

(b) (6) ANALYTICAL METHOD REVIEW MEMO

To: BLA STN 125835/0

From: (b) (6) /CBER

Through: (b) (6) /CBER

(b) (6) /CBER

Product: MNEXSPIKE

Applicant: ModernaTX, Inc.

Subject: Review of Analytical Methods used for MNEXSPIKE (mRNA, 2019 novel coronavirus (SARS-CoV-2) mRNA-1283 Drug Substance (DS) and Drug Product (DP) Lot Release

Recommendation: Approval

Summary:

The following analytical methods used for lot release of MNEXSPIKE, and the associated analytical method validations or method transfer qualifications, were reviewed:

1. (b) (4)
2. Percent (b) (4)
3. Identity

Conclusion: The analytical methods and their validations/method transfer qualifications reviewed for the MNEXSPIKE drug substance and drug product were found to be adequate for their intended use.

Documents Reviewed:

Information in sections of the original submission that describe control of DS and DP (3.2.S.4, and 3.2.P.5, respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validation of these analytical procedures were reviewed. Additional information in amendments #125735/0.21 and #125835/0.37 received on February 07, and March 28, 2025, were also reviewed.

Background:

Moderna submitted an original BLA, STN 125835 for mRNA-1283, a messenger RNA (mRNA) based vaccine against COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) on September 30, 2024. The mRNA-1283 is supplied as a suspension for injection for active immunization.

mRNA-1283 (b) (4) DS is an mRNA-lipid complex dispersion containing RNA- (b) (4) mRNA ((b) (4)) and four lipids: (b) (4) (SM-102), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and 1- monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). RNA- (b) (4) encodes the linked N-terminal domain (NTD) and receptor-binding domain (RBD) of the spike glycoprotein of the SARS-CoV-2 omicron variant lineage XBB.1.5, component of Covid-19 vaccines (2023-2024 Formula).

The RBD and NTD subdomains of the S1 region of the spike protein are known to elicit protective immune responses, whereas the S2 region is not considered to be protective. The antibody-mediated protection against SARS-CoV-2 is mainly driven by anti-RBD antibodies, and to a lesser extent by antibodies targeting the NTD domain. The encoded linked RBD-NTD polypeptide is attached with a (b) (4) linker to a 23 amino acid transmembrane domain from influenza Hemagglutinin, which anchors the linked RBD-NTD polypeptide into the cell membrane of antigen-expressing cells. The linked RBD-NTD antigen is presented as a cell surface anchored monomeric protein, whereas SPIKEVAX encodes the full-length spike protomer of SARS-CoV-2, and after translation, 3 protomers combine into a membrane bound spike trimer.

mRNA-1283 DP is manufactured as a sterile, preservative-free, single-dose, ready-to-use product comprising 10 µg/0.2 mL mRNA-1283 LNP solution in a buffer containing (b) (4) mM Tris, and (b) (4) g/L sucrose at pH (b) (4) in 1 mL prefilled syringe (PFS) for intramuscular (IM) administration.

The following analytical methods and their validations are approved for mRNA-1273 SPIKEVAX (STN 125752) and mRNA-1345 mRESVIA (STN 125796) are followed to assess MNEXSPIKE DS and DP. In this review memo, method validation or method transfer qualifications for the following facilities were reviewed.

1. ModernaTX, Inc., Norwood, MA
2. (b) (4)
3. Moderna Madrid Lab, Spain

(b) (4)

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

(b) (4)

2. Percent RNA (b) (4)

Introduction

Moderna uses SOP-1000, the (b) (4) assay (b) (4) for determination of (b) (4) in (b) (4) DP (b) (4) (SOP-0999). The (b) (4) assay is performed at Moderna's QC laboratory in Norwood, MA. Validation of the assay was performed in the same facility. The (b) (4) specification for (b) (4) DP is (b) (4).

This method is (b) (4)

This method SOP-1000 has been validated using mRNA-1273 (b) (4) DP as representative materials. No additional validation activities are required as the (b) (4)

The method verification was performed using mRNA-1283 (b) (4)/DP PPQ lots and all (b) (4)/DP PPQ lots were within specification, (b) (4)

The method (SOP-1000) has been transferred from Moderna QC lab in Norwood, MA to the following testing laboratories with no changes to the SOP or specification. Transfer report is provided in amendment #125735/0.21 received on February 07, 2025, and reviewed below.

Method Transfer:

a) (b) (4) :

(b) (4) previously performed the full validation of the analytical method (SOP-1000); the validation is documented in report AST-CMO-0174, reviewed in previous submission (STN 125796/0) and approved for testing (b) (4).

b) Moderna Madrid Lab, Spain:

The method (SOP-1000) transfer is documented in report #RPT-72926. Intra-lab precision (repeatability, intermediate precision) was performed by (b) (4) analysts ((b) (4)) at Moderna Madrid QC Lab. The results at Moderna Madrid Lab were compared against precision data generated at the Norwood QC lab for the same DP (Lot# (b) (4)).

Intra-lab precision of the assay was demonstrated by (b) (4)

Inter-lab precision was assessed from the data at the Moderna's QC laboratory by (b) (4)

The inter-lab and intra-lab precision met pre-determined acceptance criteria defined for SOP: 1000 (b) (4).

Conclusion

The (b) (4) assay transfer was appropriately qualified and is suitable for mRNA-1283 (b) (4) DP lot release testing at Moderna Biotech Spain, SL, Madrid, Spain QC Lab.

3. Identity (b) (4)

Introduction

Identity via (b) (4) (SOP-1337) is an approved method for Spikevax and MRESVIA vaccines for STN 125752 and STN125796, respectively. Identity testing is performed for (b) (4) DP release at the Moderna Quality Control (QC) Laboratory in Norwood, MA. The purpose of this assay is to confirm that the (b) (4) of the mRNA in (b) (4) DP by (b) (4).

. The identity specification for (b) (4) DP is that the (b) (4).

The method (SOP-1337) has been validated using mRNA-1283 (b) (4)/DP in Moderna QC lab in Norwood, MA and transferred to the following testing laboratories with no changes to the SOP or specification. Method validation and transfer reports are provided in amendment #125735/0.21 received on February 07, 2025, and reviewed below.

Method Validation

(b) (4)

Conclusion

The Identity assay was appropriately validated and is suitable for mRNA-1283 (b) (4) DP lot release testing at Moderna's Norwood QC Laboratory.

Method transfer:

a) (b) (4) :

The method validation (SOP-1337, v2.0) was performed using (b) (4) according to protocol P-2024-VAL-QC-009 Rev 1.0 and is documented in RPT-15579. (b) (4)

b) Moderna Madrid Lab, Spain:

The method validation (SOP-1337) was performed using (b) (4) according to protocol MQP-0350 and is documented in RPT-16816. (b) (4)

Conclusion

The Identity assay was appropriately qualified and is suitable for mRNA-1283 (b) (4) DP lot release testing at (b) (4) and Moderna Madrid Labs.