

Chemistry, Manufacturing, and Controls Statistical Review

Application Type	Original BLA
STN	125835/0
Applicant	ModernaTX, Inc.
Trade Name	mNEXSPIKE
Pharmacologic Class	Vaccine
Indication	SARS-CoV-2
Review Priority	Priority
CBER Received Date	09/30/2024
Action Due Date	05/31/2025
Product Office	OVR
(b) (6)	(b) (6)
(b) (6)	(b) (6)
(b) (6)	(b) (6)
CMC Statistical Reviewer	(b) (6)
Supervisory Concurrence # 1	(b) (6)
Supervisory Concurrence # 2	(b) (6)
Supervisory Concurrence # 3	(b) (6)

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1. EXECUTIVE SUMMARY

ModernaTX, Inc. submitted BLA 125835/0 for mRNA-1283, a new generation of mRNA vaccine indicated for active immunization to prevent COVID-19 caused SARS-CoV-2 in individuals over 12 years of age on September 30, 2024, using a (b) (4)

This memo focuses on the statistical review of the Chemistry, Manufacturing and Control (CMC) data, namely, assay validations, comparability studies and stability studies during product development process.

Compared to the older generation vaccine Spikevax (mRNA-1273), the new generation vaccine encodes part of the spike glycoprotein and shared similarities with Spikevax, and hence the sequence-agnostic platform methods are shared between the vaccines. Specific validations have been reviewed for new methods developed for mRNA-1283 and for an old method on the new material. These methods are all (b) (4)-based.

- mRNA purity, a key sequence-dependent attribute, was validated similarly with mRNA-1273 but with mRNA-1283 material for (b) (4) DP (SOP-1142).
- (b) (4) method for (b) (4) (SOP-2187).

For the (b) (4)-based assays, the reportable value is (b) (4) which is defined as (b) (4). To evaluate the linearity, accuracy, and precision across a reasonable range of (b) (4), the applicant should vary the theoretical (b) (4) and then compare it with the observed (b) (4). However, the applicant used (b) (4) to generate (b) (4) DP samples, which resulted in (b) (4) area across these samples as the (b) (4) remained unchanged.

Regarding the validation of mRNA purity on (b) (4) samples, the study covered (b) (4) purity levels, but the applicant claimed a range of (b) (4). I consulted with CMC and DBSQC reviewers and both of them thought SOP-1142 has been fully validated for mRNA-1273 and is a well-controlled platform method. Therefore, no additional validation is requested for mRNA purity (including (b) (4) DP).

For the (b) (4) method for (b) (4), I requested the applicant to perform additional validation studies across (b) (4) in an information request (IR) on April 18, 2025. The applicant agreed to FDA's request and submitted a validation study protocol on May 9 and will submit results by July 11, 2025. The protocol is acceptable.

In addition, the applicant conducted comparability studies to compare the product quality of DP produced by the commercial scale process with that of the clinical lots.

- For sequence-dependent attributes, it was originally proposed that comparability is demonstrated if all the development and clinical lots meet the specification limits of PPQ (commercial process). This is inappropriate because the quality of

PPQ lots were to be assessed and cannot be used to build the acceptance criteria. We requested the applicant to perform equivalence tests between clinical and PPQ lots. Due to the limited number of PPQ lots, the applicant used the quality range approach (99%/95% tolerance interval [TI]) from mRNA-1283 development and clinical lots instead and the results are acceptable.

- For sequence-independent attributes, comparability is demonstrated if all the PPQ lots of mRNA-1283 fall in the 95% confidence/99% coverage tolerance intervals (99%/95% TI) generated from (b) (4) lots of mRNA-1273. The results are acceptable.

For end of shelf life studies, most of the stability lots were exposed to (b) (4) condition, while the proposed shelf life includes 3 conditions sequentially. The applicant used these data to generate models to predict the EoSL values for critical attributes. The results are reproducible. Based on FDA's request, the applicant submitted data from (b) (4) additional sublots which underwent incomplete sequential storages, and the results appear to be consistent with the predicted values based on the previous stability lots. Furthermore, the applicant indicated that the complete end-to-end study is still ongoing and will be completed by the end of 2025. The applicant also performed the shelf-life analyses for (b) (4) by visual assessments and results are acceptable.

Based on the information above, I recommend approval of this BLA.

2. REGULATORY BACKGROUND AND SOURCE OF INFORMATION

mRNA-1283 is a lipid-encapsulated mRNA-based vaccine. Unlike the applicant's licensed SARS-CoV-2 vaccine, Spikevax (mRNA-1273), which encodes the full-length spike protein, mRNA-1283 only encodes part of the SARS-CoV-2 spike protein. Spikevax and mRNA-1283 share similar manufacturing processes, compositions, and formulations. The main difference between the two vaccines is the mRNA sequence used. Therefore, sequence-independent assays are the same and sequence-independent product quality attributes are expected to remain the same between the two vaccines. Therefore, this review focuses on the validation of sequence-dependent quantitative assays and of new quantitative assays developed for mRNA-1283.

mRNA-1283 drug product (DP) is manufactured from (b) (4) drug substances (DS): (b) (4)

This CMC statistical memo reviews the manufacturing information contained in the original application (BLA 125835/0 SN 0000) and the applicant's responses to the following CMC statistical IRs:

- STN 125835 SN 0000 module 3 received on September 30, 2024

- STN 125835 SN 0011 modules 1 and 3 received on January 10, 2025 (Applicant's response for Item 1 calculating EoSL was not clear. Assay validation reports were submitted, while corresponding calculations were not included. Two follow-up IRs were sent on February 25 and March 5, 2025.)
- STN 125835 SN 0030 module 1 received on March 11, 2025 (Applicant's response for Items 1 to 4 for comparability studies were acceptable. Response to Item 5 calculating EoSL was not clear enough and a follow-up IR was sent on March 14, 2025.)
- STN 125835 SN 0031 module 1 received on March 11, 2025 (Applicant submitted excel workbook for assay validation studies and the calculations were not fully acceptable. A follow-up IR was sent on April 18, 2025.)
- STN 125835 SN 0035 module 1 received on March 19, 2025 (Applicant submitted scripts for calculating EoSL values and response was acceptable.)
- STN 125835 SN 0039 module 3 received on March 31, 2025 (Applicant submitted stability data to address CMC reviewer's question. The stability data for sequential storage are not complete. Applicant indicated the study would be completed by end of 2025.)
- STN 125835 SN 0040 module 1 received on April 28, 2025 (Applicant's committed performing additional validation studies for (b) (4) and response was acceptable.)
- STN 125835 SN 0057 module 3 received on May 9, 2025 (Applicant submitted validation study protocol for (b) (4) and response was acceptable.)

The specifications were justified based on risk assessments, clinical studies, and process platform knowledge. No statistical analyses of CMC data were presented; therefore, the justification of specifications was not reviewed.

3. DISCUSSION OF PROTOCOLS, STUDIES OR ANALYSES, AND RESULTS

3.1 mRNA Purity/Product Related Impurities by (b) (4)

The assay (SOP-1142) was previously validated for testing Spikevax (see BLA 125752). In this submission, the applicant validated this assay on mRNA-1283 (b) (4) DP.

(b) (4)

(b) (4)

(b) (4)

This review focuses on the assay performance including linearity, accuracy, precision, quantitation limit and range.

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

(b) (4)

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3.1.3. *Drug Product*

- **Linearity and accuracy**

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

3.4 Drug Product Shelf Life

The applicant proposed a shelf life of 12 months at -40°C to -15°C, including up to 90 days at 2°C to 8°C and up to 24 hours at room temperature (up to 25°C). Statistical analyses were only performed for the quantitative attributes that are expected to change over time: purity, (b) (4), and total lipid impurities.

Reviewer's Comment: *The statistical analysis (graphical assessment) results of following attributes (mRNA purity, RNA (b) (4) Total Lipid Impurities) seem acceptable. The attributes are within specification limits under each temperature range for the pre-specified time.*

To support the proposed shelf life, the applicant predicted the EoSL value for each quality attribute, based on the following equation which uses upper or lower release limits as appropriate:

(b) (4)

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

(b) (4)

4. CONCLUSIONS

This memo focuses on the statistical review of assay validations for certain assays, comparability studies between (b) (4), and stability studies during product development process.

For assay validation studies, the applicant evaluated linearity and accuracy of method for mRNA purity (SOP-1142) and (b) (4) (SOP-2187) across (b) (4) levels and consequently tested precision (b) (4) purity or (b) (4) level. The CMC reviewer thinks the SOP-1142 (mRNA purity) is a fully validated platform method and the attribute is well controlled during the manufacturing process and on release, the results are adequate. Therefore, we sent an IR to the applicant requesting supplemental testing for SOP-2187 across (b) (4). The applicant acknowledged our request and submitted a protocol on May 9, and will submit validation results by July 11, 2025. The protocol is acceptable.

For DP comparability study, (b) (4)

For end of shelf studies, most of the stability lots were exposed to (b) (4) condition, while the proposed shelf life includes 3 conditions sequentially. The applicant used these data to generate models to predict the EoSL values for critical attributes. The results are reproducible. Based on FDA's request, the applicant submitted data from (b) (4) additional sublots which underwent incomplete sequential storages, and the results appear to be consistent with the predicted values based on the previous stability lots. Furthermore, the applicant indicated that the complete end-to-end study is still ongoing and will be completed by the end of 2025. The applicant also performed the shelf-life analyses for (b) (4) by visual assessments and results are acceptable.

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