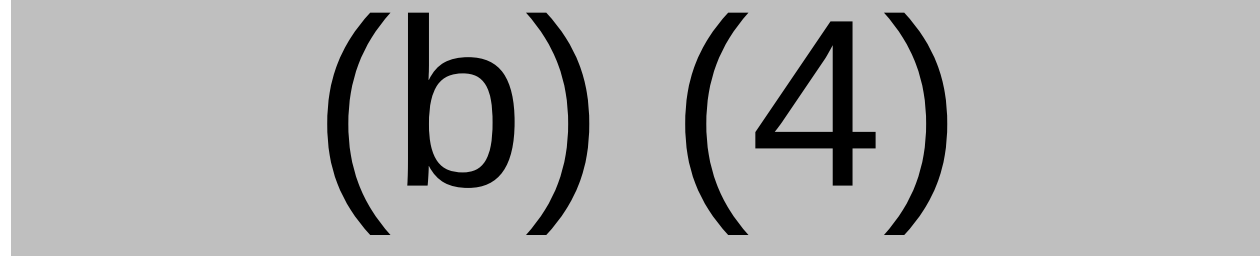
(b) (4)

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(b) (4)

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(b) (4)

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Overall Reviewer's Assessment of Section 3.2.P.3.3

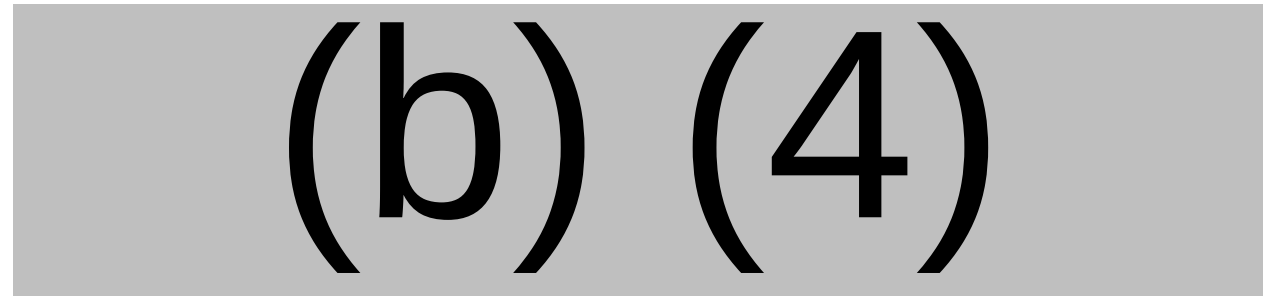
The information provided is acceptable.

3.2.P.3.4 Control of Critical Steps and Intermediates

Critical Process Parameters (CPPs) and their proven acceptable ranges (PARs) for the DP manufacturing process are provided in the table below.

CPPs

(b) (4)

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(b) (4)

Microbial Control Strategy: at (b) (4), the (b) (4) steps are carried out in a Grade (b) (4) manufacturing area. (b) (4) is performed in Grade (b) (4) area into the filling isolator (Grade (b) (4)). Filling and plunger placement are performed in Grade (b) (4) within Grade (b) (4) area. (b) (4) facility utilize product-family dedicated multi-use or single-use sterile materials for product contact equipment. (b) (4) equipment are product-family dedicated and (b) (4) between batches. The container closure system is received sterile and ready to use. Manufacturing controls specifically intended for microbial control of the DP manufacturing process are listed in the table below.

Microbial Controls

Step	Operation / IPC	Test / Description	Limit	Environment Background Classification
(b) (4)				
Filling and Plunger Placement	Filler qualified for sterile operations			Grade (b) (4)

Abbreviations: (b) (4)

(b) (4)

The Critical In-Process Control (CIPC) testing and associated acceptance criteria for the DP manufacturing process are summarized in the table below.

Critical In-Process Controls

Process Step	CIPC	Acceptance Criteria	Rationale
(b) (4)	(b) (4)		
Filling	(b) (4)		
Plunger Placement			

Abbreviations: (b) (4)

Overall Reviewer’s Assessment of Section 3.2.P.3.4

The information provided is acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

A PPQ of the DP manufacturing process for mRNA-1010 was conducted per protocol at the (b) (4) on the (b) (4) line. UDP (b) (4) was conducted at (b) (4). LDP assembly, label, and pack were conducted at (b) (4) . All qualifications were performed per protocols. PPQ lots are summarized in the table below. The PPQ batches were manufactured per the DP manufacturing process using (b) (4)

PPQ Lots Executed for the DP Manufacturing Process

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The excipients in DP are listed in the table below.

DP Excipients

Excipient	Function	Grade	Specifications
Tris ^(a)	Buffer components in Tris buffer	(b) (4)	(b) (4)
Tris-HCl ^(a)			Table below
Sucrose	Cryoprotection		(b) (4)
WFI	Solvent		(b) (4)

Abbreviations: (b) (4) ;

WFI = water for injection

^a Tris is referred to as Tromethamine in the (b) (4) and as Trometamol in the (b) (4)

Excipients are tested and released for use in compliance with current (b) (4) (see above table) or master specification (for Tris-HCL, see table below).

Tris-HCl Master Specification

Attribute	Test Methods/conditions	Acceptance Criteria
(b) (4)		

Abbreviations: (b) (4)

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

The (b) (4) excipients are tested per the indicated (b) (4). The commercially available (b) (4) excipients Tris-HCl and DSPC are tested per the respective specifications. The methods used to test the custom (b) (4) excipients SM-102 and PEG2000-DMG were previously reviewed under BLA 125835 and found to be acceptable. Specifications for SM-102 and PEG2000-DMG were provided (amendment 98) and are acceptable. The qualifications of some of the analytical methods of commercially available (b) (4) and (b) (4) excipients are performed by the vendors and the applicant reviewed the CoAs after receipt of

the excipients. The qualification of the identity method was completed with representative samples at each receiving site. The validation of the methods used to test the custom (b) (4) excipients SM-102 and PEG2000-DMG were previously reviewed under BLA 125835 and found to be acceptable.

3.2.P.4.4 Justification of Specifications

The commercially available excipients sucrose and Tris are tested to (b) (4) requirements. The specification for the commercially available, (b) (4) excipient Tris-HCl is established by the respective supplier.

3.2.P.4.5 Excipients of Human or Animal Origin

There are no excipients of human or animal origin in the DP.

3.2.P.4.6 Novel Excipients

There are no novel excipients in the DP. The information for the two custom (b) (4) lipids SM-102 and PEG2000-DMG was previously reviewed under BLA 125835 and found to be acceptable.

Overall Reviewer's Assessment of Section 3.2.P.4

The information provided is acceptable.

3.2.P.5 Control of DP

3.2.P.5.1 Specifications and Justification of specifications

The release and shelf-life specifications for the DP are listed in the table below (as updated in amendments 65, 78, and 102).

DP Specification for mRNA-1010

Test Method	Release Sampling Point	Release Acceptance Criteria	Stability Acceptance Criteria
Appearance by Visual Inspection	(b) (4)	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
Identity by (b) (4)	(b) (4)	(b) (4)	
(b) (4)			
Total RNA Content by (b) (4)			
(b) (4)			

mRNA Purity by (b) (4)

Product-Related Impurities
by (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Lipid Identity by (b) (4)

SM-102
Cholesterol DSPC PEG2000-
DMG

Lipid Content by (b) (4)

SM-102
Cholesterol DSPC PEG2000-
DMG

Lipid Impurities by (b) (4)
(b) (4)

(b) (4)

(b) (4)

(b) (4)

Bacterial Endotoxins by (b) (4)

Sterility by (b) (4)

(b) (4)

No Growth

N/A

Deliverable Volume by (b) (4)

(b) (4)

(b) (4)

(b) (4)	
Container Closure Integrity	
(b) (4)	

Abbreviations: (b) (4)

(b) (4)

Justification of Specification

The DP specifications have been established in accordance with (b) (4), considering CQAs outlined in (b) (4). These CQAs and the DP release and stability specifications are based on risk assessments, process and product characterization knowledge from mRNA-1010, prior knowledge from other mRNA vaccine products, including Spikevax, clinical experience, (b) (4) requirements, and manufacturing process capability *in vivo*. The justification of each specification is summarized in the table below.

Justification of Specification Summary

Test Method	Release Sample	Acceptance Criteria	Justification
Appearance by Visual Inspection	(b) (4)	White to off-white dispersion. May contain visible, white or translucent product related particulates	These criteria are based on the currently available release and stability data from mRNA-1010 as well as prior knowledge from mRNA-1273.
Identity by (b) (4)	(b) (4)	(b) (4)	This criterion is set to specifically confirm that each intended RNA is included to ensure that the correct proteins are encoded.
(b) (4)			(b) (4)
Total RNA Content by (b) (4)			These criteria are set to enable delivery of the target dose and control the concentration variability. Supported by available release and stability data from mRNA-1010 as well as prior knowledge from mRNA-1273.
mRNA Purity by (b) (4)			The shelf-life specification is justified incorporating mRNA-1010 and (b) (4) clinical experience and prior knowledge from mRNA-1273 and is further supported by non-clinical <i>in vivo</i> immunogenicity data from mRNA-1010 DP. The minimum release limit is calculated to ensure product meets the shelf-life specification throughout the DP shelf-life and further supported by available release and stability data from mRNA-1010.
Product-related Impurities by (b) (4)			

	(b) (4)	
(b) (4)		(b) (4)
(b) (4)		(b) (4)
(b) (4)		(b) (4)
(b) (4)		(b) (4)
Lipid Identity by (b) (4)		The presence of 4 lipids which compose the LNP are confirmed to establish identity.
Lipid Content by (b) (4)		These criteria have been defined based on process capability assessment performed for DP release data of mRNA-1273 and mRNA-1010.
Lipid Impurities by (b) (4)		The shelf-life specification is justified incorporating mRNA-1010 clinical experience and prior knowledge from six clinical studies across four mRNA vaccine programs—(b) (4), mRNA-1273 (Spikevax), mRNA-1345 (mRESVIA), and (b) (4) and is further supported by an non-clinical <i>in vivo</i> immunogenicity data. The minimum release limit is calculated based on process capability and to ensure product meets the shelf-life specification throughout the DP shelf-life. Supported by (b) (4) guidelines.
(b) (4)		(b) (4)
Deliverable Volume by (b) (4)		These criteria are established to allow for delivery of the target volume.
(b) (4)		(b) (4)

(b) (4)	(b) (4)		
(b) (4)	(b) (4)		
(b) (4)	(b) (4)		
Bacterial Endotoxins by (b) (4)	This criterion is required by (b) (4) for patient safety. (b) (4) represents a maximum exposure of (b) (4) for DP of mRNA-1010.		
Container Closure Integrity by (b) (4)	N/A ^(a)	Pass	Container closure integrity is performed to confirm maintenance of sterility during stability.
Sterility by (b) (4)	UDP	No growth	This criterion is required by (b) (4) to ensure a sterile final product. DP for mRNA-1010 is expected to be free of microbial and fungal contamination based on the manufacturing process and controls in place.

Abbreviations: (b) (4)

End of shelf-life specifications for RNA purity and product related impurities.

The immunogenicity of mRNA-1010 DP has been evaluated in clinical and non-clinical studies over a broad range of dose levels, mRNA Purity values, and storage conditions. These studies indicate that immune responses are primarily driven by the Effective Delivered Dose (EDD; (b) (4)). See below, JUSTIFICATION OF EDD, after Section 3.2.P.8. The DP safety profile is not expected to be impacted by these RNA product related impurities. This is supported by results from clinical-dose-escalation study mRNA-1010-P101 demonstrating that higher levels of product related impurities in the (b) (4) dose, which is more than (b) (4) the commercial dose of 37.5 µg, did not have an impact on tolerability. Also, clinical data demonstrating consistent safety across multiple mRNA vaccine programs encompassing a range of doses and impurity levels. See below, Reviewer's Comments.

3.2.P.5.2 Analytical Procedures

The release test methods that are common to the LNP DS and DP (Appearance by Visual Inspection, Total RNA Content by (b) (4), and Bacterial Endotoxin) are described in section 3.2.S.4.2 LNP. The tests specific to the DP are described below.

Identity (b) (4): the method is used to determine the identity and (b) (4) of multivalent DP samples by (b) (4)

(b) (4)

Purity and Product Related Impurities: mRNA Purity/Product-related impurities method is used to assess the integrity of multivalent mRNA purity and associated impurities of DP. The method (b) (4) using (b) (4). As all of the (b) (4) in the mRNA-1010 DP are of (b) (4). Detection is performed by (b) (4). mRNA purity and product-related impurities are (b) (4). Details of the procedure and system suitability criteria are provided.

Sterility: DP is tested for sterility in accordance with the (b) (4)

(b) (4)

Container closure integrity: (b) (4) test is used to evaluate the container closure integrity of DP sample. (b) (4)

Deliverable volume: this test is performed in accordance with (b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.5.3 Validation of Analytical Procedures

Most of the analytical methods for release and stability testing of DP of mRNA-1010 are shared across mRNA vaccines for both commercial (Spikevax, mNEXSPIKE, and mRESVIA) and clinical programs. These methods perform consistently across mRNA vaccines. To support this registration, the (b) (4) analytical methods that are utilized for release and stability testing of DP have all been validated either using mRNA-1273 or using mRNA-1010 materials. For (b) (4) -agnostic platform methods, validation was performed using representative mRNA-1273 material (Spikevax). Specific validations for mRNA-1010 have been performed for any new methods developed for mRNA-1010, as well as for methods that are not (b) (4) -agnostic. These methods are the identity and (b) (4) method, mRNA purity and product-related impurities method, and the (b) (4) method. These methods have also been verified using mRNA-1010 material at each testing site. The complete information regarding the laboratories that performed the initial assay validation and the laboratories that have assays being transferred to them was submitted to BLA 125835. More details on these assays can be found in the CMC review memo of BLA 125835.

Identity (b) (4) : this method was initially fully validated with mRNA-1010 DP (b) (4) in the QC laboratory at Moderna (b) (4) is composed of three monovalent LNPs, which contain mRNA encoding seasonal influenza antigens. The assay performance characteristics evaluated, the validation test design and results are provided and are acceptable. With the transition from the LNP-100 process to LNP-102 process and the change in influenza strains as recommended by WHO, additional supplemental validation was performed with the mRNA-1010 DP (b) (4) with LNP-102 inputs in the QC laboratory at Moderna (b) (4) is composed of three monovalent LNPs which contain RNAs encoding seasonal influenza antigens. This method was successfully transferred from Moderna (b) (4) QC lab using mRNA-1010 DP ((b) (4)) as the representative material. The assay performance characteristics evaluated, and results are provided and are acceptable.

mRNA purity/product-related impurities by (b) (4) : this method has been successfully co-validated in both QC labs in ModernaTX (b) (4) Moderna (b) (4) using (b) (4) DP as representative material, since both mRNA-1010 DP and (b) (4) DP share the (b) (4). A supplemental method validation has been successfully completed at Moderna (b) (4) lab using mRNA-1010 DP. This method has been successfully transferred from Moderna (b) (4) using mRNA-1010 DP. The assay performance characteristics evaluated, the test design and results are provided and are acceptable.

(b) (4)

Total RNA content: this method is used for release and stability testing of multiple mRNA vaccine products with the use of a product specific RM. It has been previously validated using DP for mRNA-1273, as well as qualified for (b) (4) different DPs ranging in length from (b) (4) nucleotides, across a range of product

formulations and lipid matrices. Therefore, it is considered that no additional validation activities are required. This method was fully validated in ModernaTX (b) (4) QC lab. It was successfully transferred from ModernaTX (b) (4) QC lab using DP for mRNA-1273 as a representative material. This method has also been verified by testing PPQ materials from mRNA-1010 and it was also successfully transferred from ModernaTX (b) (4) QC lab to Moderna (b) (4) QC lab with DP for mRNA-1273 as a representative material. The assay performance characteristics evaluated, the transfer test design and results are provided and are acceptable.

(b) (4)

(b) (4)

Lipid ID, lipid content, and Lipid Impurity by (b) (4) : this method is used for release and stability testing of multiple products that contain the same lipid matrix. This method has been previously validated in ModernaTX (b) (4) QC lab with LNP and DP of mRNA-1273 as representative materials., as well as qualified for two other products. The method was first successfully transferred from ModernaTX (b) (4) with DP of mRNA-1273 (b) (4) is an intermediate lab as part of the initial transfer, but it is not intended for this registration). This method was then transferred from (b) (4) QC lab with DP for mRNA-1273. Additionally, this method has been verified by testing PPQ materials from mRNA-1010. The method was also successfully transferred from ModernaTX (b) (4) to Moderna (b) (4) QC Lab with DP for mRNA-1273. The assay performance characteristics evaluated, the validation test design and results are provided and are acceptable.

(b) (4)

Validation Summary for (b) (4) with (b) (4) : Specificity

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.1- 3.2.P.5.6

The information provided is acceptable. Validation reports and detailed descriptions or SOPs of all non-(b) (4) test methods are provided in the BLA and are acceptable. Supplemental method validations were performed at (b) (4) lab with mRNA-1010 DP and were successful.

3.2.P.5.4 Batch Analyses

Batch analysis results for commercial scale PPQ lots (both, UDP and LDP), clinical lots, and supportive lots are provided. All tests met specifications. UDP and LDP lots are listed in the tables below. Batch analyses results from selected lots are shown.

DP Commercial Scale UDP Lots for mRNA-1010

(b) (4)

LDP lots and batch analysis results for representative lots are listed in the tables below.

DP Commercial Scale LDP Lots for mRNA-1010

LDP ID	Moderna Lot # (CMO Lot #)	DOM	Manufacturer	Use
(b) (4)				PPQ, Comparability, Stability
				PPQ, Comparability, Stability
				PPQ, Comparability
				PPQ, Comparability, Stability
				PPQ, Comparability, Stability
				PPQ, Comparability
				PPQ, Comparability, Stability
				PPQ, Comparability, Stability
				PPQ, Comparability
				Comparability
				Comparability, Stability

Abbreviations: CMO = contract manufacturing organization; DOM = date of manufacture; LDP = labeled drug product; PPQ = process performance qualification; (b) (4)

Batch analysis of DP PPQ LDP Lots for mRNA-1010

(b) (4)

3.2.P.5.5 Characterization of Impurities

The impurity profile of the DP is the same as that of the LNP (discussed above), except (b) (4) as described below, because there are no new impurities anticipated to form or be introduced during DP manufacturing, except for leachables and extractables from process or container components. Product-related (b) (4) may appear in (b) (4) and are not considered impurities. (b) (4) may manifest as (b) (4) and is assessed as part of product release and stability testing. During the LNP manufacturing process, (b) (4) are introduced as a component of (b) (4)

step of the DP process; the resulting (b) (4) DP contains approximately (b) (4) at this concentration poses no safety concerns. (b) (4)

. Furthermore, the enormous clinical experience from mRNA-1010, Spikevax™ (mRNA-1273), and mRESVIA™ (mRNA-1345) pose no safety concerns on the similar or higher levels of (b) (4) included in mRNA-1010 DP.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5

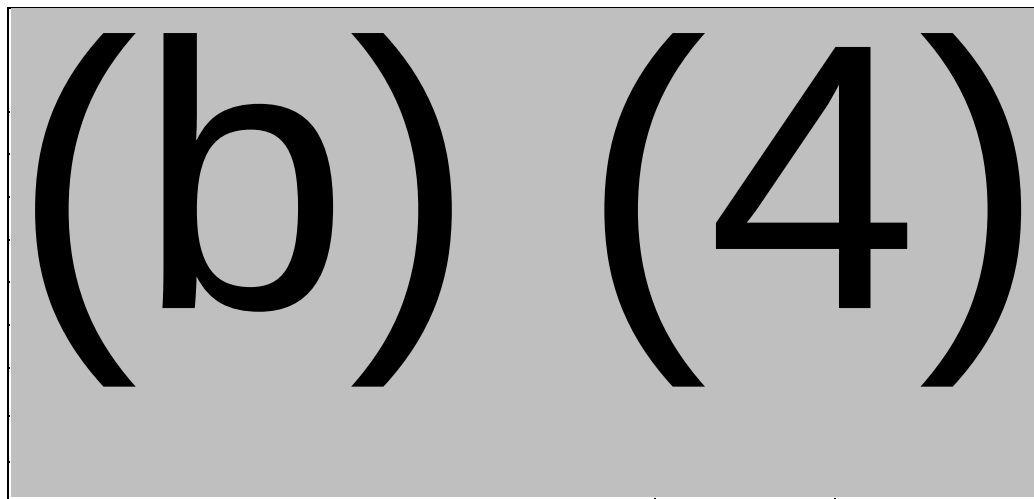
The information provided is acceptable. All DP specifications were met. Release testing results support consistency of product manufacture.

3.2.P.6 Reference Standards or Materials

The RM program has been established in accordance with (b) (4) to guide the qualification, requalification, storage, and distribution of RMs used for testing mRNA-1010 DP. For DP testing, LNP RMs are used as a system suitability standard for mRNA Purity and Product-Related Impurities by (b) (4), as a positive control for (b) (4), as a reference standard for Total RNA Content by (b) (4), and (b) (4). The suitability of using LNP RM for analysis of DP samples was verified with collective experimental data showing no significant difference when using LNP or DP RMs. DP RM is used as a (b) (4), and as a reference standard for the (b) (4). RMs (SM-102, Cholesterol, DSPC, and PEG2000-DMG) are used as reference standards for Lipid Content, Lipid Identity and Lipid Impurities by (b) (4).

A two-tiered RM program is established to support analytical testing of commercial lots. It consists of one in-house primary RM (PRM) lot and multiple working (secondary) RM (WRM) lots prepared from an appropriate source such as a recent pilot, clinical, or commercial lot. The use of this two-tiered system, with qualification of new WRMs against a PRM, allows for consistency across WRMs. Qualification and requalification of PRM and WRMs will be performed according to the qualification and requalification protocols including release and extended characterization testing panels as provided in the table below. A season specific RM will be qualified with seasonal strain updates for the (b) (4), where a season specific RM is used to ensure consistent and acceptable seasonal product (b) (4).

Qualification and Requalification Testing for DP RMs



(b) (4)

Abbreviations: (b) (4)

The DP PRM lot (b) (4) are used for analysis of commercial scale mRNA-1010 DP lots with LNP-100 and LNP-102 inputs, respectively. These PRM lots were generated with a process representative of the DP commercial scale process intended for registration and stored at (b) (4). The PRMs were each assigned to (b) (4) as they were the initial RMs established for each mRNA-1010 DP made with LNP-100 or LNP-102 inputs and were demonstrated to have consistent (b) (4) with the DP lot used in the mRNA-1010-P304 pivotal study (b) (4) to ensure (b) (4) assessments are clinically relevant.

For the (b) (4)

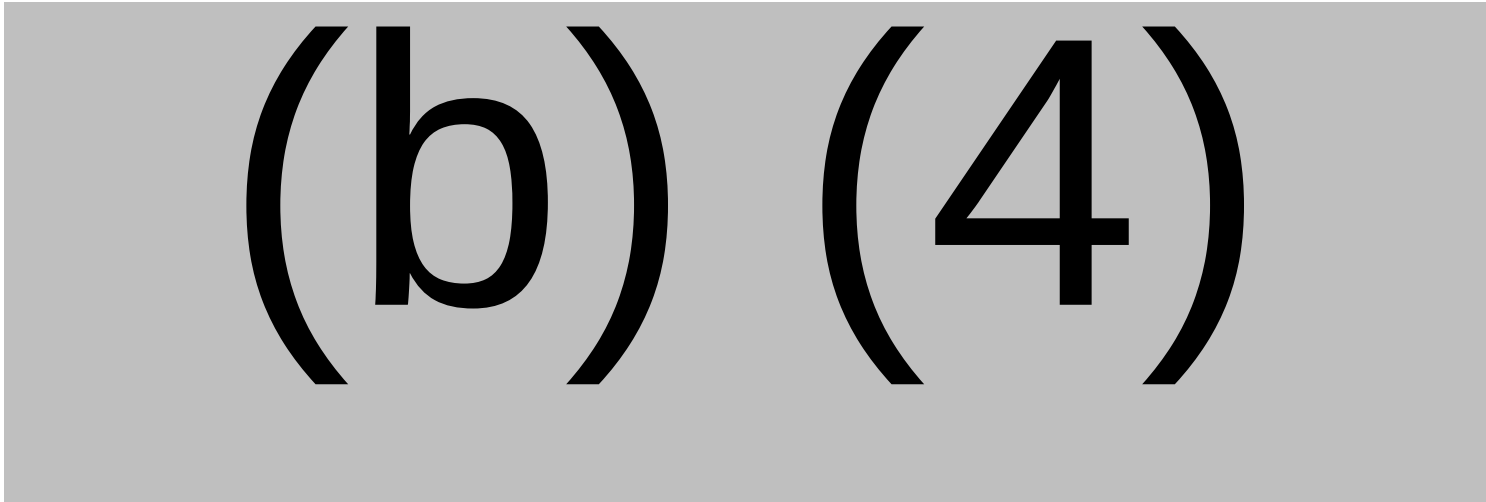
(b) (4)



(b) (4)



(b) (4)



(b) (4)



3.2.P.7 Container Closure System

The DP is presented as a single-dose product in a prefilled syringe (PFS). The PFS consists of a 1-mL long syringe, a 1-mL long plunger, and a plunger rod.

Empty, ready-to-use (RTU) 1-mL long COC syringes and plungers are received sterile, in plastic tubs. (b) (4) sterilization of the syringe barrels and (b) (4) sterilization of the plungers are performed according to (b) (4). The 1-mL long COC syringe and the 1-mL long plunger are compliant with applicable (b) (4) requirements. No animal derived materials are used in the manufacturing of the container closure. Plunger rods are received non-sterile. DP container closure components are received, inspected, and released for use according to established procedures. The secondary packaging for DP is an assembled and labeled PFS, packed into a carton. One patient information leaflet (PIL) or prescribing information (PI) is also placed in the secondary carton, as applicable. Cartons are then placed into a case, and the cases are closed.

Overall Reviewer's Assessment of Section 3.2.P.6 and 3.2.P.7

The DP container was assessed for extractables and leachables. The firm leverages the E&L data from their other licensed vaccine presented in PFS. The data is acceptable.

3.2.P.8 Stability

3.2.P.8.1. Stability summary

The DP stability program for mRNA-1010 is being executed according to (b) (4).

The proposed shelf life is 2°C to 8°C storage up to 12 months, including up to 12 hours at 8°C to 25°C. The (b) (4) model is used to estimate the average slope and the standard error in the estimated slope for each temperature, and the assay variability combined across all temperatures (as the methodology outlined in (b) (4)).

Stability data generated from representative DP lots (b) (4) manufactured with LNP-102 process with the corresponding statistical analysis are leveraged to support the shelf-life assessment of mRNA-1010 DP with LNP-102 inputs (see table below). (b) (4)

. See below, Reviewer's Comments, for updated stability data from mRNA-1010 DP manufactured with LNP-102 LNPs (data from amendment 57) and see above Section 3.2.P.2.3 Comparability for a comparability assessment between mRNA-1010 LNP-100, mRNA-1010 LNP-102, and representative seasonal influenza LNP-102 ((b) (4)) lots.

LNP-102 DP Lots Used for Shelf-Life Assessment of mRNA-1010 DP

DP ID	ModernaTX Lot #	Lot Type	Manufacturing Site	LDP DOM	Fill Volume (mL)	Container Closure	Conditions		Available Data (M)
							Temperature	Duration (M)	
(b) (4)	(b) (4)	Primary Stability Batch	ModernaTX (b) (4)	(b) (4)	(b) (4)	COC PFS	(b) (4)	12	12
							2°C to 8°C	12	12
							23°C to (b) (4)	1	1
		Primary Stability Batch	ModernaTX (b) (4)			COC PFS	(b) (4)	12	12
							2°C to 8°C	12	12
							23°C to (b) (4)	1	1
		Primary Stability Batch	ModernaTX (b) (4)			COC PFS	(b) (4)	12	12
							2°C to 8°C	12	12
							23°C to (b) (4) C	1	1
		Development	ModernaTX (b) (4)			COC PFS	(b) (4)	12	1
							2°C to 8°C	12	1
							23°C to (b) (4) C	1	1

(b) (4)	(b) (4)	Development	ModernaTX (b) (4)	(b) (4)	(b) (4)	COC PFS	(b) (4)	12	1
							2°C to 8°C	12	1
							23°C to (b) (4) C	1	1

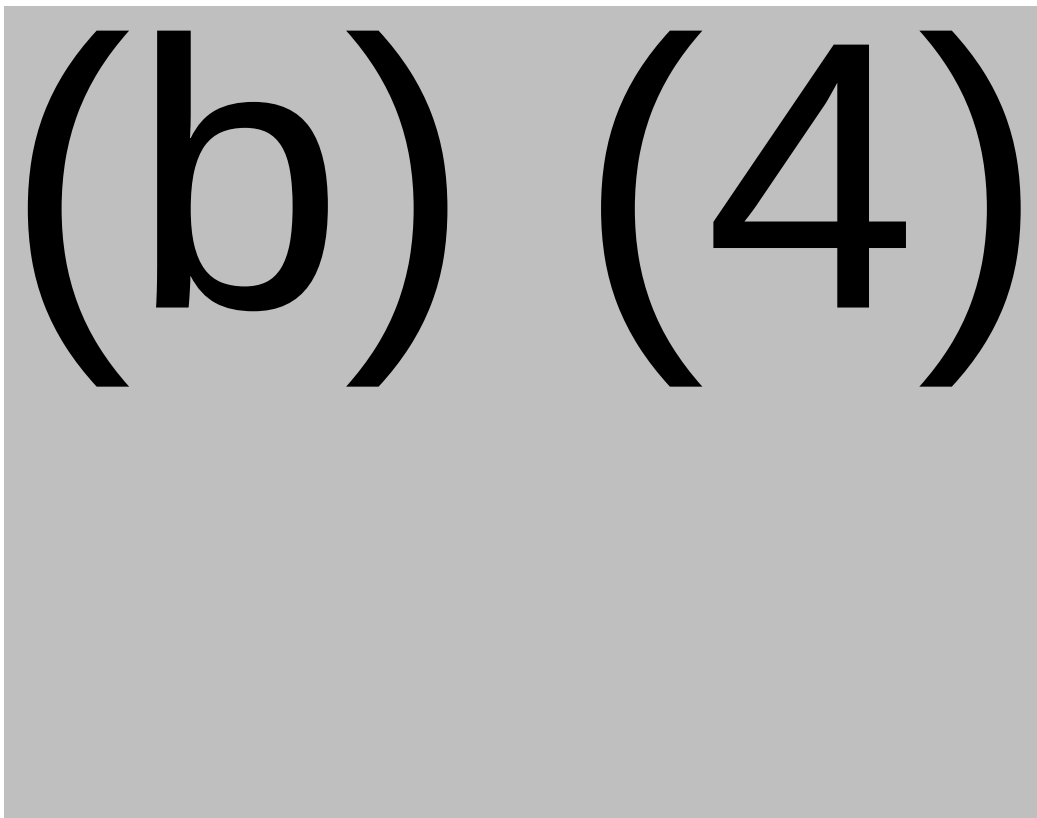
Abbreviations: COC PFS = cyclic olefin copolymer; DOM = date of manufacture; M = months; LDP = labelled drug product

Stability assessment.

The CQAs that were assessed on stability include Appearance, mRNA Purity, product-related impurities (b) (4), Total Lipid Impurities, Lipid Content, (b) (4), Total RNA Content, (b) (4), Container Closure Integrity (b) (4), Deliverable Volume, and Bacterial Endotoxins. Only quantitative attributes that have been identified to be stability indicating were assessed toward the determination of product shelf-life. Bacterial Endotoxins, (b) (4), Deliverable Volume are performed to confirm product quality through the product shelf life and no trends have been observed. For all lots evaluated in this assessment, mRNA Purity, (b) (4) and Total Lipid Impurities show change over time. (b) (4) show no or limited change over time. Total RNA Content and Lipid Content are expected to remain stable. Total RNA Content, Lipid Content, (b) (4) are not expected to show change over time, and therefore statistical analysis was not performed. Stability assessments for some of the evaluated CQAs are presented below.

Stability Assessment for mRNA Purity: all available mRNA Purity data for representative seasonal influenza LNP-102 lots are shown in the figure below; regression lines are shown for lots with at least three data points. The mRNA Purity assay provides a composite measurement of the all the mRNAs in the DP. This approach is appropriate because the DP, regardless of the valency, and LNPs, shows consistent degradation in the recommended and in accelerated storage conditions for multiple seasonal influenza LNPs.

(b) (4)



Stability Assessment for Product Related Impurities (b) (4) : For all lots evaluated in this assessment, (b) (4) exhibit an increasing trend over time at (b) (4), 2°C to 8°C, and 23°C to (b) (4) C, as anticipated.

Stability Assessment for (b) (4) : for all lots evaluated in this assessment, (b) (4) show no or minimal changes over time at all stability storage conditions of (b) (4), 2°C to 8°C, and 23°C to (b) (4) C.

Stability Assessment for (b) (4) : for all lots evaluated in this assessment, (b) (4) shows no change over time at all stability storage conditions of (b) (4), 2°C to 8°C, and 23°C to (b) (4) °C.

Stability Assessment for Total Lipid Impurities: for all lots evaluated in this assessment, Total Lipid Impurities show no or limited degradation over time at the (b) (4) stability storage conditions of (b) (4) and shows an increasing trend over time at 2°C to 8°C and 23°C to (b) (4), as expected.

Release Limits and Shelf Life: the shelf life of mRNA-1010 DP was determined using the stability data from representative (b) (4) DP lot manufactured with LNP-102 inputs. For each attribute, at each stability storage temperature representing the long-term storage conditions (2°C to 8°C and 23°C to (b) (4) C), the principles in (b) (4) were applied to fit a regression model. The table below provides the estimated rate change, the standard error of the estimated rate change, and the combined assay variance for all temperatures.

Summary of Estimated Degradation Rates and Assay Variability

Attribute	Temperature	Estimated Rate of Change (per month, $\hat{b}_k$)	Standard Error of Rate of Change (per month, $s_{\hat{b}_k}$)	Combined Assay Variance from All Temperatures (s^2_{assay})
ln(mRNA Purity (%))	2°C to 8°C	(b) (4)	(b) (4)	(b) (4)
	23°C to (b) (4) C			
(b) (4)	2°C to 8°C			
	23°C to (b) (4) C			
(b) (4)	2°C to 8°C			
	23°C to (b) (4) C			
Total Lipid Impurities (%)	2°C to 8°C	(b) (4)	(b) (4)	(b) (4)
	23°C to (b) (4)			

^a Estimated rates of change are not statistically significant at 95% confidence level.

The table below provides a summary of the estimated mean and 95% CL(s) for each attribute after 12 months at 2°C to 8°C and 12 hours at 23°C to (b) (4) C. The prediction is made based on a hypothetical worst-case lot that is released at the specification limit. The shelf-life analysis confirms that a worst-case lot with a value equal to the release specification limit will remain within the EoSL specification limit when stored at the long-term storage condition of 2°C to 8°C for 12 months, including up to 12 hours at 8°C to 25°C.

**Predicted Means and 95% CL(s) at Expiry, Representative Seasonal Influenza LNP-102 Lots,
Stored for 12 months at 2°C to 8°C and 12 hours at 23°C to (b) (4) C**

Attribute	Release Acceptance Criteria as Starting Value	Predicted Mean at Expiry	Lower 95% CL at Expiry	Upper 95% CL at Expiry	Stability Acceptance Criteria	CL falls within EoSL Limits at Proposed Expiry? (Y/N)
mRNA Purity (%)		(b) (4)				
(b) (4)						
(b) (4)						
Total Lipid Impurities (%)						

The figure below displays a plot representing the intended expiry period across both storage temperatures for RNA purity. Real-time data is provided for each stability storage temperature. Estimated mean and 95% CL(s) for the individual storage temperature are shown in green. Estimated mean and 95% CL(s) for sequential storage at all three temperatures based on calculations from (b) (4) are shown in blue.

(b) (4)

A similar statistical analysis is provided for (b) (4), and Total Lipid Impurities. All analysis showed that specifications are met for each quality attribute at the end of shelf life.

Photostability: an (b) (4) -compliant photostability study was performed on the commercially representative LDP presentation (1-mL long COC PFS) for mRNA-1010, either with or without commercially representative secondary packaging. DP quality attributes were assessed following exposure to the conditions shown in the table below.

(b) (4) Photostability Study Conditions Summary

(b) (4)

Abbreviations: N/A = not applicable; PFS = prefilled syringe; (b) (4)

Results are provided and indicate that: no substantial change in biophysical or biochemical attributes on light exposure was observed compared to the corresponding dark control at 25°C, for PFS without secondary packaging, and a decrease in mRNA purity and a slight increase in total lipid impurities on light exposure for PFS without secondary packaging. Full (b) (4) exposure to (b) (4) visible light resulted in substantial change compared to the corresponding dark control at 25°C. The change in DP attributes on light exposure based on (b) (4) guidelines demonstrates that the product requires protection from light. Hence, a “Protect from Light” precautionary statement will be included on the DP label.

(b) (4)

(b) (4)

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The firm commits to placing a minimum of (b) (4) stability (b) (4). If a variant change is made to the DP, one DP lot for the new variant will be placed on stability. The stability trend of the lots will continue to be monitored to verify that the trend is as expected. The stability protocols are provided in the tables below (as updated in amendment 78, submitted on 6.16.26).

LDP Stability Protocol (2°C to 8°C)

Test Method	Initial	Time Point (month)			
		3	6	9	12
Appearance by Visual Inspection	X	X	X	X	X
(b) (4)	X	X	X	X	X
mRNA Purity by (b) (4)	X	X	X	X	X
Product-Related Impurities by (b) (4)	X	X	X	X	X
(b) (4)	X	X	X	X	X
(b) (4)	X	X	X	X	X
(b) (4)	X	-		-	X
(b) (4)	X	-		-	X
Total RNA Content by (b) (4)	X	-		-	X
Lipid Content and Lipid Impurities by (b) (4)	X	X	X	X	X
Bacterial Endotoxins by (b) (4)	X	-	-	-	X
(b) (4)	X	-	-	-	X
(b) (4)	X	-	-	-	X
(b) (4)	X	-	-	-	X
Container Closure Integrity by (b) (4)	X	-	-	-	X
Sterility by (b) (4)	X	-	-	-	-
(b) (4)	X	X	X	X	X

Abbreviations: (b) (4)

per stability protocol; - = not required per stability protocol

X = required

LDP Stability Protocol (23°C to (b) (4) °C) after 12 Months at (2°C to 8°C)

Test Method	Time Point (hours)	
	Initial ^(a)	12
Appearance by Visual Inspection	X	X
(b) (4)	X	X
mRNA Purity by (b) (4)	X	X
Product-Related Impurities by (b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
Total RNA Content by (b) (4)	X	X
Lipid Content and Lipid Impurities by (b) (4)	X	X
Bacterial Endotoxins by (b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
Container Closure Integrity by (b) (4)	X	X
Sterility by (b) (4)	-	X
(b) (4)	X	X

Abbreviations: (b) (4)

X = required per stability protocol; - = not required per stability protocol

^a Initial time point of the 23 °C to (b) (4) °C condition corresponds with the 12-month timepoint of 2°C to 8°C.

3.2.P.8.3 Stability data

The stability data for representative DP containing seasonal influenza LNPs manufactured with LNP-102 process (referred to as seasonal influenza LNP-102 lots, (b) (4) lots), PPQ, commercial scale, PSB and clinical lots for mRNA-1010 are summarized in the table below. Additional stability data for development/PSB DP lots of mRNA-1010 are provided. (b) (4) lots are described above, 3.2.P.8.1. Stability summary.

mRNA-1010 PPQ and Commercial Scale Lots (LNP-100 and LNP-102 lots)

DP ID	Moderna Lot # (CMO Lot #)	Lot Type	Manufacturer (DP Fill Line)	DOM	Fill Volume (mL)	Container Closure	Conditions		Data Available (M)
							Temperature	Duration (M)	
(b) (4)	(b) (4)	PPQ	(b) (4)	(b) (4)	(b) (4)	COC PFS	(b) (4)	12	3
							(b) (4)	12	3
							2°C to 8°C	12	3

(b) (4)	PPQ	(b) (4)	COC PFS	23°C to (b) (4) C	(b) (4)	(b) (4)	
				(b) (4)	12	3	
				(b) (4)	12	3	
				2°C to 8°C	12	3	
	PPQ		COC PFS	23°C to (b) (4) C	(b) (4)	(b) (4)	
				(b) (4)	12	3	
				(b) (4)	12	3	
				2°C to 8°C	12	3	
	Commercial Scale		COC PFS	23°C to (b) (4) C	(b) (4)	(b) (4)	
				(b) (4)	12	1	
				(b) (4)	12	1	
				2°C to 8°C	12	1	
						23°C to (b) (4) C	(b) (4)

Abbreviations: COC = cyclic olefin copolymer; DOM = date of manufacture; LDP = labelled drug product; M = month; PFS = cyclic olefin copolymer pre-filled syringe; PPQ = process performance qualification

mRNA-1010 Commercial Scale/PSB Lots (LNP-100 lots)

DP ID	Moderna Lot # (CMO Lot #)	Lot Type	Manufacturer (DP Fill Line)	DOM	Fill Volume (mL)	Container Closure	Conditions		Data Available (M)
							Temperature	Duration (M)	
(b) (4)	(b) (4)	Commercial Scale LNP-100 PSB	(b) (4)	(b) (4)		COC PFS	(b) (4)	12	12
							2°C to 8°C	12	12
							23°C to (b) (4) C	(b) (4)	(b) (4)
		Commercial Scale LNP-100 PSB			COC PFS	(b) (4)	12	12	
						2°C to 8°C	12	12	
						23°C to (b) (4) C	(b) (4)	(b) (4)	
		Commercial Scale LNP-100 PSB			COC PFS	(b) (4)	12	12	
						2°C to 8°C	12	12	
						23°C to (b) (4) C	(b) (4)	(b) (4)	
		Commercial Scale LNP-100 PSB			COC PFS	2°C to 8°C	6	6	
						2°C to 8°C + 23°C to (b) (4) C	(b) (4)		
						2°C to 8°C + 23°C to (b) (4) C			
						2°C to 8°C + 23°C to (b) (4) C			
						2°C to 8°C + 23°C to (b) (4) C			
		Commercial Scale LNP-100 PSB			COC PFS	2°C to 8°C	6 M	6 M	
						2°C to 8°C + 23°C to (b) (4) C	(b) (4)		
						2°C to 8°C + 23°C to (b) (4) C			
						2°C to 8°C + 23°C to (b) (4) C			
						2°C to 8°C + 23°C to (b) (4) C			
		Commercial Scale			COC PFS	Conditions		Data	
						Temperature	Duration (M)	Available (M)	

(b) (4)	LNP-100 PSB		(b) (4)		2°C to 8°C + 23°C to (b) (4) C	(b) (4)	
					2°C to 8°C + 23°C to (b) (4) C		
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The tables below show stability data for one representative seasonal influenza LNP-102 Lot used for shelf-life assessment of mRNA-1010 DP.

(b) (4)

(b) (4)

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

(b) (4)

Regarding stability data for storage at 2°C to 8°C followed by storage at 23°C to (b) (4) °C, an end-to-end stability study consisting of storage at 2°C to 8°C for 12 months followed by a storage at 23°C to (b) (4) °C for 12 hours will be conducted to support the proposed DP shelf life. The firm committed to provide the result of this study no later than October 2027.

Overall Reviewer's Assessment of Section 3.2.P.8

The shelf-life analysis is based on stability data from representative DP lots containing (b) (4). These stability data (obtained at different storage temperatures) support the proposed shelf life. One DP lot will be placed on stability (b) (4). An end-to-end stability study consisting of storage at 2°C to 8°C for 12 months followed by storage at 23°C to (b) (4) °C for 12 hours will be conducted to support the proposed DP shelf life.

In response to IR#35 (amendment 57), the firm provides all available stability data for mRNA-1010 DP lots manufactured using LNP-102 inputs. mRNA-1010 DP lots manufactured with LNP-102 include (b) (4) development lots (b) (4) and (b) (4) commercial scale lot (b) (4). Up to nine months stability data at 4°C are provided. The firm's

analyzed: a. mRNA-1010 shelf-life using mRNA-1010 LNP-102 data; b. comparability between mRNA-1010 LNP-102 and (b) (4) degradation profiles; and c. Degradation assessment of (b) (4) between mRNA-1010 and (b) (4).

a. mRNA-1010 shelf-life assessment using the mRNA-1010 LNP-102 data. The estimated degradation rates at 2°C to 8°C and 23°C to (b) (4) were calculated (and provided). The estimated (b) (4)-based EoSL band-limit of each attribute are shown in table below.

Predicted mean and estimated (b) (4)-based EoSL band-limit(s)

Attribute	Release Acceptance Criteria as Starting Value	Predicted Mean at Expiry	Lower 95% CL at Expiry ^a	Upper 95% CL at Expiry ^a	Stability Acceptance Criteria	CL Falls within EOSL Limit at Proposed Expiry? (Y/N)
mRNA Purity (%)	(b) (4)					
(b) (4)						
Total Lipid Impurities (%)	(b) (4)					

Note: in amendment 98, the firm tightening of the mRNA Purity EoSL specification from (b) (4)

The statistical analysis supports the proposed shelf life for mRNA-1010 LNP-102 DP.

b. Comparability between mRNA-1010 LNP-102 and (b) (4) degradation profiles. Results of equivalence testing at conditions 23°C to (b) (4) °C and 2°C to 8°C are provided. Comparisons of degradation and a graphical depiction of the equivalence results for each attribute (23°C to (b) (4) °C and 2°C to 8°C) are provided. Selected examples are shown in the figures below.

(b) (4)

(b) (4)

The degradation profile comparability assessment demonstrated equivalent results for all except some attributes. The firm provides an explanation for these exceptions which is acceptable. The available (b) (4) DP data are considered representative of the mRNA-1010 DP data.

c. (b) (4) and Composite (b) (4) Assessment Across mRNA-1010 and (b) (4). The firm compared (b) (4) degradation rates of mRNA-1010 vs (b) (4) (LNP-100; (b) (4) data is not available for the (b) (4) LNP-102 DP lots used to originally establish the shelf life), and composite (b) (4) degradation for the (b) (4) DP and mRNA-1010 LNP-102 DP. The estimated (b) (4) degradation rates and the corresponding 95% CI were calculated and are provided. The results indicate highly consistent degradation behavior across the evaluated influenza strains of (b) (4) and composite (b) (4), providing supportive evidence that degradation behavior is comparable across the three influenza strains and between mRNA-1010 and (b) (4). Given a) these supporting data; b) a correlation between RNA purity and (b) (4) c) the variability of the (b) (4) test; and d) the lack of a clear minimum (b) (4) that correlate with clinical immunogenicity, the (b) (4) test was not included in the shelf-life assessment of the DP.

In conclusion, the use of (b) (4) stability data is acceptable based on the demonstrated comparability of degradation profiles between mRNA-1010 and (b) (4) across the three influenza strains. In addition, the analysis of all available mRNA-1010 LNP-102 lots provides direct mRNA-1010-specific stability evidence that further supports the proposed shelf life.

JUSTIFICATION OF MINIMUM EDD

This section describes the minimum EDD that will result in an immune response comparable to the immune response observed in pivotal clinical trials (original submission, amendments 25, 44, 70, 79, and 98).

The firm proposes an influenza strain-specific EDD of (b) (4) as a clinically supported minimum EDD. The proposed lower bound is supported by the following clinical studies that used EDDs from (b) (4) :

Summary of Clinical Studies Supporting mRNA-1010 EDD Assessment

Program	Clinical Study	Total Dose (µg)	Dose per Influenza Strain (µg)	EDD per Influenza Strain (µg)	Role
mRNA-1010	mRNA-1010-P304	37.5	12.5	(b) (4)	Product-specific CTM lots used to demonstrate clinical efficacy
mRNA-1010	CRID-004	(b) (4)	(b) (4)	(b) (4)	Product-specific assessment of lower EDD achieved through lower dose
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Direct comparison of mRNA-1010 CTM from mRNA-1010-P304 with (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Supportive pivotal influenza-component anchor
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Supportive lot-comparability bridge; includes lowest EDD evaluated in clinical supportive bridging data

Study mRNA-1010-P304: the CTM lots used to demonstrate clinical efficacy had strain specific EDD values ranging from (b) (4) per strain.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

CRID-004: this study evaluated mRNA-1010 (b) (4)

. The mRNA-1010 DP used in CRID-004 was manufactured using RNA produced with the intended commercial sequence design and process, including the RNA-101 process, (b) (4) identical to those in the proposed commercial material, and incorporation of the two influenza B strain amino acid substitutions. In this study, Day 29 HAI GMTs following the (b) (4) dose were robust across the evaluated influenza strains with similar GMTs and overlapping 95% CIs relative to those following the 50 µg dose (see table below).

mRNA-1010 Day 29 HAI Responses in CRID-004

Strain	mRNA-1010 25 µg GMT (95% CI) N=28	mRNA-1010 50 µg GMT (95% CI) N=56	mRNA-1010 25 µg vs. mRNA-1010 50 µg GMR (95% CI)
A/H1N1	334.3 (237.1, 471.3)	365.5 (286.5, 466.4)	0.91 (0.60, 1.39)
A/H3N2	221.9 (159.3, 309.2)	220.6 (174.6, 278.7)	1.01 (0.67, 1.51)

B/Victoria	159.7 (122.8, 207.8)	190.7 (158.2, 229.9)	0.84 (0.61, 1.16)
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An ANCOVA model was fit for each strain, with (b) (4) Day 29 HAI titer as the dependent variable, vaccine group and receipt of 2022-2023 influenza vaccine as categorical variables, and (b) (4) baseline HAI titer as a covariate. GMTs and GMRs and corresponding 95% CIs were estimated (b) (4).

Reviewer's comments

1) Given the results from the clinical trials mentioned above, I consider that the firm provided sufficient data to support that an EDD of (b) (4) per influenza strain is as immunogenic as EDD of (b) (4) per influenza strain (the EDD used in the pivotal trial mRNA-1010-P304). One point to consider is that study (b) (4) showed that (b) (4) at EDD = (b) (4) induced lower HAI (and SCR) than the HAI induced by mRNA-1010 (including lower GMR and lower SCR) in study mRNA-1010-P304 (EDD = (b) (4)). However, I consider that given that these were two different studies, it is expected to obtain different GMT and different GMRs. Of note, studies (b) (4) and CRID cited above evaluated different EDDs in the same study. Therefore, I don't think this issue should preclude the above conclusion. Another point to consider is that all the studies mentioned above evaluated people <65 yoa, including people less than 50. Therefore, these studies show that mRNA-1010 at lower EDD is as immunogenic as at EDD = (b) (4) in people <65 yoa. There is no HAI data at lower EDD for people >65 yoa.

2) While the firm states in amendment 70 that the proposed EoSL specification is "equivalent to (b) (4) per strain", during the late cycle meeting the firm acknowledged that this EoSL is based on a lot released at the targeted RNA content (0.1 mg/mL, which I think about it as 100% for my calculations below) and targeted (b) (4). The firm also acknowledged that lots released at the minimum allowed release specifications for RNA content (b) (4) (and given the minimum EoSL spec for RNA Purity of (b) (4) at the time of this discussion), could result in an EoSL EDD of (b) (4) per strain (b) (4). This value is below the clinically supported minimum EDD. The firm stated that the probability of releasing a lot at these minimum specs is negligible, and therefore such EDD are not expected to be achieved. This is supported by the Monte Carlo simulation, a summary of which is included in the submission. Please see the point below.

3) In relation to point 2 above, the firm states that the probability of releasing a lot at the minimum release spec of RNA content (b) (4) is negligible. However, according to the data in section 3.2.P.5.6 Justification of Specifications, a significant proportion of mRNA-1010 lots are released at RNA content of (b) (4) (and even at (b) (4) for mRNA-1283 lots, figure 4) and a significant amount of mRNA-1010 lots are released at (b) (4) (for one of its components). A lot released at (b) (4) of RNA content (b) (4) with an EoSL specification for Purity of (b) (4), is expected to have an EoSL EDD of (b) (4), below the clinically supported minimum EDD. In addition, the (b) (6) reviewer concluded that the Monte Carlo simulation model is inadequate to support that DP manufactured within established controls will maintain an EDD of (b) (4) per strain at EoSL.

Therefore, to assure the minimum EDD of (b) (4) per strain at EoSL, based on a targeted RNA content of 12.5 ug/strain and an EoSL Purity specification of (b) (4) (the firm tightened the EoSL RNA Purity specification from (b) (4) which is supported by the stability data), the following DP release specification will be included:

(b) (4)

Other quality attributes

(b) (4)

(b) (4)

(b) (4)

Reviewer's comments

I consider that DP lots with lower Lipid Content or lower (b) (4) could have lower amount of functional LNPs resulting in decreased immune responses. However, the amount of intact LNP is not considered by the EDD. Indirect parameters, included in the release specifications of DP, that assess amount of intact LNP are (b) (4), Lipid Content, and (b) (4) is not included in the release specifications. Regarding Lipid Content, while the stability data shows that Lipid Content is stable at the refrigerated storage conditions, a lower Lipid Content at release could mean a lower content of intact LNP. The firm does not provide data for lots bearing Lipid Content

close to the release specification. Regarding (b) (4), the firm provides a clinical study and concludes that (b) (4) levels within the specification range (b) (4) do not impact immunogenicity. While in this study the GMT ratios were acceptable for lots with (b) (4) these data may not reflect the performance of lots at the EoSL with EDD close to the lower limit, and (b) (4) at the lower limit. In addition, as expected, the data showed a visual correlation between (b) (4) levels and immune responses. Also, data submitted by the firm show that a decrease of (b) (4) and an increase in (b) (4) resulted in a decrease in (b) (4) which could impact the functionality of the DP. Finally, an analysis conducted by the firm using non-clinical data revealed that several product quality attributes, apart from EDD, contribute to observed immunogenicity outcomes (among these, (b) (4) were found to be statistically significant predictors of residual variance in immune responses). Therefore, I consider that, ideally, the immunogenicity of lots bearing the lower limit of (b) (4) and Lipid Content at release should be considered in the determination of the end of shelf life.

Given that:

- a) the firm proposes to tighten (b) (4) release and stability acceptance criteria from (b) (4)
 - b) the lots used in the critical clinical trials bear a (b) (4) of approx. (b) (4) proposed release specification)
 - c) the manufacturing process, in particular the LNP-102 process, produces batches with consistent LNP (b) (4) and high (b) (4)
 - d) data shows that (b) (4) and LNP (b) (4) are stable at the refrigerated storage conditions
- It is expected that the commercial lots will be comparable to the pivotal clinical trial lots with regard to (b) (4) and LNP (b) (4). Therefore, it seems to me that, although not ideal, the firm proposal to not considering (b) (4) and LNP (b) (4) in determination of EoSL is acceptable.

STRAIN UPDATE (2026-2027 influenza season)

Given the natural variability of the RNA-based influenza viruses (antigenic drift and antigenic shift), the strain composition of the influenza vaccine may need to be updated for each influenza season. The WHO and other institutions monitor the circulating influenza strains and provide strain selection recommendations for each influenza season. In accordance with the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendation for the NH 2026–2027 U.S. influenza season for the formulation of cell- or recombinant-based influenza vaccines, the firm submitted an annual strain update in amendments 18, 59, 88, and 93 to the BLA.

The recommended strains are as follows:

- A/H1N1: A/Missouri/11/2025 (D.3.1)
- A/H3N2: A/Darwin/1415/2025 (K)
- B/Victoria lineage: B/Pennsylvania/14/2025 (C.3.1)

The firm include the following strains in the mRNA-1010 vaccine:

- A/H1N1: A/Missouri/11/2025 (H1N1)
- A/H3N2: A/Michigan/105/2025 (an A/Darwin/1415/2025 (H3N2)-like virus)
- B/Victoria lineage: B/Pennsylvania/19/2025 (a B/Pennsylvania/14/2025-like virus)

To ensure that the new strains are as immunogenic as the strains used to demonstrate efficacy and immunogenicity in the pivotal clinical trials, traditional vaccines (as protein-based vaccines) are tested by (b) (4) assay that uses specific sera. For mRNA-1010, a comprehensive analytical assessment will be conducted and is included in the BLA submission. See below, Introduction of Annual Seasonal Influenza Strain(s) Update for mRNA-1010 under Section 3.2.R, for details.

(b) (4)

(b) (4)

DRUG PRODUCT

Comparability DP

An initial assessment of (b) (4) compared to previous strains in the (b) (4) (lot (b) (4)) has been performed using the (b) (4) mRNA-1010 DP composition that includes the new A/H3N2 and A/H1N1 strains (lot (b) (4)). Additionally, a non-clinical immunogenicity study in mice was performed to demonstrate immunogenicity of the new A/H3N2 and A/H1N1 strains (see below, Section 4). A comparison of the compositions of the mRNA-1010 DPs is shown in Table 1.

Comparison of DP used in the Initial (b) (4) Assessment and the NH 26/27 Season

(b) (4)

(b) (4)

(b) (4)

Validation of Analytical Procedures DP

Analytical reports for RNA identity and (b) (4) are provided and show that the test perform appropriately. As the availability of the (b) (4) did not allow for the generation of the (b) (4) data, this report will be submitted in a follow-up amendment by July 15, 2026.

Batch Analyses DP

Batch analysis data for (b) (4), containing (b) (4) are provided and show that all results met the acceptance criteria.

Reference Standards or Materials DP

The (b) (4) DP PRM, lot (b) (4), is used for analysis of commercial mRNA-1010 DP lots with the Northern Hemisphere 2026/2027 strain composition and LNP-102 inputs. The (b) (4) of the (b) (4) DP PRM was demonstrated to be consistent with the previous PRM through an (b) (4) characterization assessment using (b) (4) (data is provided). Additionally, non-clinical immunogenicity studies were performed and showed that the mRNA-1010 DP lot produced with the (b) (4) composition induced binding and functional HAI antibody responses against all encoded influenza HA antigens in (b) (4) mice (see below, PHARMACOLOGY STUDIES).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

For new seasonal PRMs derived from new strains, predefined acceptance criteria for (b) (4) comparability are established for the (b) (4) assay relative to the previous PRM. The firm proposes that equivalence is concluded when the 90% confidence interval for the geometric mean ratio (new seasonal PRM vs previous PRM) falls within a predefined (b) (4) acceptance range. The proposed acceptance criteria range is supported by:

- Clinical experience: clinical immunogenicity data in adults ≥ 65 years in Study P303C and P304 provide evidence that the seasonal-composition matched DP (b) (4), respectively) generates robust and consistent HAI responses. These clinical data suggest that variability observed in the (b) (4) analysis does not result in meaningful changes in clinical immunogenicity (see the table below for DP composition and the figure below the (b) (4) results).

HA Strains Represented in Seasonal DP Compositions

Season	DP Composition	H3N2 Strain	H1N1 Strain	B/Victoria Strain
NH24/25	(b) (4)	A/Massachusetts/18/2022	A/Wisconsin/67/2022	B/Austria/1359417/2021
NH23/24		A/Darwin/6/2021	A/Wisconsin/67/2022	B/Austria/1359417/2021
SH26		A/Sydney/1359/2024	A/Missouri/11/2025	B/Austria/1359417/2021
Preliminary NH26/27		A/Michigan/105/2025 (same amino acid sequence as A/Darwin/1415/2026)	A/Missouri/11/2025	B/Austria/1359417/2021
NH26/27		A/Michigan/105/2025 (same amino acid sequence as A/Darwin/1415/2026)	A/Missouri/11/2025	B/Pennsylvania/19/2025 (same amino acid sequence as B/Pennsylvania/14/2025)

(b) (4)

- Lot-to-lot variability for DP and assay variability. Assay variability observed across multiple (b) (4), dose levels, and independent analytical runs remained within the predefined (b) (4) acceptance range in the dataset.

Collectively, these data demonstrate that across strains and DP compositions with demonstrated clinical performance, the results remain within the proposed (b) (4) range supporting its suitability as predefined acceptance criterion. The firm will continuously assess these acceptance criteria against experience with new DP compositions from upcoming seasons.

PHARMACOLOGY STUDIES

In support of the 2026/2027 Annual Strain Update, 3 pharmacology studies were performed:

1. MOD-7776-1010 using 2 of the 3 recommended strains for the NH2026/2027 flu season in combination with the B/Austria/1359417/2021 strain (previous year strain)(amendment 18);
2. MOD-7816-1010 using the 3 recommended strains for the NH2026/2027 flu season (amendment 59);
3. MOD-7875-1010 using the 3 recommended strains for the NH2026/2027 flu season and comparing immune responses to animals immunized in the same study with the NH2024/2025 strains (amendment 111).

Results from studies MOD-7776-1010 and MOD-7816-1010 show that mRNA-1010 induced HA IgG binding antibody titers as well as HAI antibody titers against the 3 influenza strains encoded by the vaccine. In study MOD-7816-1010, the HAI titers elicited by B/Pennsylvania/14/2025 at all doses were lower than the titers observed with B/Austria/1359417/2021 strain. Therefore, it is possible that the immunogenicity of B/Pennsylvania/14/2025 in mice in the Moderna vaccine is lower than other B Victoria strains tested. However, it should be noted that: a. different viruses were used in the HAI assays; b. in all studies, the acceptance criterion proposed by the firm (b) (4) was met (including when using B/Pennsylvania/14/2025 at the lower dose); c. studies using B/Austria show variable titers; d. no head-to-head comparisons were done in the same study (as using B/Pennsylvania/14/2025 and B/Austria in the same study). Therefore, it seems to me that no robust conclusions could be taken about the relative immunogenicity of B/Pennsylvania/14/2025. Importantly, B/Pennsylvania/14/2025 showed to be immunogenic. Also, the firm cites immunogenicity data published by the Crick Institute (WHO-collaborating center for influenza) that shows a wide range of HAI titers (particularly for H3N2 and influenza B viruses) and data for B/Pennsylvania/14/2025 that shows a low homologous HAI titer of only (b) (4) (compared to some other influenza B strains at exceeding titers of (b) (4)). The firm concludes that the data are pointing to the variability being driven by the virus strain utilized in the assay rather than differences in immunogenicity of the vaccine. This is further supported by the in vitro data (b) (4) generated for the B/Pennsylvania/19/2025 strain, which show expression levels in line with prior season's B HAs.

In study MOD-7875-1010, the immunogenicity of mRNA-1010 was evaluated in (b) (4) mice using the 3 strains to be used for the Annual Strain Update (NH2026/2027) in comparison to the 3 strains from the NH2024/2025 season (strains used in the mRNA-1010 P304 clinical efficacy study). Results include a. HAI elicited by mRNA-1010 NH26/27 vaccine composition against homologous NH26/27 (3 levels, D21 and D36); b. HAI elicited by mRNA-1010 NH24/25 vaccine composition against homologous NH24/25 (3 levels, D21 and D36); c. HAI elicited by mRNA-1010 NH24/25 vaccine composition against heterologous NH26/27 (3 levels, only D36). HAI elicited by mRNA-1010 NH26/27 vaccine composition against heterologous NH24/25 is not provided. Results for the B HA indicate that (see figures below):

- a. the 26/27 vaccine is less immunogenic than 24/25 vaccine against the respective homologous B virus (figure 1 vs 2, right panel)
- b. the 26/27 vaccine is similar or just above placebo for the first dose (D21) at the three dose levels and even for the second dose (D36) at the lower dose levels (titers are 27 vs 11)
- c. the 26/27 vaccine is more immunogenic (3x) than the 24/25 vaccine against the 26/27 B virus (figure 1 vs 3, right panel, higher and middle dose levels).

Results for H1N1 and H3N2 indicate that:

- d. the 26/27 vaccine is much more immunogenic than the 24/25 vaccine against the respective homologous H3N2 virus (figure 1 vs 2, middle panel)
- e. the 26/27 vaccine is less immunogenic than the 24/25 vaccine against the respective homologous H1N1 virus (figure 1 vs 2, left panel)
- f. of note, the 26/27 vaccine is slightly less immunogenic than the 24/25 vaccine against the 26/27 H1N1 virus (figure 1 vs 3, left panel, D36).

1) HAI elicited by mRNA-1010 NH26/27 vaccine composition against NH26/27 homologous HAs

(b) (4)

(b) (4)

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

I did not review this section. Please refer to the memo from (b) (6) reviewer.

3.2.A.2 Adventitious Agents Safety Evaluation

There are no materials of animal or human origin used in the manufacture of the RNA, (b) (4), LNP or DP.

3.2.A.3 Novel Excipients

Section 3.2.A.3 is not included in the BLA. There are no novel excipients in the DP. The information for the two custom (b) (4) lipids SM-102 and PEG2000-DMG was previously reviewed under BLA 125835 and found to be acceptable.

Overall Reviewer's Assessment of Section 3.2.A

The information provided is acceptable.

3.2.R COMPARABILITY PROTOCOLS

3.2.R.1. Comparability Protocol for Implementation of ModernaTX (b) (4) as an Alternate Manufacturer for mRNA-1010 (b) (4)

This protocol outlines the qualification strategy to introduce ModernaTX, (b) (4) as an alternate manufacturer for (b) (4). Manufacturing and testing will be performed in accordance with cGMPs at the ModernaTX (b) (4) facility. Raw materials will be supplied by approved, qualified suppliers and are released prior to use per cGMP guidelines. All raw materials are confirmed to conform with Certificates of Analysis or Certificates of Compliance, which includes verification of bovine spongiform encephalopathy/transmissible spongiform encephalopathy certificates. The use of aligned (b) (4) specifications ensures an appropriate level of quality for materials from both manufacturers. Qualification of an alternate manufacturer for mRNA-1010 (b) (4) will include:

- (b) (4)

The data will be submitted as a PAS as requested by (b) (6)

3.2.R.2 Introduction of Annual Seasonal Influenza Strain(s) Update for mRNA-1010

To support the introduction of the updated strain(s), process verification (PV) will be conducted for mRNA-1010 RNA and LNP at the respective registered manufacturing and testing sites. A comprehensive analytical comparability assessment will be conducted across all applicable materials. The RNA and LNP manufacturing processes will remain unchanged, except for the substitution of starting materials: the use of a (b) (4) specific for the updated strain in the RNA process and the use of the corresponding RNA input in the LNP process.

One representative DP lot will be executed with the LNP(s) containing the updated strain in combination with the LNP (s) containing unchanged strain(s) from the previous season. This DP lot will be manufactured with the representative DP manufacturing process. No changes are proposed to RNA, LNP and DP release, extended characterization and stability tests, or associated acceptance criteria as registered in the filing. A comparability assessment will be performed to ensure that LNP quality attributes of materials produced in the PV run with the updated strains are consistent with those from PPQ runs and those from lots evaluated in mRNA-1010 clinical studies (b) (4) will be manufactured, and all process performance test results from this PV run are expected to meet the predefined acceptance criteria (including CQA, CPP, CIPC, IPC, and PP). The comparability limits for sequence-dependent release attributes are based on a one-sided 95% confidence/99% coverage tolerance intervals. For (b) (4) agnostic attributes, comparability criteria were tightened compared to release specifications, using RNA comparability criteria of Spikevax. In addition to the CMC package, non-clinical immunogenicity studies in mice will be conducted to confirm that updated strains elicit an immune response. The inclusion of data from

non-clinical studies for each updated strain will be reassessed once sufficient data from multiple strains are available. The firm was informed through an IR that the strain update data generated according to the CP for the Introduction of Annual Seasonal Influenza Strain (s) Update should be submitted under an Annual Strain Change supplement as a PAS. The firm acknowledged.

Other eCTD Modules

MODULE 1

1. ENVIRONMENTAL ASSESSMENT

The firm claims a categorical exclusion from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement which I find to be acceptable.

MODULES 4 AND 5

4. NON-CLINICAL STUDIES

During clinical development, several modifications were introduced to mRNA-1010 including the following: update of the ORF sequences for RNAs corresponding to influenza B strains to encode two point mutations; update of the untranslated RNA regions for all influenza A and B strains (evaluated in a mouse immunogenicity study and pivotal GLP repeat-dose toxicity study, Report MOD-5814-1010 and 20457846 Amendment 1, respectively); removal of the B/Yamagata strain for the trivalent (TIV) composition per WHO recommendation (evaluated in two non-clinical pharmacology studies, MOD-7512-1010-TIV and MOD-7488-1010-TIV); and a change in the LNP manufacturing process (LNP-102 process), evaluated in MOD-7488-1010-TIV. Overall, non-clinical data from immunogenicity, efficacy, and toxicity studies with mRNA-1010 support the licensure application of mRNA-1010.

Pharmacology studies

The table below summarizes the non-clinical pharmacology program for mRNA-1010.

Summary of Non-clinical Pharmacology Program Supporting mRNA-1010

Study Type	Test Article ^a and Dose (µg) ^b	Species, Strain	Method of Administration; Immunization Schedule	GLP	Report Number
Primary Pharmacology					
Evaluation of <i>in vivo</i> immunogenicity and protective efficacy of mRNA-1010 in mice	mRNA-1010-SH21 ^{c,d} (10 µg) FLUAD (6 µg)	(b) (4) mice	IM; Prime only (Day 0) Intranasal challenge with 10 ⁴ TCID ₅₀ H3N2 A/Hong Kong/1/1968 or 10 ⁵ TCID ₅₀ of H1N1pdm09 A/Netherlands/602/2009 virus on Day 21	No	2810880

Evaluation of <i>in vivo</i> immunogenicity and protective efficacy of mRNA-1010 in ferrets	mRNA-1010-SH21 ^{c,d} (100 µg) FLUAD (60 µg)	<i>Mustela putorius furo</i> ferrets	IM; Prime/Boost (3-week interval) Intranasal (0.3 mL, 10 ⁵ TCID ₅₀) and intrathecal (3.0 mL, 10 ⁵ TCID ₅₀) challenge with H1N1pdm09 A/Victoria/2570/2019 virus on Day 42	No	2810881
Evaluation of the impact of (b) (4) on the immunogenicity of mRNA-1010 in mice	mRNA-1010 NH21/22 or mRNA-1010 NH21/22 ^{(b) (4) e} (0.5, 1, 2, or 4 µg)	(b) (4) mice	IM; Prime only	No	MOD-4731
Evaluation of <i>in vivo</i> immunogenicity of different versions of mRNA-1010 in (b) (4) mice	mRNA-1010 ^f mRNA-1010.6 ^f mRNA-1010.4 ^f (2 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-5814-1010
Evaluation of <i>in vivo</i> immunogenicity (antibody and T cell responses) of a trivalent mRNA vaccine against influenza virus	mRNA-1010 TIV ^g (1.5 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-7512-1010-TIV
Evaluation of <i>in vivo</i> immunogenicity of a trivalent mRNA vaccine against influenza virus comparing 2 LNP manufacturing processes	mRNA-1010 TIV LNP-100 ^{g, h} mRNA-1010 TIV LNP-102 ^{g, h} (0.5, 1, or 2 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-7488-1010-TIV
Evaluation of <i>in vivo</i> immunogenicity of mRNA-1010 encoding for hemagglutinin of seasonal influenza viruses ⁱ	mRNA-1010 (0.045, 0.19, or 0.75 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-7776-1010
Evaluation of <i>in vivo</i> immunogenicity of mRNA-1010 encoding for hemagglutinin of NH26/27 seasonal influenza viruses ^j	mRNA-1010 (0.045, 0.19, or 0.75 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-7816-1010
Evaluation of <i>in vivo</i> immunogenicity of mRNA-1010 encoding hemagglutinin of NH26/27 or NH24/25 seasonal influenza viruses ^k	mRNA-1010 (0.045, 0.19, or 0.75 µg)	(b) (4) mice	IM; Prime/Boost (3-week interval)	No	MOD-7875-1010

Abbreviations: DP = drug product; FLUAD = adjuvanted influenza vaccine; GLP = Good Laboratory Practice; H1N1 = influenza A virus; H3N2 = influenza A virus subtype H3N2; HA = hemagglutinin; (b) (4); IM = intramuscular; LNP = lipid nanoparticle; mRNA = messenger RNA; NCS = non-coding sequences; NH = Northern Hemisphere; RNA = ribonucleic acid; SH = Southern Hemisphere; TCID₅₀=median tissue culture infectious dose; TIV = trivalent vaccine; (b) (4); WHO = World Health Organization.

a. See Table 1 in the submission for a detailed description of the mRNA-1010 DPs used in the nonclinical pharmacology studies.

b. Doses refer to the total dose of RNA.

c. Multiple test articles were assessed in this study. Only data pertaining to mRNA-1010 are discussed in this dossier.

d. mRNA-1010-SH21 is referred to as “mRNA-1010” in Report 2810880 and Report 2810881.

e. The mRNA-1010 NH21/22^{(b) (4)} is called mRNA-1010 NH21/22^{(b) (4)} in the nonclinical report. (b) (4) refers to (b) (4)

- f. mRNA-1010 contained the same (b) (4) and similar RNA manufacturing process relative to those used to support early mRNA-1010 clinical studies. mRNA-1010.6 contained updated (b) (4) and similar RNA manufacturing process relative to those used to support early mRNA-1010 clinical studies. mRNA-1010.4 contained updated (b) (4) (same as in mRNA-1010.6), and the RNA manufacturing process contained fewer unit operations than that described in mRNA-1010 and mRNA-1010.6 due to the introduction of co-transcriptional capping; mRNA-1010.4 is representative of the (b) (4) and RNA manufacturing process for the vaccine intended for licensure. The study evaluated versions of mRNA-1010 using (b) (4) material.
- g. mRNA-1010 TIV contained 3 RNAs encoding membrane-bound HA proteins of 3 different influenza strains recommended by the WHO for the NH24/25 season: A/Wisconsin/67/2022, A/Massachusetts/18/2022, and B/Austria/1359417/2021. The RNAs were combined at a 1:1:1 mass ratio.
- h. mRNA-1010 TIV DPs were manufactured using 2 different LNP manufacturing processes: LNP-100 and LNP-102. The LNP-100 and LNP-102 processes differed by a single change: the addition of (b) (4) step in the LNP-102 process. This process modification ensures the (b) (4) (Module 3).
- i. mRNA-1010 in this study contained 3 RNAs encoding membrane-bound HA proteins of 2 of the 3 influenza strains recommended by the WHO for the NH26/27 season: A/Missouri/11/2025 (H1N1), A/Michigan/105/2025 (A/Darwin/1415/2025-like H3N2) in combination with B/Austria/1359417/2021 strain (previous year strain). The RNAs were combined at a 1:1:1 mass ratio.
- j. mRNA-1010 in this study contained 3 RNAs encoding membrane-bound HA proteins of the 3 influenza strains recommended by the WHO for the NH26/27 season: A/Missouri/11/2025 (H1N1), A/Michigan/105/2025 (A/Darwin/1415/2025-like H3N2), and B/Pennsylvania/19/2025 strain (B/Pennsylvania/14/2025-like). The RNAs were combined at a 1:1:1 mass ratio.
- k. mRNA-1010 in this study contained 3 RNAs encoding membrane-bound HA proteins of the 3 influenza strains recommended by the WHO for the NH26/27 season: A/Missouri/11/2025 (H1N1), A/Michigan/105/2025 (A/Darwin/1415/2025-like H3N2) and B/Pennsylvania/19/2025 strain (B/Pennsylvania/14/2025-like) or all 3 influenza strains recommended by the WHO for the NH24/25 season: A/Wisconsin/67/2022, A/Massachusetts/18/2022, and B/Austria/1359417/2021. For both mRNA-1010 compositions, the RNAs were combined at a 1:1:1 mass ratio.

A summary of some of the pharmacology studies is provided below.

An efficacy study with QIV mRNA-1010 was conducted in female ferrets (Report 2810881). Ferrets were vaccinated with mRNA-1010 (100 µg) or FLUAD (15 µg/HA or 60 µg total) on a prime (Day 0)/boost (Day 21) schedule and challenged with an intranasal and intratracheal infection of H1N1pdm09 A/Victoria/2570/2019 virus on Day 42. The HAI antibody titers induced by mRNA-1010 were similar to those induced by FLUAD. The mRNA-1010-vaccinated ferrets exhibited lower detectable viral loads compared to the placebo group across different tissues, with complete protection of the lung. Compared to FLUAD, mRNA-1010 showed lower virus levels in the nose, throat, and nasal turbinate.

For characterization of the (b) (4) of RNAs, (b) (4). The immunogenicity of mRNA-1010 containing the unique (b) (4) was assessed in female (b) (4) mice following IM immunization with 0.5, 1, 2, or 4 µg of mRNA-1010 with or without the unique (b) (4) (Report MOD-4731). On Day 21, robust IgG antibody titers against HA were observed with and without the unique (b) (4).

A study was conducted to assess the immunogenicity of mRNA-1010 QIV with updated coding sequences for the influenza B HA antigens (containing 2 point substitutions) and updated (b) (4). Female (b) (4) mice were administered 2 µg/dose of mRNA-1010 IM on a prime/boost schedule on Days 1 and 22 (Report MOD-5814-1010). Immunization with the optimized mRNA-1010 vaccines induced IgG-binding and HAI antibodies against all four encoded antigens. The antibody titers were similar in magnitude to those induced by the original mRNA-1010 vaccine and therefore were not impacted by the updated (b) (4). The influenza B HA substitutions resulted in a small increase in binding antibody titer to B/Austria HA (B/Victoria-lineage) after Dose 1 but did not impact the response to B/Phuket HA (B/Yamagata-lineage). All versions of mRNA-1010 induced CD8+ and CD4+ Th1 T cell responses against the encoded influenza HA proteins.

The immunogenicity of mRNA-1010 TIV composition was evaluated comparing the LNP-100 versus LNP-102 manufacturing process. Female (b) (4) mice were administered IM with 0.5, 1, and 2 µg of mRNA-1010 LNP-100 or mRNA-1010 LNP-102 on a prime/boost schedule on Days 1 and 22 (Report MOD-7488-1010-TIV). A dose response was observed at Day 21 and Day 36 between the highest dose and the lowest dose, and titers were boosted at Day 36 compared to Day 21. Overall results indicated immunogenicity equivalence between

LNP-102 and LNP-100 manufacturing processes for all three influenza strains (NH24/25 season) at the 1 µg and 2 µg dose levels at both Day 21 and Day 36 timepoints, while results were more variable at the lowest dose of 0.5 µg, with the LNP-102 process inducing slightly higher antibody titers at that dose (see the figure below).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

In summary, results from pharmacology studies show that immunizations induced robust IgG binding and HAI antibodies, and CD4+ Th1 and CD8+ T cell responses against the encoded influenza virus HA proteins.

Pharmacokinetic (PK) studies

Non-clinical PK evaluations included *in vivo* distribution, persistence, and clearance of mRNAs, SM-102 lipid, and/or expressed proteins using other representative mRNA-LNP DPs formulated in the same 4 lipids as mRNA-1010. PK studies used in support of the licensure of mRNA-1010 are listed in the table below.

Summary of Non-clinical PK Program Supporting mRNA-1010

Type of Study	Test Article: Dose	Test System	Method of Admin.	GLP	Report Number
Distribution					
Single-dose biodistribution study of (b) (4) mRNA in SM-102/PEG2000-DMG	(b) (4) mRNA in SM-102/PEG2000-DMG-containing LNPs: 100 µg/dose ^a	(b) (4) rats	Single IM dose	No	2308-582 Amendment 1
Single- or repeat-dose biodistribution study of mRNA-1273	mRNA-1273: 78 µg/dose ^a	(b) (4) rats	Single- or repeat IM dose on Days 1 and 28	No	20456513 Amendment 1
Single-dose tissue distribution study of (b) (4)	(b) (4)	(b) (4) rats	Single IM dose	No	5002121 Amendment 2
Metabolism					
Identification and profiling of metabolites of SM-102 in	(b) (4) mRNA in SM-102-	Cryopreserved hepatocytes from	Incubation of SM-102-	No	NCS-BA-2022-010

rat, monkey, and human hepatocytes	containing LNPs: 10 µM SM-102	(b) (4) rats, (b) (4) monkey, and human	containing LNPs with rat, monkey, and human hepatocytes		
Metabolite profile and identification of SM-102 in rat plasma, urine, and bile following IV infusion of SM-102-containing LNPs to male (b) (4) rats	(b) (4) mRNA in SM-102-containing LNPs: 0.7 mg/kg/dose ^a	(b) (4) rats	Single 10- minute IV infusion	No	QV-0236-DA-RE-RPT-01
PEG2000-DMG in vitro metabolite profiling and identification	PEG2000-DMG: 122.5 µM ^b	Rat, monkey, and human serum	Incubation of PEG2000-DMG with rat, monkey, and human serum	No	NCS-BMA-2023-06
Excretion: Assessed in QV-0236-DA-RE-RPT-01 (see above)					

Abbreviations: Admin = administration; GLP = Good Laboratory Practice; IM = intramuscular; IV = intravenous; LNP = lipid nanoparticle; mRNA = messenger RNA; (b) (4) ; PEG2000-DMG = 1,2-dimyristoyl-racglycero-3-methylpolyoxyethylene glycol-2000; PK = pharmacokinetic; RNA = ribonucleic acid; SM-102 = heptadecan-9-yl8-((2-hydroxyethyl)(6- oxo-6-((undecyloxy) hexyl) amino) octanoate).

a. Dose refers to the total dose of RNA encapsulated in the administered LNP.

b. Calculated with average molecular weight of PEG2000-DMG, with (b) (4) .

Biodistribution studies

The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics and route of administration (as opposed to the mRNA cargo). Consequently, mRNAs are expected to distribute similarly when encapsulated by LNPs of the same composition and administered via the same route of administration. A summary of the distribution studies and the obtained results is presented below.

To support the development of mRNA-1010, 3 biodistribution studies in rats were conducted using mRNA-LNP DPs comprised of the same 4 lipids and generally similar lipid:mRNA ratios as mRNA-1010. The biodistribution and kinetics of SM-102 lipid, mRNA, and/or expressed protein(s) following a single IM administration were evaluated using (b) (4) mRNA encapsulated in SM-102/PEG2000-DMG-containing LNPs and (b) (4) . In another study using mRNA-1273, the biodistribution and kinetics of SM-102 lipid, mRNA, and/or expressed protein(s) was analyzed following a single or repeat-dose IM administration. Results from the biodistribution studies showed similarities in exposure tissue rank order and kinetics across mRNA-LNP DPs (highest concentrations of mRNA and SM-102 were observed at the injection site, spleen, and lymph nodes). Tissue distribution of mRNA and SM-102 lipid is similar following 1 or 2 administrations of mRNA-1273. While expressed (b) (4) protein in tissues was largely not quantifiable, expressed SARS-CoV-2 protein was generally higher in tissues than in serum, where lymph nodes, injection site, spleen, and/or liver had highest exposures. Exposures of expressed SARS-CoV-2 protein in brain, heart, and lung were generally undetectable. In a single-dose biodistribution study conducted using (b) (4) in male rats, all (b) (4) mRNA constructs contained within (b) (4) were detected in plasma and tissues, with the highest concentrations observed at the injection site, lymph nodes, and spleen. Only a small fraction of the administered dose reached distant tissues, and mRNA concentrations in most tissues became undetectable within 1 to 3 days, except at the injection site, lymph nodes, and spleen.

Metabolism and excretion studies

No exclusive non-clinical metabolism and excretion studies with mRNA-1010 were performed. The metabolism of SM-102 and PEG2000-DMG were evaluated using formulated mRNA-LNP DPs containing (b) (4) mRNA or as individual components. A summary of metabolism and excretion studies and the obtained results are provided below.

The metabolism of SM-102 and PEG-2000-DMG was evaluated *in vitro* in hepatocytes and serum from rat, monkey, and human. A study in rats using an SM-102-containing LNP DP encapsulating (b) (4) mRNA characterized the *in vivo* metabolism and excretion of SM-102. The IV route of administration was used in the *in vivo* metabolism study. The metabolism of SM-102 was evaluated *in vitro* and *in vivo*, and its excretion characteristics were evaluated *in vivo*. Results showed that SM-102 and PEG2000-DMG are efficiently and extensively metabolized. *In vivo* data showed that SM-102 and its metabolites are eliminated via both renal and hepatic routes. *In vitro* incubation of SM-102-containing LNPs with rat, (b) (4) monkey, and human hepatocytes yielded ester-hydrolyzed and β -oxidized metabolites with no human-specific metabolites detected. In rats, the primary circulating species after IV dosing of SM-102-containing LNPs was intact SM-102. Low molecular weight, hydrophilic metabolites were detected in relatively higher amounts (approximately 10-fold) in urine compared to plasma and bile. The data indicate that SM-102 is unlikely to accumulate upon repeat IM dosing. The *in vitro* metabolism of PEG2000-DMG was evaluated by spiking PEG2000-DMG into rat, (b) (4) monkey, and human serum which resulted in the formation of identical metabolites, namely PEG-glycerol and PEG-MMG isomers. The metabolism of PEG2000-DMG showed similar patterns in terms of rate and extent across all three species over a 24-hour time course. The increase in the PEG-glycerol metabolite was consistent among species, while the metabolism of PEG-MMG isomers was faster and more extensive in rats. No human-specific metabolites were found.

Overall Reviewer's Assessment of Relevant Sections of Module 4 (clinical pharmacology)

The information provided is acceptable. The non-clinical evaluation of this vaccine included studies in different animal models which demonstrated the vaccine to be safe and immunogenic. A study comparing the immunogenicity (binding antibodies) between DPs manufactured with LNP that were manufactured with the LNP-100 and LNP-102 processes was successfully conducted. Studies evaluating the immunogenicity (HAI and binding antibodies) of DP containing two or all three of the three updated influenza strains were also successfully conducted.

In amendment 44, the firm submitted additional non-clinical information for updated vaccine strains.

In vivo immunogenicity data from multiple seasonal mRNA-1010 DPs (see the table below) are presented and shows that a post-boost HAI GMT of $\geq 1:40$ at Day 36 was achieved in mice for all mRNA-1010 vaccine compositions tested (see figure below). In addition, robust IgG binding antibody titers were observed (data is provided, showing a similar pattern as the HAI data).

HA Strains Represented in Seasonal DP Compositions

Season	DP Composition	H3N2 Strain	H1N1 Strain	B/Victoria Strain
NH24/25	(b) (4)	A/Massachusetts/18/2022	A/Wisconsin/67/2022	B/Austria/1359417/2021
NH23/24		A/Darwin/6/2021	A/Wisconsin/67/2022	B/Austria/1359417/2021
SH26		A/Sydney/1359/2024	A/Missouri/11/2025	B/Austria/1359417/2021
Preliminary NH26/27		A/Michigan/105/2025 (same amino acid sequence as A/Darwin/1415/2026)	A/Missouri/11/2025	B/Austria/1359417/2021

NH26/27	(b) (4)	A/Michigan/105/2025 (same amino acid sequence as A/Darwin/1415/2026)	A/Missouri/11/2025	B/Pennsylvania/19/2025 (same amino acid sequence as B/Pennsylvania/14/2025)
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HAI Antibody Titers Following Immunization with mRNA-1010 of the NH24/25, SH26 or Preliminary NH26/27 Compositions

(b) (4)

Reviewer’s comments

The firm proposes achievement of a geometric mean HAI titer of at least (b) (4) at Day 36 (post-dose 2) at the mid dose level as a predefined immunogenicity acceptance criterion for newly updated strains. The firm states that this acceptance criterion was achieved in mice for all mRNA-1010 vaccine compositions tested. It is not clear to me the rationale to choose this acceptance criterion. Of note, this acceptance criterion was achieved when using the lower dose level as well. Please see below, response to IR#57.

Summary WT vs 2xmut B strain used in clinical studies: the first two mRNA-1010 Phase 3 studies (Study mRNA-1010-P301 and Study mRNA-1010-P302) were conducted using WT HA from influenza B. In Study P301, noninferiority criteria for immunogenicity were met for influenza A strains but not for influenza B strains, and in Study mRNA-1010-P302 positive rVE was observed for influenza A strains but not for B strains (and mRNA-1010 had lower GMTs for the B/Victoria strain. In Study mRNA-1010-P303, using

B/Austria-2xmut, superiority criteria for immunogenicity were met for all influenza A and B strains in both Part B (versus SD comparator in adults ≥ 18 to < 65 years) and Part C (versus HD comparator in adults ≥ 65 years).

Clinical immunogenicity of WT B/Austria from Study mRNA-1010-P302 with B/Austria B/Austria-2xmut from Study mRNA-1010-P303A are provided. HAI titers following a single 50 μ g dose of mRNA-1010 containing B/Austria-2xmut were higher than for WT B/Austria in mRNA-1010-P302 (see the table below).

Comparison of immunogenicity as measured by HAI titer for B/Victoria with and without substitutions, A/H1N1 and A/H3N2 in Studies P302 and P303A

B/Victoria		mRNA-1010*	
		P302	P303 Part A
50- <65	N in PPIS	306	349
Day 1	GMT	79.77 (72.50, 87.77)	101.47 (93.54, 110.07)
	Titer $\geq 1:40$ (%)	92.20	97.4
Day 29	GMT	144.50 (131.42, 158.87)	251.95 (228.95, 277.26)
	GMFR	1.81 (1.68, 1.95)	2.48 (2.27, 2.71)
	SCR (%)**	13.4 (9.79, 17.73)	30.1 (25.32, 35.20)
	Titer $\geq 1:40$ (%)	97.4 (94.91, 98.86)	100
≥ 65	N in PPIS	138	268
Day 1	GMT	81.02 (71.13, 92.30)	123.57 (111.83, 136.55)
	Titer $\geq 1:40$ (%)	92.8	98.9
Day 29	GMT	130.25 (115.09, 147.41)	278.54 (249.83, 310.54)
	GMFR	1.61 (1.46, 1.77)	2.25 (2.04, 2.49)
	SCR (%)**	12.3 (7.34, 18.99)	24.6 (19.59, 30.24)
	Titer $\geq 1:40$ (%)	99.3 (96.03, 99.98)	100

* In P302 and P303A, mRNA-1010 strain selection was based on WHO recommendations for the NH 2022 cell- or recombinant-based vaccines. In P302, the mRNA-1010 B/Victoria component was the wild-type B/Austria/1359417/2021 and in P303A, it was B/Austria/1359417/2021 with 2 antigen optimizing mutations. Module 2.2, Table 1 provides descriptions of the drug product used in each clinical study.

** For each strain, seroconversion was defined as the proportion of participants with either a preinjection HAI titer $< 1:10$ and a postinjection titer $\geq 1:40$ or a preinjection HAI titer $\geq 1:10$ and a minimum 4 fold rise in postinjection HAI antibody titer.

Non-clinical immunogenicity data were generated with mRNA-1010 QIV DPs containing an mRNA encoding for either the B/Austria WT HA or the B/Austria 2xmut. The mRNA encoding for the B HA 2xmut elicited higher ELISA and HAI titers relative to the matched WT B HA against the homologous (WT) virus.

(b) (4) and HAI titers in mice immunized with B/Austria/1359417/2021 and a C.5.4 subclade strain, B/Catalonia/3514402NS/2023 at a 0.01 μ g dose

(b) (4)

In a clinical research head-to-head study (CRID-004) a 2-fold improvement was observed (see the figure below).

Geometric Mean HAI Titer and Geometric Mean Fold Rise against B/Austria/2021 Virus Comparing mRNA-1010 that Contains the WT B HA versus mRNA-1010.4 that Contains the Optimized B HA (from CRID-004 Clinical Research Study)

(b) (4)

Reviewer's comments

1) Both clinical and non-clinical data show increases in immune responses when the 2 mutations are introduced. Of note, the first non-clinical study (Report No. MOD-5814-1010) shows a moderate increase in immune response only against B/Austria (not against B/Phuket), only by (b) (4) (not HAI), and only at 21 days (not 36). This can be explained because the dose used in this study was a saturated dose (b) (4) while the study shown in the above graph was conducted with a non-saturating dose ((b) (4)

2) To confirm the immunogenicity of new strains included in future vaccines, the firm proposes to use: 1) in vitro expression data (b) (4) analyses) to confirm adequate (b) (4) levels, 2) immunogenicity data from a mouse study including the new season's and previous-season's compositions of mRNA-1010 to perform cross-season immunogenicity comparisons and, 3) comparisons of HAI titers from mouse immunogenicity studies integrated across dose levels and timepoints, of the new season's mRNA-1010 strains to the corresponding P304 vaccine strains to monitor for meaningful titer reductions. The firm is optimizing its assays to reduce the background in the sera from control animals. For the analysis of the *in vivo* data, the firm proposes that for each HA subtype/lineage in a given updated mRNA-1010 composition, HAI titers 4-fold lower than those elicited by the corresponding P304 subtype/lineage would serve as an appropriate trigger for additional investigation, as smaller than 4-fold changes are possibly due to inherent HAI assay variability. Results from the new 2026-2027 DP composition compared to the 2025-2026 DP were submitted (amendment 111). See above, STRAIN UPDATE.

5. ANALYTICAL PROCEDURES FOR ASSESSMENT OF CLINICAL AND ANIMAL STUDY ENDPOINTS

Immunological and virological assays were used to assess vaccine performance, as shown in the table below.

Pharmacology Bioassays per Clinical Phase Development

Type of Method	Assay Name	Methodology (Endpoint)	Applicable to Study Development Status (Vendor)
Molecular diagnostic assays of	RT-PCR (b) (4) assay in nasopharyngeal swabs	Qualitative detection of respiratory pathogens nucleic acid (infection status)	STUDY P101: Validated (b) (4)
			STUDY P301: Validated (b) (4)

respiratory pathogens			STUDY P302: Validated (b) (4) Verified and Validated (b) (4))
			STUDY P303 Part A: Validated (b) (4)
	(b) (4) testing in nasal, nasopharyngeal, and midturbinate swabs on the (b) (4)	Qualitative detection of respiratory pathogens nucleic acid (infection status)	STUDY P304: Validated (b) (4)
Antigenic typing	H3N2 seasonal influenza virus (SH22); MN-based antigenic typing analysis	Quantification of anti-influenza Ab levels compared to reference sera (antigenic distance)	STUDY P302: Validated (b) (4)
	Seasonal influenza viruses (SH22); Antigenic typing analysis	Quantification of anti-HA Ab compared to reference sera (antigenic distance)	STUDY P302: Validated (b) (4)
	Antigenic typing of viral isolates for seasonal influenza strain	Quantification of anti-HA Ab compared to reference sera (antigenic distance)	STUDY P304: Validated (b) (4)
Ab quantification	Quantification of anti-HA Abs by HAI assay	Evaluation of functional anti-HA Ab levels	STUDY P101: Qualified (b) (4)
			STUDY P301: Validated (b) (4)
			STUDY P302: Validated (b) (4)
			STUDY P303: Validated (b) (4)
			STUDY P304: Validated (b) (4)
	(b) (4)-based MN assay for influenza virus	Quantification of anti-influenza nAb levels for seasonal strains	STUDY P303: Validated (b) (4)
			STUDY P304: Validated (b) (4)
Cellular activation	(b) (4) assay (b) (4)	T cell activation assessment (cell mediated immunity)	STUDY P101 (Phase 1/2): Validated at ModernaTX (b) (4) STUDY P304: Validated at ModernaTX (b) (4)

Abbreviations: Ab(s) = antibody(ies); AIM = activation-induced markers; DDL = development, design, and delivery; (b) (4); HA = hemagglutinin; HAI = hemagglutination inhibition; (b) (4); MN = microneutralization; nAb = neutralizing antibody; (b) (4)

Immunological assays for antibody quantification

Quantification of anti-HA Abs by HAI assay

This assay was used to assess primary endpoints. (b) (4)

The proprietary serological method “CSP 039-01 Quantification of anti-HA Antibodies by Hemagglutination Inhibition (HAI) Assay” was initially developed and qualified by (b) (4)

, and was applied in Study P101. The proprietary serological methods “(TSOP.119.01032-FDX) HAI

Test for Titrating Influenza Virus A and B Specific Antibodies-(b) (4) was validated by (b) (4) for both influenza A and B strains used in Studies P301, P302, and P303 (Part A and B). The predefined acceptance criteria are acceptable. All parameters evaluated met the acceptance criteria showing that the assay is adequate for its intended use. Validation parameter results are presented in the tables below.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)-based MN assay for quantification of anti-influenza virus antibodies

The (b) (4)-based MN assay detects and quantifies influenza-specific neutralizing antibodies in clinical serum samples. (b) (4)

(b) (4)

. The validation parameter results are provided and are acceptable.

Immunological assays for (b) (4)

(b) (4)

The validation parameter results are provided and are acceptable.

Molecular diagnostic assays of respiratory pathogens

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Antigenic typing

Antigenic typing of viral isolates for seasonal influenza strain

In this HAI based assay, strain specific antisera are tested against the strains included in the vaccine and the field isolates, capable of agglutinating RBCs. The fold differences in HAI titers are an indication of the degree of antigenic similarity between strains. (b) (4)

. These validation parameter results are provided and are acceptable.

Overall Reviewer's Assessment of Relevant Sections of Module 5 (clinical assays)

In amendment 44 the firm confirms that both HAI and MN assays in mRNA-1010-P303 and mRNA-1010-P304 studies employed cell-propagated viruses. This assay format was selected to align the test reagents as closely as possible with circulating influenza viruses, which replicate in mammalian hosts during natural human transmission (in contrast, propagation in eggs can introduce adaptive changes that alter HA antigenicity). (b) (4)



(b) (4)



(b) (4)

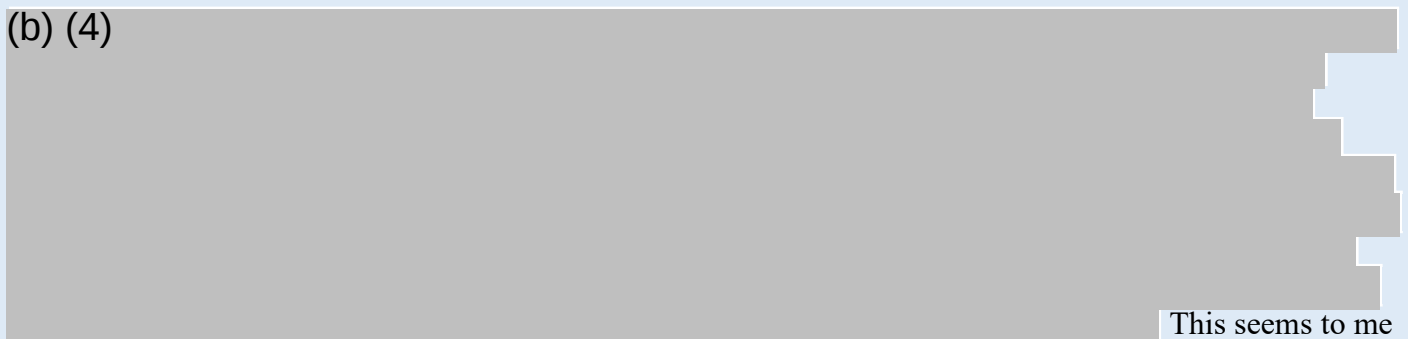
(b) (4)



(b) (4)

Reviewer's comments

(b) (4)



This seems to me to be significant because it is plausible to think that using egg-derived viruses in the HAI will favor the vaccine comparator (manufactured in eggs), and still mRNA-1010 performed better. One issue to consider is that, for the B strain for which vaccine efficacy was not demonstrated (probably because the low number of influenza B cases during the trial), immunogenicity data is necessary for the traditional approval of mRNA-1010 for population 50 to 65 years of age. Moreover, the immunogenicity data supporting the efficacy of the mRNA-1010 vaccine for the population >65 years of age (study mRNA-1010-P303C) is the basis for

accelerated approval for this age group, and the residual uncertainty on the potential bias created with the use of cell-derived virus in the HAI assay that may affect the immunogenicity assessment of the mRNA-1010 clinical trials still remains. The firm proposed to conduct a PMC post marketing immunogenicity study concurrently with the PMR efficacy study to evaluate immune responses using the HAI assay that uses egg-derived viruses or both egg- and cell-derived viruses in subjects 65 years of age and older.

UNII assignment: I concur with the list of ingredients for mRNA-1010 as identified by the Substance Registration System (SRS) team.