RESPONSE TO FDA COMMENTS ON INFORMATION REQUEST#28 for BLA 125752 DATED 07 DECEMBER 2021

The Sponsor acknowledges FDA Comments on INFORMATION REQUEST#28 dated 07 DECEMBER 2021 in (**BOLD**)

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Lot Release Protocol Template:

Our review of your August 24, 2021 submission (STN 125752/1) is ongoing. We have the following request for additional information regarding your Lot Release Protocol Template:

Note: Page numbers referenced below are from Adobe page numbering of your LRP template document QC-OTH-0609 submitted in STN 125752/1.

Throughout the document:

ITEM 1:

Footer

- **Please resolve the page numbering (current template has two different page numberings).**
- **Please correct the overwrites.**

Sponsor Response:

The Sponsor has resolved the page numbering and corrected the overwrites on QC-0TH-0609.

ITEM 2:

Please review and ensure the test methods (including SOP) and acceptance criteria are correct. For example, on pages 4 and 9 of 12, please correct the test method SOP for purity and product-related impurities to SOP-1142. The LRP template currently references SOP-0996.

Sponsor Response:

The Sponsor has reviewed the test methods, SOPs and acceptance criteria and replaced SOP-0996 with SOP-1142 in Spikevax Lot Release Protocol template.

ITEM 3:

Page 1 of 12:

Please refer to page 4 of this document, for an example of the first page of an LRP template. Use this as the basis for page 1 of the Spikevax LRP template.

Sponsor Response:

The Sponsor has aligned page 1 of Spikevax Lot Release Protocol template with the example provided by the Agency.

ITEM 4:

Please move the mRNA 1273 Drug Product Composition table to the page after the current page 3 of 12.

In addition, please note that in the header of the LRP, the reason for submission is checked as "Surveillance," which is incorrect. The LRP is intended for lots to be submitted for official lot release in accordance with 21 CFR 610.2 so please change this to "Release" for all lots submitted.

Sponsor Response:

The Sponsor has revised the header to reflect "release" and repositioned the mRNA-1273 Drug Product Composition table as requested by the Agency.

Please note, Moderna has requested that Spikevax lots be placed on surveillance in lieu of routine release to fulfill the requirements of 21 CFR 610.2 (a) in Section 1.12.5 BLA 125752 SN 0003 dated August 24, 2021. This request is based on the high degree of characterization attained for mRNA vaccines and the demonstrated continued control of the manufacturing process and facilities.

Approximately (b) (4) lots of mRNA-1273 Drug Product lots have been produced through 30 September 2021 with very small reject rates, supporting the consistency and control of the manufacturing process. In addition, the use of biologically sourced raw materials for mRNA-1273 is limited to (b) (4) during the (b) (4) (b) (4) process. The Sponsor has systematically and thoroughly assessed the properties of the mRNA-1273 vaccine with respect to those attributes that affect product quality and potency. The degree of characterization of mRNA-1273 meets or exceeds that for other well-characterized biotech products such as recombinant DNA-derived proteins and monoclonal antibodies. The mRNA-1273 vaccine has demonstrated consistent and robust control through process and product understanding, impurity clearance, and strong analytical capabilities.

ITEM 5:

<u>Pages 2 through 12 of 12:</u>

Please remove the header. This information is should be on page 1 only.

Sponsor Response:

The header has been removed for all pages except page 1 of the Spikevax Lot Release Protocol template.

ITEM 6:

Pages 4 through 8 of 12:

6. Please remove the following tables:

- **Table 1.** (b) (4) **and Production of DNA Plasmid - page 4**
- **Table 3. Manufacture of** (b) (4) **- pages 5 – 6**
- **Table 4. Manufacture of mRNA-1273 Lipid Nanoparticles, Drug Substance (DS) – pages 7 - 8**

Please note that CBER expects the tests on the DNA Plasmid, (b) (4) (b) (4) **, and mRNA-1273 Lipid Nanoparticles Drug Substance to be performed and documented in accordance with 21 CFR 610.1, but we are requesting that only the results of testing of the CX-024414 mRNA and mRNA-1273 Drug Product be submitted to CBER for lot release.**

Sponsor Response:

The Sponsor acknowledges that the tests on the DNA Plasmid, (b) (4) and mRNA-1273 LNP will continue to be performed and documented in accordance with 21 CFR 610.1, but this testing has been removed from the Spikevax Lot Release Protocol template.

ITEM 7:

Page 9 of 12:

For the In vitro translation test, please include additional information as stated in the proposed template below:

Test Samples	Acceptance Criteria	Date of Test	Results
Positive Control Lot#	(b) (4)		
DP sample			

Sponsor Response:

The additional information for the In vitro translation test has been added to the Spikevax Lot Release Protocol template.

ITEM 8:

Page 11 of 12:

Sterility test – please include the test method and test result details. Include the information as stated in the proposed template below:

SOP number: _____

On Test Date	Medium/Temperature	Number of vials tested	Off Test Date

Result:

Specification:

Sponsor Response:

The additional information for the Sterility test has been added to the Spikevax Lot Release Protocol template.

ITEM 9:

Endotoxin test – please include the test details. Include the information as stated on the proposed template below.

Limulus Amebocyte Lysate Test

Method ☐ (b) (4) ☐ (b) (4)

Test date _____

Name of Lysate Manufacturer _____

Lysate Lot number _____

Standard Curve Information

Endotoxin lot number _____

Endotoxin Mfr/Supplier_____

Standard Curve

	Standard Endotoxin Concentration IU/mL	Mean Onset Time (seconds)	CV%
1			
2			
3			
4			
5			
6			

Correlation coefficient (r): _____ Intercept: _____ Slope: _____

Product Test Summary

MVD _____

	Results IU/mL	Test Dilution	Mean Onset Time	CV%	% Spike Recovery
Beginning					
Middle					
End					

Results (IU/mL): _____ Specifications:

_____

Calculations or additional comments

Sponsor Response:

The additional information for the Endotoxin test has been added to the Spikevax Lot Release Protocol template.