

Application Type	BLA, Original Application
STN	125752/0
CBER Received Date	August 24, 2021
PDUFA Goal Date	April 24, 2022
Division / Office	DVRPA/OVRR
Committee Chair	Sudhakar Agnihothram
CMC Reviewer(s)	Alena Dabrazhynetskaya
Project Manager	Joseph Kulinski; Josephine Resnick
Priority Review	Yes
Reviewer Name	Ye Yang, Mathematical Statistician, DB/VEB
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Concurring Reviewer, DB/VEB
Supervisory Concurrence	Tsai-Lien Lin, Branch Chief, DB/VEB
Supervisory Concurrence	John Scott, Director, DB
Applicant	ModernaTX, Inc.
Established Name	COVID-19 Vaccine, mRNA
(Proposed) Trade Name	SPIKEVAX
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, Intramuscular
Dosing Regimen	Two 0.5 mL doses, four weeks apart
Indication(s) and Intended Population(s)	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older

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GLOSSARY

BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CMC	Chemistry, Manufacturing and Controls
COVID-19	Coronavirus Disease 2019
DP	Drug Product
EUA	Emergency Use Authorization
(b) (4)	
LNP	Lipid Nanoparticle
RNA	Ribonucleic Acid
RSD	Relative Standard Deviation
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure

1. Executive Summary

The Moderna Coronavirus Disease 2019 (COVID-19) Vaccine (mRNA-1273) was authorized under an Emergency Use Authorization (EUA) on December 18, 2020 for active immunization to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals ≥ 18 years of age. Moderna initiated a rolling Biologics License Application (BLA), STN 125752/0, to seek licensure of this vaccine in the same population. The submission was completed on August 24, 2021. This memo covers the statistical review of the nonclinical data.

The potency of mRNA-1273 drug product (DP) during release and stability is assessed based on 1) total ribonucleic acid (RNA) content as measured by (b) (4) under Standard Operating Procedure (SOP)-0999, and 2) RNA purity as measured by (b) (4) under SOP-1142. While the current method for assessing RNA purity under EUA is performed under SOP-0996, SOP-1142 will be implemented instead following licensure. This statistical review focuses on the validations of SOP-0999 and SOP-1142 and specification calculations for RNA content and purity.

The validation data support the (b) (4)

[REDACTED]

Similarly, the validation data support the (b) (4)

[REDACTED]

The DP release and stability specification for (b) (4)

[REDACTED]

[REDACTED] As the specifications for RNA purity were supported by data obtained under SOP-0996 and the bridging data suggest that SOP-1142 tends to

report higher RNA purity, the applicant stated that the limits will be re-assessed as data from SOP-1142 become available.

I defer to the Chemistry, Manufacturing and Controls (CMC) reviewer on the overall adequacy of SOP-0999 and SOP-1142 to support mRNA-1273 DP potency testing within their respective specifications for release and stability, and the acceptability of the justification of the specifications for RNA content and purity.

2. Clinical and Regulatory Background

The Moderna COVID-19 Vaccine, mRNA-1273, was authorized under an EUA on December 18, 2020 for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥ 18 years of age. Moderna initiated a rolling BLA on May 28, 2021 to seek licensure of the vaccine in the same population. The BLA submission was completed on August 24, 2021. This memo covers the statistical review of the nonclinical data.

3. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

3.1 Review Strategy

This statistical review focuses on the validations of SOP-0999 and SOP-1142 and specification calculations for RNA content and purity.

3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents supporting the BLA are reviewed:

STN 125752/0:

1. Amendment 1 (submitted on 8/16/2021)
 - Module 3. Quality
2. Amendment 10 (submitted on 10/12/2021)
 - Module 3. Quality
3. Amendment 26 (submitted on 11/30/2021)
 - Module 3. Quality
4. Amendment 40 (submitted on 12/21/2021)
 - Module 1. Administrative Information and Prescribing Information
5. Amendment 41 (submitted on 12/22/2021)
 - Module 1. Administrative Information and Prescribing Information
 - Module 3. Quality

4. VALIDATION OF SOP-0999 FOR QUANTIFYING RNA CONTENT

4.1 Description

RNA concentration in the DP for release and stability is measured using (b) (4)

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

(b) (4)

[Redacted]

[Redacted]

5. VALIDATION OF SOP-1142 FOR QUANTIFYING RNA PURITY

5.1 Description

(b) (4) performed under SOP-1142 is used to assess the integrity of mRNA contained within the DP. (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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(b) (4)



(b) (4)



(b) (4)



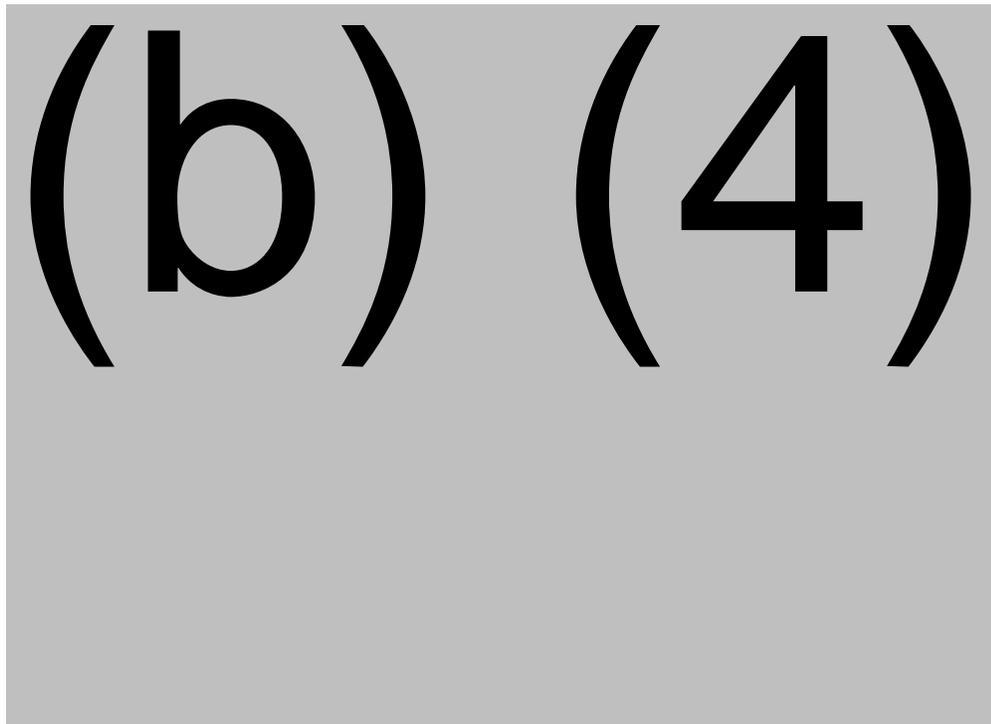
6. SPECIFICATIONS

6.1 RNA Content

The DP release and stability specifications for total RNA content were based on a 95% confidence, 99% coverage tolerance interval from concentrations obtained from ^{(b) (4)} DP lots. Figure 4 shows the distribution of the concentrations, which appeared approximately normal. The resulting specification was (b) (4)



(b) (4)



Reviewer Comment:

- *The validation of (b) (4) used to determine RNA content demonstrated linearity at (b) (4) while the specification was set at (b) (4). Based on discussions with the CMC reviewer, samples are typically (b) (4) prior to testing, hence the difference in concentration ranges.*

6.2 RNA Purity

The release and end of shelf-life specifications for RNA purity are as follows: (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

[Redacted text block]

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I defer to the CMC reviewer on the overall adequacy of SOP-0999 and SOP-1142 to support mRNA-1273 DP potency testing within their respective specifications for release and stability, and the acceptability of the justification of the specifications for RNA content and purity.