

Food & Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: BLA STN 125835/0

From: Sang Hyuk Lee, Ph.D., CMC Reviewer, CBER/OCBQ/DBSQC/LAC

Through: Kenneth Phillips, Ph.D., LAC Chief, CBER/OCBQ/DBSQC/LAC
Maryna Eichelberger, Ph.D., Division Director, CBER/OCBQ/DBSQC

Product: Spikevax mRNA-1283 "next generation" (mRNA-1283)

Applicant: ModernaTX Inc.

Subject: Review of analytical procedures for the lot release of Spikevax mRNA-1283 "next generation" COVID-19 vaccine : (b) (4)
(b) (4) drug substance (DS) and mRNA-1283 LNP drug product (DP)

Recommendation: Approval**Summary:**

On September 30, 2024, ModernaTX Inc. submitted BLA 125835/0 for Spikevax mRNA-1283 "next generation", (mRNA-1283), an mRNA-based vaccine against the 2019 novel coronavirus (SARS-CoV-2). The verifications or validations of the following analytical methods used for lot release of (b) (4) (drug substance, DS), and drug product (DP) were reviewed:

- (b) (4) :
1. Appearance ((b) (4) DP)
 2. (b) (4)
 3. (b) (4)
 4. Particulate Matter (DP)
 5. Deliverable Volume (DP)
- (b) (4) :
6. Total RNA Content ((b) (4) DP)
 7. (b) (4)
 8. Lipid Identification, Content, Impurities ((b) (4) DP)
 9. mRNA Purity (DP)

Analytical methods and their qualifications reviewed for mRNA-1283, DS, and DP were found to be adequate for their intended uses.

Information Reviewed

1.2	Cover letters
3.2.S.4.1	DS Specifications
3.2.S.4.2	DS Analytical Procedures
3.2.S.4.3	DS Validation of Analytical Procedures
3.2.S.4.4	DS Batch Analyses
3.2.S.4.5	DS Justification of Specification
3.2.P.5.1	DP Specifications
3.2.P.5.2	DP Analytical Procedures
3.2.P.5.3	DP Validation of Analytical Procedures
3.2.P.5.4	DP Batch Analyses
3.2.P.5.5	DP Justification of Specification

Background

The Spikevax mRNA-1283 "next generation" DP is an RNA-lipid nanoparticle complex. RNA- (b) (4) used in the mRNA-1283 vaccine encodes the linked N-terminal domain and receptor-binding domain of the spike glycoprotein of SARS-CoV-2 Omicron XBB.1.5 subvariant. The mRNA-1283 (b) (4) (DS) is a RNA-lipid complex dispersion containing RNA- (b) (4) and four (b) (4) lipids: cholesterol, (b) (4) (SM-102, a custom-manufactured, ionizable lipid), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG). The DP is supplied as a sterile, single-dose, liquid solution for intramuscular administration in a 1-mL prefilled syringe with 10 µg of RNA and 200 µg of total lipids in 0.2 mL of preservative-free buffer containing (b) (4) mM Tris and (b) (4) g / L sucrose at pH (b) (4).

The submission lacked clear information regarding sites performing lot released testing. This information was requested on February 5, 2025, Information request (IR) #16. Based on a response received on March 3, 2025, in amendment number 24, several testing sites carry out the release testing of mRNA vaccine. One Moderna Way Norwood, MA 02062 USA (Moderna Norwood) performs tests for mRNA and DS. DP release testing is performed at Moderna Biotech Spain, SL Calle Julián Camarillo, 31, Planta 4a, Madrid 28037 Madrid, Spain (Moderna Madrid); (b) (4)

The release testing results from Moderna Madrid was not included in the original submission and therefore an IR was sent on April 16, 2025, requesting an explanation. Based on the response received on April 23, 2025, in amendment number 46, the Moderna Madrid site did not perform any PPQ lot release testing for this product. In lieu of testing this product, the sponsor stated that these are platform analytical procedures that have previously been verified or validated in BLA submission 125752/0 for the mRNA-1273 vaccine (Spikevax). The sponsor submitted procedures and justification for using a representative material for testing. Considering the only difference between the mRNA, DS and DP in this application and previous Moderna mRNA-LNP products is the mRNA

(b) (4)

, I agree that these are platform methods and that material that is not (b) (4) is acceptable for demonstrating suitability of each method.

Review Narrative

1. Appearance of (b) (4) DP

Appearance Specification	
Material	Appearance Description
(b) (4)	
(b) (4)	
DP	white to off-white dispersion in preservative-free buffer

Method

The appearance by visual inspection method, SOP-0278, is a (b) (4) method and compliant to (b) (4). Also, this is a platform method used for testing SpikeVax (STN 125752/0). (b) (4) DP are assessed in (b) (4).

Color and clarity of the sample is assessed against (b) (4)

Method Verification

The method was adequately verified for SpikeVax STN 125752. The sponsor has verified suitability of the method for this produce by providing batch analysis data from each of the test sites. The appearance test was verified at Moderna Norwood by batch analysis of (b) (4) lots of mRNA-1283; all the results met their specifications. For appearance testing of DP, (b) (4) and Moderna Madrid are testing sites and were previously approved for the appearance release testing of mRNA-1273 ((b) (4): R-2020-VERIF-QC-032, Moderna Madrid: QC-MVR-0001). The sponsor did not report additional verification of appearance testing for mRNA-1283, because there was no change in composition or RNA concentration. The mRNA-1283 DP batch analyses (3.2.P.5.4) results show (b) (4) DP lots met their appearance specification.

Conclusion: Based on the information provided, the appearance test is adequately described. The suitability of the appearance testing for (b) (4) was verified, while the suitability of DP testing is demonstrated by batch analyses and is a platform method currently approved and used for a similar product.

One page has been determined to be not releasable: (b)(4)

(b) (4)

4. Particulate Matter of DP

Specification

The particulate matter specifications of DP are (b) (4)

Method

The particulate matter method, SOP-509, is a (b) (4) method and (b) (4)

Also, this is a platform method because the test results are independent of mRNA sequence; it is also used for testing SpikeVax (STN 125752/0). This test assesses (b) (4) particulate matter in DP.

The method was not detailed in the original submission and therefore an IR was sent on March 11, 2025, requesting the SOP. In the response received on March 17, 2025, in amendment number 33, SOP-509 was provided to describe the Particulate Matter method in detail. (b) (4) particulates in DP sample taken from the (b) (4)

Method Verification

The method was adequately verified for SpikeVax STN 125752. The sponsor has verified suitability of the method for this product by providing batch analysis data from each of the test sites. The particulate matter test was verified with (b) (4) in (b) (4) (RPT-18766) and Moderna Madrid (RPT-17972). Based on mRNA-1283 batch analyses (3.2.P.5.4), all particulate matter results of DP met their specification.

Conclusion: Based on the information provided, the particulate matter method is adequately described and verified. Particulate matter testing is suitable for DP release at (b) (4) and Moderna Madrid.

5. Deliverable Volume of DP

Specification

The deliverable volume specification of DP is (b) (4) 0.2 mL per syringe.

Method

Deliverable volume method, SOP-5183, is performed in accordance with (b) (4) . This is a platform method because mRNA sequence does not impact the test performance; it is also used for testing SpikeVax (STN 125752/0). The method was not detailed in the original submission and therefore an IR #27 was sent on March 11, 2025, requesting the SOP. In the response received on March 17, 2025, in amendment 33, SOP-5183 was provided. It describes the deliverable volume method in detail. (b) (4) . Based on document REC-14568, the volume is calculated from (b) (4) .

Method Verification

The method was adequately verified for SpikeVax STN 125752 at (b) (4) (STM-08650-1), and Moderna Madrid (RPT-18581). The sponsor verified suitability of the method for this product by providing batch analysis data from each of the test sites. (b) (4) and Moderna Madrid performed the DP deliverable volume test; the mRNA-1283 DP batch analyses (3.2.P.5.4) results show the tested (b) (4) DP lots met their deliverable volume specification.

Conclusion: Based on the information provided, the deliverable volume method is adequately described and verified. The method is suitable for lot release testing.

6. Total RNA Content of (b) (4) DP

Total RNA Content Specification	
Material	Total RNA content description (mg/mL)
(b) (4)	
DP	(b) (4)

Method

(b) (4) , SOP-999, is used to quantitate the total RNA content. This is a platform method because the analysis is independent of mRNA sequence; it is also used for testing SpikeVax (STN 125752). (b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

Method Verification

The method was adequately validated for SpikeVax STN 125752. The sponsor has verified suitability of the method for this product by providing batch analysis data from each of the test sites. The total RNA content by (b) (4) method is a platform method and was validated with (b) (4) lots of mRNA-1273 at Moderna Norwood (RPT-71385). The test method was validated with (b) (4) of mRNA-1273 (BLA submission 125752) in (b) (4) (PRT-15291) and Moderna Madrid (RPT-73121). The sponsor justified the testing of representative material for the testing of the mRNA-1283 (b) (4) DP because (b) (4)

and the validated range sufficiently covers the expected concentration of (b) (4) DP. The batch analyses (3.2.S.4.4) showed that (b) (4) lots of mRNA-1283 tested in Moderna Norwood met the specification. The batch analyses (3.2.P.5.4) showed that (b) (4) DP lots of mRNA-1283 met the specification.

Conclusion: Based on the information provided, the total RNA content test by (b) (4) is adequately described. Total RNA content method was validated as a platform method for testing (b) (4) DP at each site and further confirmed as suitable by batch analyses of the new product.


(b) (4)

(b) (4)

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

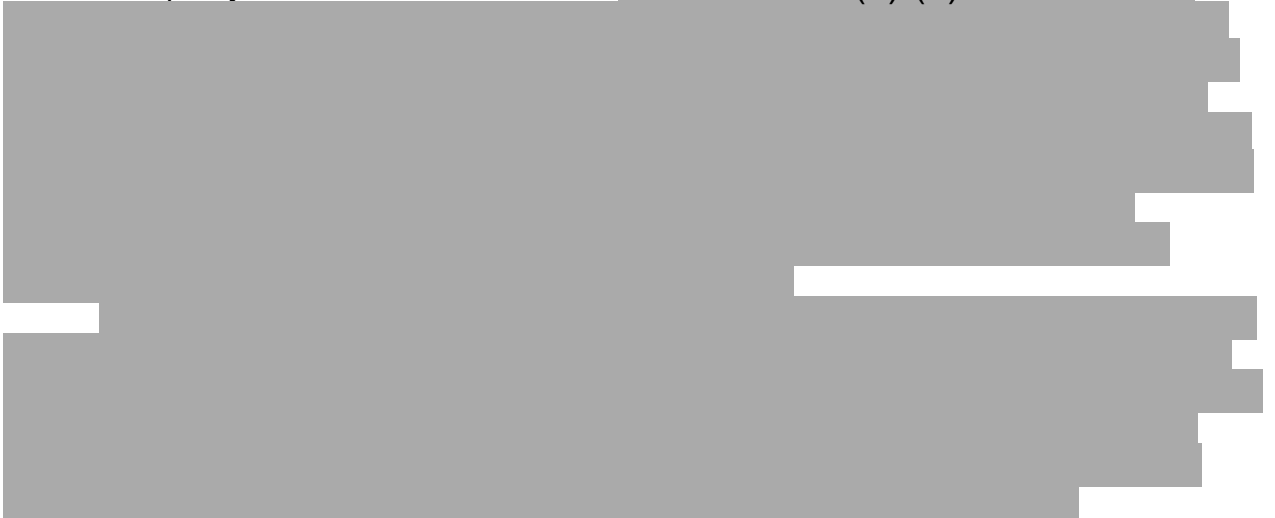


**9. mRNA Purity (DP)
Specification**

The mRNA purity specification for DP is (b) (4) .

Method

The purity method, SOP-1142, uses (b) (4)



One page determined to be not releasable: (b)(4)

Method Validation

The method for mRNA purity/product-related impurity by (b) (4) was validated for testing DP of mRNA-1283 in Moderna Norwood. For method validation, DP, (b) (4) reference standard, and DP formulation buffer and samples (b) (4) were used. The validation is summarized below:

(b) (4)

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

Moderna Madrid method transfer is summarized below:

(b) (4)

The batch analyses (3.2.P.5.4) showed that (b) (4) DP lots of mRNA-1283 met the specification.

Conclusion: Based on the information provided, the mRNA purity test is adequately described. The testing sites for DP are qualified by method validation and site transfer verifications for mRNA-1283 DP, and further confirmed by batch analyses.