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Priority Review	Yes
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Review Completion Date / Stamped Date	
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Applicant	Moderna Tx, Inc

Established Name	Respiratory Syncytial Virus Vaccine, mRNA
(Proposed) Trade Name	MRESVIA
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	RNA-lipid complex suspension containing RNA that encodes for the respiratory syncytial virus (RSV) fusion (F) glycoprotein stabilized in the prefusion conformation, and four lipids that act as protectants and carriers of the RNA. The four lipids are SM-102, cholesterol, DSPC, and PEG2000-DMG.
Dosage Form(s) and Route(s) of Administration	Injectable suspension for intramuscular (IM) administration.
Dosing Regimen	A single dose of 0.5 mL.
Indication(s) and Intended Population(s)	For active immunization for the prevention of lower respiratory tract disease (LRTD) (b) (4) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older.

TABLE OF CONTENTS

GLOSSARY	4
1. EXECUTIVE SUMMARY	5
2. REGULATORY BACKGROUND	5
3. SUBMISSION QUALITY	6
4. SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES	6
4.1 Chemistry, Manufacturing, and Controls	6
5. SOURCES OF INFORMATION CONSIDERED IN THE REVIEW	6
5.1 Review Strategy	6
5.2 BLA/IND Documents That Serve as the Basis for the Review	7
6. DISCUSSION OF PROTOCOLS, ANALYSES, AND STUDY REPORTS.....	7
6.1 Process Characterization	7
6.2 Validation of (b) (4) mRNA Purity Assay	9
6.2.1 Linearity	10
6.2.2 Accuracy	11
6.2.4 Precision	12
6.2.5 Range	14
6.3 Release and Stability Specifications.....	14
6.3.1 Drug Substance	14
6.3.2 Drug Product	16
7. CONCLUSIONS	18
7.1 Statistical Issues and Collective Evidence	18
7.2 Conclusions and Recommendations.....	18

GLOSSARY

BLA	biologics licensing application
CMC	chemistry, manufacturing, and control
CPP	critical process parameter
CQA	critical quality attribute
DOE	design of experiment
DP	drug product
DS	drug substance

(b) (4)

LNP	lipid nanoparticle
MRL	minimum release limit
mRNA	messenger ribonucleic acid
PAR	proven acceptable range
PP	process parameter
RSD	relative standard deviation
SL	shelf life

1. EXECUTIVE SUMMARY

In this original BLA, Moderna seeks licensure for its messenger ribonucleic acid (mRNA) vaccine (mRNA-1345) for active immunization for the prevention of lower respiratory tract disease caused by respiratory syncytial virus in adults 60 years of age and older.

This statistical review focuses on the chemistry, manufacturing, and controls (CMC) and related materials for the drug substance (DS) and drug product (DP), mRNA-1345, including process characterization study for DS; validation of the mRNA purity assay (b) (4)) for (b) (4) DP; and specifications and shelf lives for DS and DP.

Moderna validated their mRNA purity assay for (b) (4) DP by assessing the accuracy, precision, linearity, and range. The design and results of the (b) (4) DP mRNA purity validation studies were appropriate and met their acceptance criteria.

Moderna submitted stability data from (b) (4) lots at (b) (4) different temperature conditions to support an (b) (4) shelf life (SL) at (b) (4) that includes (b) (4) of up to (b) (4) at (b) (4) for (b) (4). The application also contained stability data from (b) (4) lots at (b) (4) different temperature conditions to support an SL of 18-month at -40°C to -15°C, including up to 30 days of storage at 2°C to 8°C, and up to 24 hours at room temperature (15°C to 25°C) for DP. The stability results do not suggest a concerning level risk of lots going out-of-specification within the proposed shelf lives. Therefore, the proposed shelf lives are acceptable.

Overall, Moderna has adequately validated its (b) (4), validated their DP mRNA purity assay, and submitted justification for their proposed release specifications and shelf lives. Therefore, I recommend approval.

2. REGULATORY BACKGROUND

Moderna's RNA manufacturing process and process control strategy for vaccines, termed RNA-100, was originally developed for Moderna's vaccine Spikevax. Moderna claimed that its prior experience has demonstrated the RNA-100 process and that the process control strategy established for Spikevax RNA manufacture could be applied to other RNA sequences, including mRNA-1345.

As a result, Moderna established an RNA-100 process validation master plan (see Module 3.2.S.2.5) governing the validation of the RNA-100 processes to cover multiple vaccine products, including mRNA-1345. The Applicant conducted a several studies to ensure consistent quality and process performance is maintained for critical quality attributes (CQAs) which were originally identified for Spikevax and are relevant to this vaccine. An overview for some studies covered in this review memo follows.

First, Moderna performed a process characterization of mRNA-1345 RNA. The statistical associations between CQAs and process parameters (PPs) were evaluated, a list of critical process parameters (CPPs) were curated through a series of statistical analyses, and their corresponding proven acceptable ranges (PARs) were established through Monte Carlo simulations.

Second, analytical methods' whose performance are sequence-independent and sequence-dependent were identified. For sequence-independent assays, Moderna used Spikevax material for assay validation. For sequence-dependent assays, Moderna used mRNA-1345-specific material, or a combination of Spikevax and mRNA-1345 materials, for assay validation.

Finally, release and stability data were used to evaluate changes in quantitative attributes over time across temperature conditions. mRNA purity was determined to be the primary SL-limiting attribute of mRNA-1345. For sequence-independent quantitative attributes, results from the mRNA-1345 development, clinical, and registration lots were plotted in variability charts alongside the results from the Spikevax lots used to originally determine the acceptance criteria. For sequence-dependent quantitative attributes, specifically mRNA purity, statistically based acceptance criteria were assessed to ensure consistency of future lots with those produced to-date, including those used in clinical studies.

During the review of process characterization, analytical method validations, and release and stability specifications, no statistical issues were identified, thus FDA has not sent an information request.

3. SUBMISSION QUALITY

The submission was adequately organized for conducting a complete CMC statistical review without unreasonable difficulty.

4. SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review for details.

5. SOURCES OF INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Because mRNA purity is one of the most important sequence-dependent CQAs, this review focuses on:

- mRNA purity assay validation for (b) (4) DP
- mRNA purity release and stability specifications for (b) (4) DP.

Per the CMC reviewer's request, this review also covers the (b) (4) process characterization. Important CQAs that are sequence-independent, or whose analytical methods do not involve statistical analysis (e.g., mRNA identity), are excluded from this review.

5.2 BLA/IND Documents That Serve as the Basis for the Review

This review refers to the following documents:

- BLA125775/0.0 (seq. 0001)
 - Module 3.2.S.2.5
 - process-validation-master-validation-summary.pdf
 - Module 3.2.S.2.6
 - manuf-process-dev-process-characterization.pdf
 - manuf-process-dev-manufacturing-history.pdf
 - Module 3.2.S.4.3
 - sop-1142.pdf
 - Module 3.2.S.4.3
 - val-anal-proc-mrna-purity-product-related-imp.pdf
 - qc-mvr-0061.pdf
 - Module 3.2.S.4.5
 - justification-of-specification.pdf
 - Module 3.2.S.7.1
 - stability-summary.pdf
 - Module 3.2.P.5.3
 - val-anal-proc-purity.pdf
 - Module 3.2.P.5.6
 - justification-of-specification.pdf
 - Module 3.2.P.8.1
 - stability-summary.pdf

6. DISCUSSION OF PROTOCOLS, ANALYSES, AND STUDY REPORTS

6.1 Process Characterization

The RNA vaccine manufacturing process, referred to as RNA-100, was used to manufacture Spikevax and will be used to manufacture other mRNA vaccine candidates, including mRNA-1345. Any vaccine manufactured using the RNA-100 process uses the same manufacturing steps, testing strategy, and consistent specifications regardless of sequence. Each manufacturing step is controlled by a different set of PPs.

Moderna's prior knowledge revealed that some CQAs (e.g., Spikevax versus mRNA-1345) behaved differently in certain manufacturing steps depending on the mRNA sequence. Those CQAs and the associated subset of PPs are considered sequence-dependent.

Because of the sequence dependence, the RNA-100 process needs to be adjusted by modifying sequence-dependent PPs to ensure consistent performance and quality of CQAs for mRNA-1345. The purpose of the process characterization study is to justify such modifications by re-assessing the statistical relationship between the sequence-dependent PPs and the sequence-dependent CQAs.

Once the sequence-dependent CQAs and PPs were curated using failure modes and effects analysis, Moderna performed a process characterization study to establish statistical relationships. Table 1 summarizes the process characterization study.

Finally, once a statistical relationship was established, it was used to classify CPPs and was used in a Monte Carlo simulation study to establish a PAR for each CPP. A PAR is a limit that a process parameter (including PP and CPP) needs to meet during manufacturing to ensure that the corresponding CQA is controlled.

Table 1. Process Characterization Study Overview

Manufacturing Step	Process Parameter (X)	CQA (Y)
(b) (4)		

Source: Table 10, Module 3.2.S.2.6, manuf-process-dev-process-characterization.pdf
Abbreviations: (b) (4)

Three manufacturing steps ((b) (4)) were characterized by multifactorial I-optimal design of experiments (DOE). In each manufacturing step (e.g., (b) (4)), the association between each CQA, Y (e.g., (b) (4)), and PPs, Xs (e.g., (b) (4)), was evaluated using least squares regression with main effects, interaction terms, and quadratic terms.

Reviewer’s Comment: Moderna tries to find a function that best describe the CQAs in terms of PPs:

(b) (4)

where

1. Y denotes a CQA associated with a specific manufacturing step, such as (b) (4) .

2. X denotes the corresponding PPs, see [Table 1](#) for all relevant PPs.
3. β denotes the unknown model parameters.
4. ε denotes the unknown random error term, assume $\varepsilon \sim N(0, \sigma^2)$.
5. $f()$ is a predefined function, for example: (b) (4)

The I-optimal DOE aims to identify the number of levels tested for each factor (X), given the study design constraints (e.g., limited number of experimental runs), by minimizing the relative prediction variance of Y over the space spanned by the factors (X s). Compared with other DOEs, e.g., A-optimal DOE that minimizes estimation variance, I-optimal DOE appears to be a good DOE in terms of the variance it intends to minimize.

Each least squares regression model was reduced by stepwise selection: nonsignificant (p -value > 0.05) PPs were removed starting with the largest p -value. Any PP found nonsignificant for all CQAs was not classified as critical, and its corresponding PAR was set equal to the range established by failure modes and effects analysis. PPs with significant effects for at least one CQA were classified as CPPs.

Monte Carlo simulations were used to predict multivariate process robustness and assign PARs.

Reviewer's Comment: The goal of the Monte Carlo simulations is to identify the PAR, denoted as (LL, UL), such that the probability that the CQA (Y) exceeds the upper (USL) and lower (LSL) specification limits given the PAR is below 1%.

Each factor (PP) was modeled using a uniform distribution and was varied randomly in the 10,000 simulation replicates performed. To include the associated variability of mRNA sequence and its potential impact to PAR, a uniform distribution was applied across the RNAs included in the characterization design.

PAR limits were explored dynamically using Monte Carlo simulation. PARs were assigned by adjusting limits within characterized ranges until the simulated failure rate for all CQAs was below 1%.

Reviewer's Comment: The statistical approaches used in the characterization study, including I-optimal DOE, least squares modeling, stepwise selection, and Monte Carlo simulations, are standard. Based on discussion with CMC reviewer, the final characterization study results, including CPPs selected and their corresponding PAR limits, are reasonable and thus acceptable.

6.2 Validation of (b) (4) mRNA Purity Assay

This assay determines the purity of mRNA-1345 for (b) (4) DP release and stability testing using (b) (4).

This assay was originally validated for Spikevax and was reviewed under BLA 125752. In the original validation study, accuracy, linearity, and precision were validated for (b) (4) DP samples over a range of (b) (4) total RNA content.

Because the mRNA purity is a sequence-dependent CQA, Moderna also conducted a supplemental validation study (Module 3.2.S.4.3 qc-mvr-0061.pdf) to demonstrate that the (b) (4) is suitable for testing mRNA-1345.

[Table 2](#) summarize the test articles used in this study. The following parameters were assessed: (b) (4)

Table 2. Test Articles

Sample Descriptions	Batch / Lot
Reference material	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
DP	(b) (4)

Source: Section 4.1, Module 3.2.S.4.3, qc-mvr-0061.pdf

Abbreviations: DP, drug product; (b) (4)

Reviewer's Comment: (b) (4)

I did not review the specificity results because Moderna only performed descriptive analyses and no quantitative acceptance criteria were established for specificity.

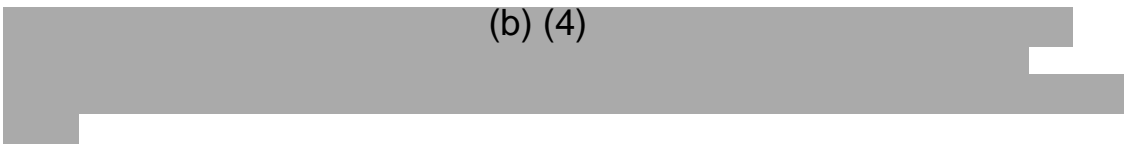
(b) (4)

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

(b) (4)

(b) (4)

(b) (4)



(b) (4)



(b) (4)



6.3 Release and Stability Specifications

Among all CQAs, the mRNA purity, representing the level of intact mRNA, is expected to change most during the manufacturing and distribution of the product. Therefore, direct measurement of mRNA degradation utilizing the mRNA purity assay by (b) (4) is the most critical stability-indicating measure of product integrity and activity. The SL is primarily justified based on statistical modeling of mRNA purity measured by (b) (4) in (b) (4) DP stability studies of mRNA-1345.

(b) (4)



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

(b) (4)

6.3.2 Drug Product

Moderna proposed an SL of 18 months for DP stored in the commercial container closure system when stored at the long-term storage condition of -40°C to -15°C, including up to 30 days of storage at 2°C to 8°C, and up to 24 hours at room temperature (15°C to 25°C) to support administration of the vaccine at the point-of-care site.

Degradation rates for mRNA purity of DP were estimated for (b) (4) different storage temperatures using the stability study results available as of March 27, 2023. mRNA purity stability data for all included DP lots were analyzed on the natural log scale.

[Figure 3](#) shows the log scale mRNA Purity by timepoint (months) at each temperature. The graphics and statistical modeling for mRNA purity were performed using only lots with a minimum of (b) (4) timepoints.

Development lot (b) (4) (teal label) was produced as part of a heat-degradation study, and therefore started at a lower mRNA purity. The slope for this lot is consistent with the other lots, suggesting a consistent degradation rate across a broad range of mRNA purity.

(b) (4)

The DP mRNA purity SL specification of $\geq 50\%$ (3.91 in [Figure 3](#)) is based on clinical results and in vivo results demonstrating that efficacy and immune responses are not impacted by variation of mRNA purity values at or above the DP SL specification. This DP SL specification applies to DP throughout its intended storage and use conditions, including at the end of SL.

To justify the proposed SL for DP, Moderna considered the minimum release limit (MRL) approach such that a batch of DP passing MRL is likely to remain above the mRNA purity SL specification throughout its SL.

To compute the MRL, Moderna followed the (b) (4) guidance on the stability evaluation of vaccines (b) (4) and derived the MRL from the SL specification (i.e., $\ln(50) = 3.91$) by adding the estimated losses in log scale mRNA purity during storage and handling, the statistical uncertainty of the estimated losses, and the mRNA purity assay uncertainty:

(b) (4)

where

CM = Clinical Minimum

t_i = Time at the i^{th} temperature

\hat{b}_i = Estimated loss rate at the i^{th} temperature

$s_{\hat{b}_i}^2$ = squared standard error of estimated loss rate at i^{th} temperature

s_{Assay}^2 = assay variability

The final estimated MRL is transformed back to the original mRNA purity scale.

Moderna used the mRNA purity specification as the clinical minimum and the root mean squared error estimate from the model fit to the data from all temperature to estimate the assay variability (s_{Assay}^2). Because degradation at lower temperatures is expected to be no greater than the degradation at higher temperatures, Moderna used the degradation rate observed at -25°C to -15°C as the degradation rate for both the -40°C and the degradation rate observed at 23 to (b) (4) $^\circ\text{C}$ as the degradation rate for 15 to 23°C .

The estimated loss rates and the uncertainties of estimates are summarized in [Table 9](#). The estimated assay variability is (b) (4).

Table 9. Estimated Loss Rates, the Uncertainties of Estimates, and Assay Variability

Storage Temperature	Loss Rate (Per Month), \hat{b}_i	Standard Error, $s_{\hat{b}_i}$	Time (Month), t_i	$t_i \hat{b}_i$	$t_i^2 s_{\hat{b}_i}^2$
-25°C to -15°C	(b) (4)				
2°C to 8°C					
23°C to (b) (4) $^\circ\text{C}$					

Source: Table 2, Module 3.2.P.8.1 stability-summary.pdf

Abbreviations: \hat{b}_i , estimated loss rate at the i^{th} temperature; $s_{\hat{b}_i}$, standard error of estimated loss rate at the i^{th} temperature; $s_{\hat{b}_i}^2$, squared standard error of estimated loss rate at the i^{th} temperature; t_i , time at the i^{th} temperature; t_i^2 squared time at the i^{th} temperature.

The final estimated MRL for %mRNA Purity is (b) (4).

Reviewer's Comment: Moderna's approach to justify the proposed DP SL by deriving MRL is appropriate. I also reproduced Moderna's MRL calculation.

Overall, the DP stability study is adequate from a statistical point of view. However, during internal discussion, the CMC reviewer pointed out two additional caveats:

1. All lots used in the stability study are unlabeled DP lots that did not undergo a (b) (4) step as labeled DP lots do for package and labeling, and
2. No lot used in the stability study underwent end-to-end storage conditions (i.e., from the beginning of (b) (4) °C to -30°C all the way to the end of 23°C to (b) (4)).

Because Moderna has stated that 1. they intend to submit additional stability studies comparing (b) (4), and 2. they will test (b) (4) and submit the data once available, we agreed not to send an information request.

7. CONCLUSIONS

7.1 Statistical Issues and Collective Evidence

Moderna validated its mRNA purity assays for (b) (4) DP by assessing the accuracy, precision, linearity, and range. The mRNA purity assay validation study design did not allow assessment of accuracy performance for (b) (4) samples around the lower end of the assay range (i.e., (b) (4) content). While the accuracy performance for DP samples at (b) (4) content is satisfactory, unless DP performance could be used to supplement the (b) (4) performance, separate assay ranges for different test samples should be established. Nevertheless, this is unlikely to be a substantial risk to the consumer because the DP assay has been adequately validated.

Moderna submitted stability data from (b) (4) lots at (b) (4) different temperature conditions. This supported an (b) (4) SL at (b) (4), including an optional interim storage of up to (b) (4) at (b) (4) for (b) (4). Moderna also included stability data from (b) (4) lots at (b) (4) different temperature conditions to support a SL of 18-month at -40°C to -15°C, including up to 30 days of storage at 2°C to 8°C and up to 24 hours at room temperature (15°C to 25°C) for DP. The stability results do not suggest a concerning level risk of lots going out-of-specification within the proposed shelf lives. Therefore, the proposed shelf lives are acceptable.

7.2 Conclusions and Recommendations

Overall, Moderna has adequately validated their mRNA purity assays, and has submitted adequate justification for their proposed (b) (4) DP shelf lives. Therefore, I recommend approval.