U.S. FOOD & DRUG ADMINISTRATION

Information Request

Our Reference: STN: 125752/2

Information Request #11

Date: October 22, 2021

To: **Michelle Olsen, Ph.D.**
ModernaTX, Inc.
Email: Michelle.Olsen@modernatx.com

From: **Josephine Resnick, Ph.D.**
DVRPA/OVRR/CBER
Email: Josephine.Resnick@fda.hhs.gov

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Analytical method procedure and Validation, Lot Release Assays.

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have the following requests for additional information:

1. Regarding determination of Protein Expression from mRNA using (b) (4) (b) (4) (SOP # 0937):

   a) (b) (4) is used for determination of protein expression in the (b) (4) in-vitro translation assay. However, there is no information provided for the qualification of a new lot of (b) (4) to verify its suitability before using in release testing. Please provide the qualification procedure for new (b) (4) lots.

2. Regarding determination of % RNA Encapsulation by (b) (4) (b) (4) (SOP# 1000):

   a) Per SOP 1000, a Response Factor (RF) of (b) (4) is used for determination of free mRNA. Please provide in detail how the RF was determined.

   b) Please provide the validation data (Attachments 1 -3) in the validation report QC-MVR-0009.

3. Regarding release testing sites:

   a) If you are planning to perform release testing at Quality Control laboratory Annex (Dedham, MA) or any other site, please provide the method transfer qualification reports.

4. Regarding SOP-0997 "Determination of (b) (4) (b) (4) Since the accuracy and precision of (b) (4) (b) (4) reasonably established but the accuracy of measuring (b) (4) (b) (4) is not, we recommend calculating the (b) (4)

(b) (4)

   Please comment.

5. Regarding SOP -0998 "Determination of Particle Size Distribution and Polydispersity by Dynamic Light Scattering" for drug substance (DS) mRNA-1273 LNP and drug product (DP) mRNA-1273 LNP: In order for CBER to perform the test, additional information is needed. Please provide a formula to calculate the (b) (4) of a sample as described in section 8.10.5.2 or attachment 5.

6. Regarding document QC-MVR-0011 "Validation Report of SOP-0998":

   a) Assay accuracy studies were conducted using standards diluted in (b) (4) (b) (4) Please demonstrate linearity and accuracy of the assay in the product matrix. Since DS and DP (b) (4) (b) (4) we suggest including a qualified DS or DP lot as control in each sample run.

   b) Linearity of the method was not validated, please demonstrate the linearity of method for DS and DP matrix with defined acceptance criteria.

   c) Validation studies were performed at your Norwood, MA facility. Please confirm that this is the only site performing this release test. Please note that if you intend for other sites to perform this or other DS or DP release tests, transfer reports need to be submitted to your file.

7. Regarding SOP-0999 "Determination of RNA Concentration in (b) (4)

a) Attachment 2 provides a typical (b) (4) standard preparation, in which a (b) (4) Please explain the measures taken, such as (b) (4), to ensure resolution of (b) (4).

b) Please provide representative (b) (4) demonstrate (b) (4) details. We recommend (b) (4) be included in your SOP if they differ from the reference standard (b) (4)

8. Regarding document QC-MVR-0008 “Validation Report of SOP-0999”:

a) Please provide (b) (4) that were used in the linearity study.

b) It is not clear how the spiked samples were prepared. To demonstrate the method is suitable for its intended purpose, we expect accuracy and linearity of the method to be validated with samples in DS/DP matrix spiked with known amounts of mRNA, and the theoretical amount of the spiked mRNA measured with an orthogonal method. Please describe how the spiked samples were prepared and if they are not representative of DS and/or DP, provide justification.

Please confirm your receipt of this request, and provide your responses as an amendment to STN 125752 at your earliest convenience but no later than November 2, 2021.

Please contact me if you have questions and include Sudhakar Agnihothram (sudhakar.agnihothram@fda.hhs.gov) and Joseph Kulinski (joseph.kulinski@fda.hhs.gov) on all communications.