RESPONSE TO FDA COMMENTS ON INFORMATION REQUEST#35 RECEIVED ON NOVEMBER 26, 2021

The Sponsor acknowledges INFORMATION REQUEST#35 dated 26 NOVEMBER 2021 in (**BOLD**)

**Product: COVID-19 Vaccine, mRNA (SPIKEVAX)**

**Subject: Validation of the (b) (4) method (SOP-1142)**

**Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have reviewed your November 30, 2021 response to IR#18 (dated November 10, 2021), regarding validation of the (b) (4) method (SOP-1142). We do not agree with your responses for the validation parameters listed below. Please respond by the requested date above. If clarification is needed, please request a technical call as soon as possible.**

**ITEM 1:**

**In comment 6, we requested data to demonstrate linearity of (b) (4) (b) (4) The developmental data you provided using stability samples (b) (4) ), suggests linearity can indeed be demonstrated, however, the results cannot be accepted because the results were not from a study with predefined acceptance criteria. Please provide data from a protocol-driven validation study using samples generated by spiking DS/DP with stressed samples. Spiking should span the appropriate range ((b) (4) ) for (b) (4) (b) (4) . Please note, we do not agree with using the (b) (4) as a surrogate for (b) (4) (b) (4) . Please evaluate linearity of (b) (4) independently, using (b) (4) (b) (4) ) in place of (b) (4) .**

**Sponsor Response:**

The Sponsor commits to performing additional linearity experiments for (b) (4) (b) (4) ) independently, using (b) (4) ) in place of (b) (4) , as requested. An approved supplemental validation protocol with predefined acceptance criteria will be followed for these studies. Target completion for this study is March 31, 2021. Transition of the purity testing of mRNA-1273 Drug Product, CX-024414 mRNA and mRNA-1273 LNP from SOP-0996 to SOP-1142 for EUA labeled product will follow successful completion of these studies.

**ITEM 2:**

**In comment 7, we requested data to demonstrate the accuracy of measurements for (b) (4) (b) (4) ). As for the linearity data, we do not agree with using (b) (4) as a "surrogate" for (b) (4) since the assay has (b) (4) (b) (4) (b) (4) In addition, the format in which you presented accuracy data is not correct: since the reportable result of the assay is (b) (4) accuracy should be determined as the**

(b) (4)

(b) (4) **. Data should be provided for** (b) (4) **throughout the assay range** (b) (4) **.**

**Sponsor Response:**

Additional experiments will be performed. The accuracy of measurements for (b) (4) will be evaluated using linearity data. The (b) (4) (b) (4) will be calculated. An approved supplemental validation protocol with predefined acceptance criteria will be followed for these studies. Target completion for this study is March 31, 2021.

**ITEM 3:**

**In comment 8, regarding intermediate precision (IP), your response stated that Table 4 in the validation report (QC-MVR-0025) provides the requested IP data, however, the data are system suitability results, not precision. The data in Table 7 and 8 include an assessment of repeatability for Analyst 1 and 2 at Norwood and Dedham, but data were not provided to demonstrate IP (i.e., assays performed on a different day/by different analyst at the same site) for each site. Please submit data to demonstrate inter-assay precision (IP) at each site.**

**Sponsor Response:**

Intermediate precision was executed by two analysts over two days and in two separate labs (Norwood QC and Dedham QC labs). However, the assessment of the method performance on a different day/by different analyst at each lab was not executed. Sponsor is committed to performing additional assessment for intermediate precision at each lab. An approved supplemental validation protocol with predefined acceptance criteria will be followed for these studies. Target completion for this study is March 31, 2021.

**ITEM 4:**

**In comment 9, your response stated the range** (b) (4) **of the method is** (b) (4) **for** (b) (4) (b) (4) **without providing data to support your claim. Range is demonstrated from linearity, accuracy, and precision and therefore data demonstrating acceptance criteria for each of these parameters are met should be provided at the lowest and highest** (b) (4) **in the range. The range should encompass the specification. Once you have established assay linearity, accuracy and precision for measuring** (b) (4) (b) (4) **independently, please determine the range of the method.**

**Sponsor Response:**

Linearity, accuracy and precision will be performed on (b) (4) to assess linearity to define the (b) (4). An approved supplemental validation protocol with predefined acceptance criteria will be followed for these studies. Target completion for this study is March 31, 2021.

**ITEM 5:**

**In response to comment 10 you provided Quantitation and Detection Limits (QL and DL) for (b) (4) . Since (b) (4) have very different attributes, the (b) (4) cannot be used as a surrogate for the determination of their QLs and DLs. Please evaluate DL/QL experimentally and/or empirically for (b) (4) independently. Empirical QL can be determined from the linearity plot ((b) (4) ), using the slope and standard deviation values of the regression line. Please provide the QL and DL, in (b) (4) , for (b) (4) (b) (4) .**

**Sponsor Response:**

QL and DL will be evaluated in (b) (4) for (b) (4) . An approved supplemental validation protocol with predefined acceptance criteria will be followed for these studies. Target completion for this study is March 31, 2021.