1. RESPONSE TO FDA COMMENTS ON INFORMATION REQUEST#29 RECEIVED ON DECEMBER 09, 2021

The Sponsor acknowledges INFORMATION REQUEST#29 dated 09 DECEMBER 2021 in (**BOLD**)

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Justification of Specifications

Our review of your August 16, 2021 submission (STN 125752/1) is ongoing. We have the following comments and requests for additional information:

To support the DP release and stability acceptance limits, please include the following information in section 3.2.P.5.6 *Justification of Specifications*:

ITEM 1:

In several IND communications including the CBER pre-BLA written responses from July 7, 2021, we had requested that a quantitative (b) (4) test be performed for DP release and stability monitoring. In the absence of such a (b) (4) test, please provide available quantitative (b) (4) results performed on DS or DP lots as a characterization test using your qualified (b) (4) (b) (4) or any other quantitative or semi-quantitative test. Please provide (b) (4) results for all DS or DP lots for which quantitative (b) (4) data are available at release or as part of stability studies together with data for RNA content (by AEX-HPLC), and RNA purity and product-related impurities (by RPIP-HPLC) from corresponding lots and time points.

Sponsor Response:

Results for RNA content, RNA purity and product-related impurities of the mRNA-1273 LNP and DP were previously provided in CTD Sections 3.2.S.2.6 {mRNA-1273 LNP, Comparability} and 3.2.P.2.3 {Comparability}of the BLA 125752 as part of the comparability assessment. (b) (4) was tested as part of the extended characterization comparability assessment for mRNA-1273 LNP lots and is also provided in CTD Section 3.2.S.2.6 {mRNA-1273 LNP, Comparability}. Release and extended characterization results were combined into a single summary table for (b) (4) lots of mRNA-1273 LNP shown in Table 1. (b) (4) testing was performed on mRNA-1273 DP lots for information purposes and release and (b) (4) results were combined into a single summary table for (b) (4) lots of mRNA-1273 DP shown in Table 2. The quantitative (b) (4) (b) (4) will continue to be included in the demonstration of analytical comparability when new scales, sites and process improvements are introduced for mRNA-1273 LNP to provide additional assurance of product consistency as part of Phase 4 (post approval) comparability as described in DPAD-PRO-0586 (provided in CTD Section 3.2.R of BLA 125752 SN 0002 dated August 16, 2021).

Table 1: (b) (4) RNA Content, Purity and Product-Related Impurities for (b) (4) mRNA-1273 LNP lots.

(b) (4)

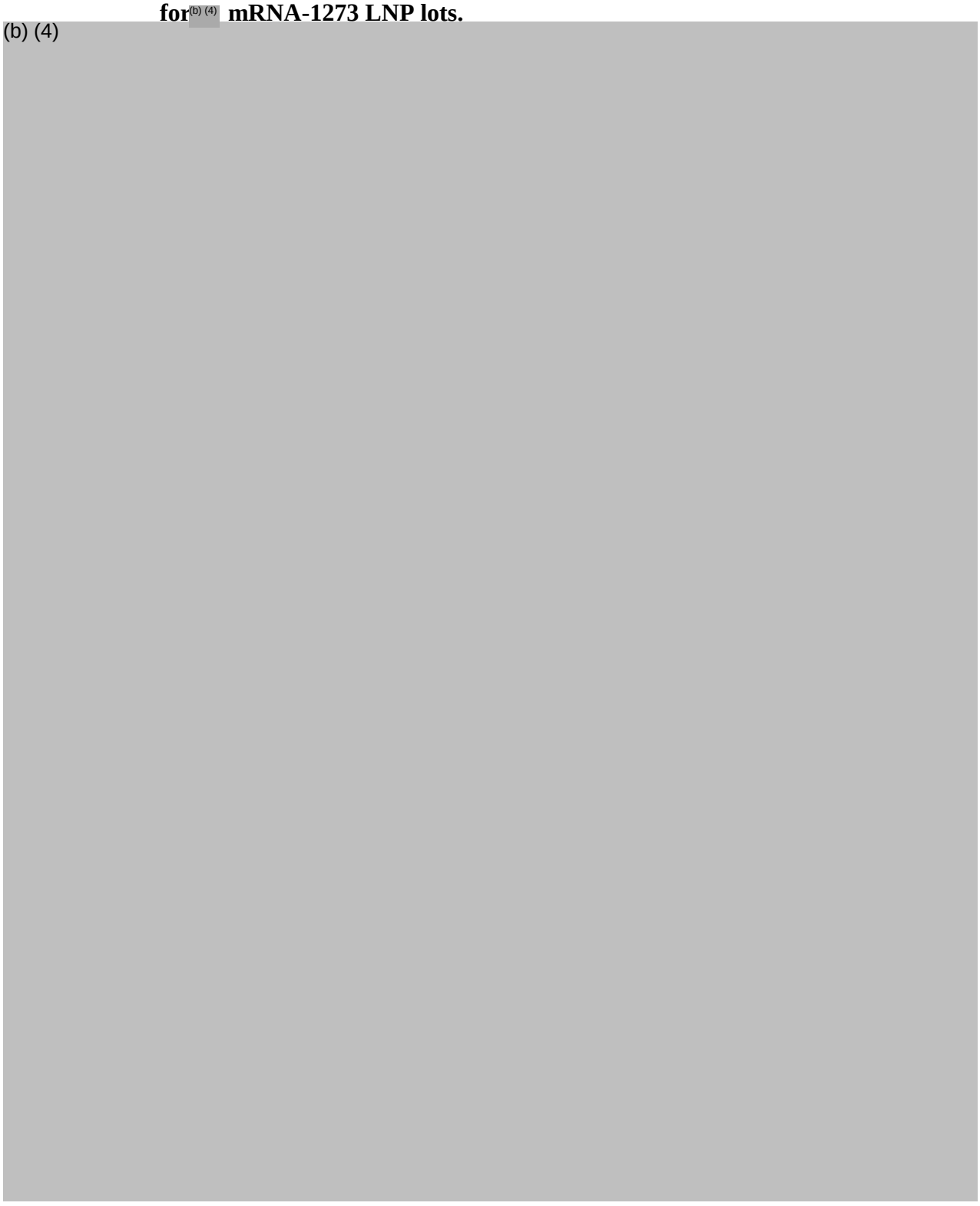
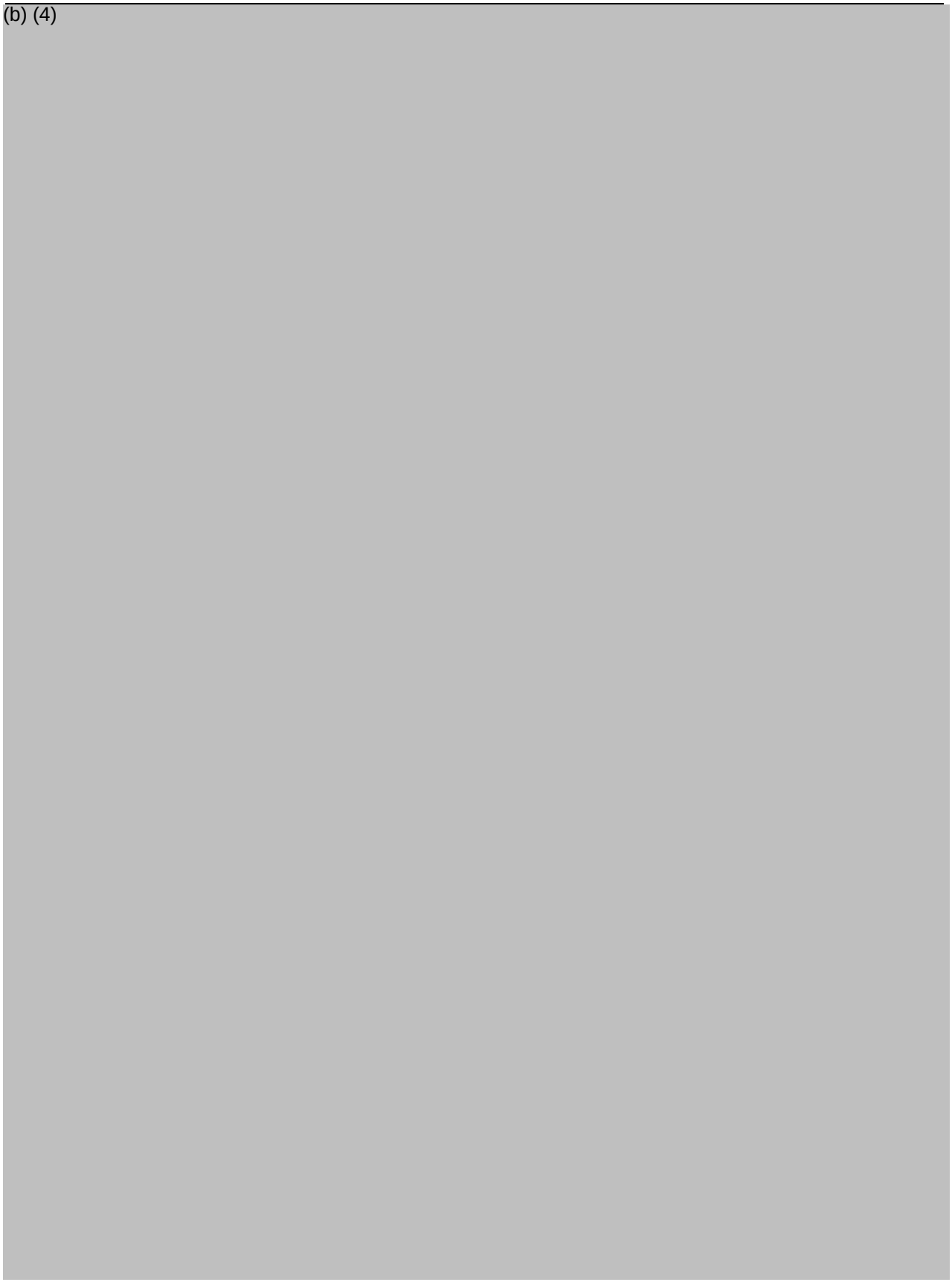


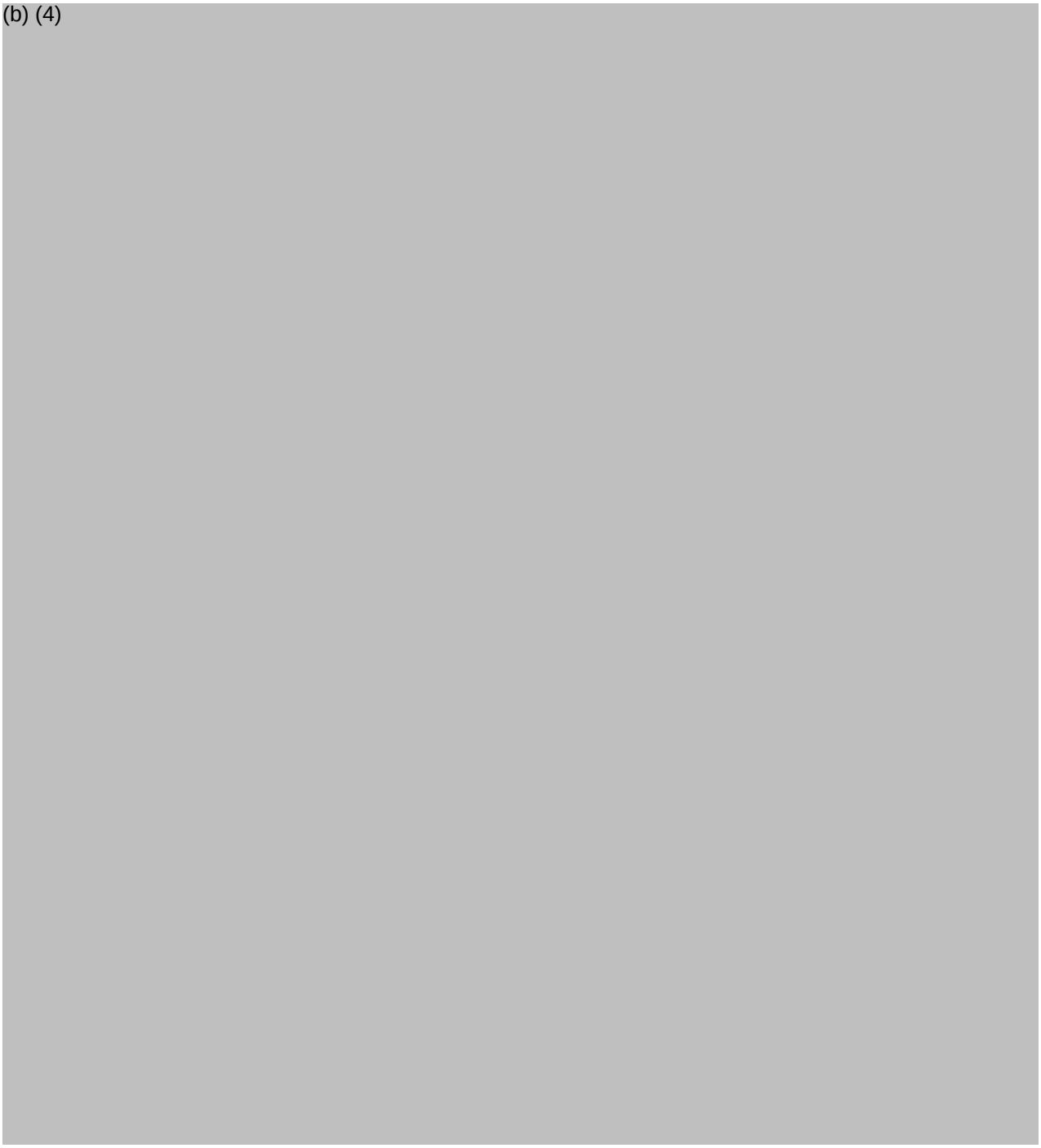
Table 2: (b) (4) RNA Content, Purity and Product-Related Impurities for (b) (4) mRNA-1273 DP lots.

(b) (4)

(b) (4)



(b) (4)



ITEM 2:

Please include a description of the (b) (4) method (or any other quantitative characterization test method used) and a summary of results for the DS in section 3.2.S.2.6 *Manufacturing Process Development {Comparability Scale A to Scale B}* and/or the DP in section 3.2.P.2 *Pharmaceutical Development {Comparability},* as applicable.

Sponsor Response:

A description of the (b) (4) method and a summary of the results for mRNA-1273 LNP lots has been added to CTD Section 3.2.S.2.6.3.3.6 {mRNA-1273 LNP, Comparability} and are provided in this response and the response to Item 1, respectively. (b) (4) testing is not required for comparability assessment of mRNA-1273 DP but has been performed for information only and results have been provided in Table 2 of this response.

(b) (4)

(b) (4)

ITEM 3:

Please provide a justification for not performing a quantitative (b) (4) test as a quality release and stability test in section 3.2.P.5.6 *Justification of Specifications*.

Sponsor Response:

CTD Section 3.2.P.5.6 has been revised to include the justification provided below for not performing a quantitative (b) (4) test as a quality release and stability test.

The proposed panel of release tests comprehensively and thoroughly evaluates quality attributes of mRNA-1273 DP relevant to (b) (4). Routine characterization of (b) (4) is appropriately conducted through characterization of quantity and integrity of mRNA, confirmation of antigen identity by In Vitro Translation, and characterization of lipid nanoparticle biophysical attributes.

The Sponsor evaluated the concordance between mRNA purity, the (b) (4) (b) (4) and *in vivo* immunogenicity in the following two studies as shown in Table 3 and Table 4. (b) (4)

Study 1:

mRNA-1273 drug product was formulated using CX-024414 mRNA with a range of purity levels (b) (4)

The mRNA-1273 test articles evaluated in this study are shown in Table 3.

Table 3: Study Test Articles

(b) (4)

The relationship between (b) (4) and in vivo immunogenicity results was estimated across the four mRNA batches, separately at each dose level and day. Figure 2 shows that there is a trend towards stronger concordance in the lower end of the dose range, for Day 21 antibody titers and at lower dose levels for Day 36. At higher titers, the relationship between (b) (4) and titer plateaus with a slope closer to zero. Table 4 shows the Pearson's correlation coefficient for each dose-day combination. The correlation coefficients range from 0.90 to 0.99 for the day 21 sample, and from 0.58 to 0.98 for the day 36 sample. Consistent with the regression model results, the magnitude of the correlation coefficient for Day 36 samples decreases as dose levels increase.

(b) (4)

(b) (4)

Study 2:

(b) (4)

(b) (4)

The relationship between (b) (4) and in vivo immunogenicity results was estimated across the DP batches, separately at each dose level and day. Figure 3 shows the concordance across the dose range tested. Table 6 shows the Pearson correlation coefficients for each dose-day combination. The correlation coefficients range from 0.96 to 0.99 for day 21 samples, and from 0.92 to 0.99 for day 36 samples. These correlations show strong concordance between (b) (4) and (b) (4) results for all doses at day 21 and day 36.

(b) (4)

(b) (4)

There is a strong quantitative correlation between RNA degradation as measured directly by mRNA purity and the resulting (b) (4) levels. However, the correlation between (b) (4) (b) (4) and purity is dampened when purity is restricted to its specification acceptance range for mRNA-1273 DP. Purity is a more sensitive measure of (b) (4) because of its greater precision relative to its specification range. The higher variability inherent to the (b) (4) assay makes it a less sensitive measure of (b) (4) relative to its specification range.

The Sponsor confirms the proposed panel of release tests comprehensively and thoroughly evaluates quality attributes of mRNA-1273 DP relevant to (b) (4). Routine characterization of (b) (4) is appropriately conducted through characterization of quantity and integrity of mRNA, confirmation of antigen identity by In Vitro Translation, and characterization of lipid nanoparticle biophysical attributes.

ITEM 4:

Regarding the release and stability acceptance limit justifications and supportive data for RNA content (release and end of shelf-life: (b) (4)) and RNA purity (release: (b) (4) and end of shelf-life: (b) (4) we acknowledge the analytical data provided for (b) (4) DP lots. In addition, please include:

a. The clinical data from dose-ranging studies and effective delivery dose (EDD) ranges in Phase 3 studies, which support the proposed lower and upper limits for RNA content and lower limit for RNA purity.

b. The data and statistical analyses used to derive the (b) (4) end of shelf-life limit for RNA purity.

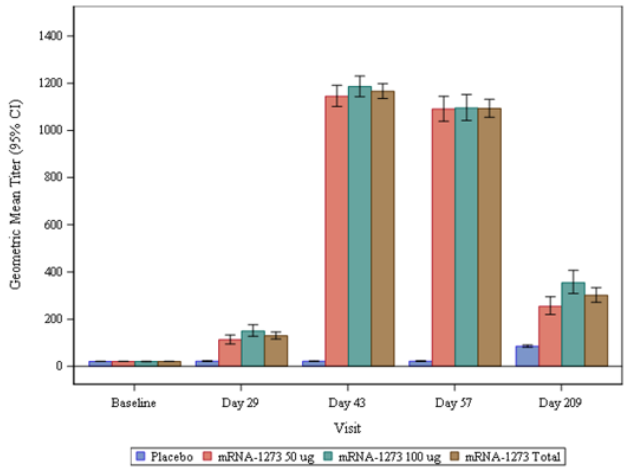
Sponsor Response:

Phase 2 Clinical Trial

The Phase 2 clinical trial was conducted using 3 Drug Product lots (8520100102, 8520100103, and 8520100104) with purities (b) (4) at release. The lot size was similar for all 3 lots, with average (b) (4) purity for the 3 lots combined. Nominal doses of 50 and 100 µg were compared to Placebo.

Two doses were administered at Days 1 and 29. Following the second dose, the responses to vaccination with either 50 or 100 µg mRNA-1273 were similar. For example, neutralizing antibody GMTs measured at Day 43 were 1145.4 for the 50 µg dose, and 1185.8 for the 100 µg dose. Figure 4 shows the MN Endpoint Titers for 180 participants receiving the Placebo, 174 participants receiving the 50 µg dose, and 181 participants receiving the100 µg dose. The median response was 1280 (upper limit of quantitation) for both groups receiving the mRNA-1273 vaccine. Source: P201 End of Part A CSR addendum

Figure 4: MN Endpoint Titer at Day 43 by Treatment Group.



Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantification; Max = maximum; Min = minimum; MN = microneutralization; nAb = neutralizing antibody; SARS-CoV-2 = severe acute respiratory syndrome coronavirus that causes COVID-19; ULOQ = upper limit of quantification.

Antibody values reported as below LLOQ are replaced by 0.5 x LLOQ. Values that are greater than the ULOQ are converted to the ULOQ.

For MN Endpoint Titer (the First Lot): LLOQ=40 and ULOQ=1280. For MN50 (the First Lot): LLOQ=91.10 and ULOQ=2031.87. For MN Endpoint Titer (the new Lot): LLOQ=160 and ULOQ=1280. For MN50 (the new Lot): LLOQ=318.46 and ULOQ=1917.83.

Confidence intervals are calculated using t-distribution of log-transformed values then back transformed to the original scale for presentation.

The Phase 2 clinical results support consistency of immune response for an effective dose of (b) (4) µg (= (b) (4) purity * 50 µg nominal dose) compared to (b) (4) (100 µg nominal dose).

Efficacy was demonstrated in the Phase 3 clinical trial using doses projected to range from (b) (4) at the time of administration

The mRNA-1273 vaccine met its primary efficacy endpoint in the Phase 3 COVE Study. Median purity for the Phase 3 doses at administration is projected to have been (b) (4), ranging from (b) (4) (b) (4) This translates to an Effective Delivered Dose range of (b) (4) for the nominal dose level 100 µg.

Purity at administration was simulated using the measured purity at release for each Phase 3 lot, the actual time per dose in storage at -70°C and 5°C, and 0 to 12 hours at 25°C during clinical use (randomly simulated from a Uniform distribution). Degradation rates at each temperature are based on all available stability study timepoints. Storage times were available for 29,694 of the 30,000 doses. Figure 5 shows the projected purity for all doses with storage times available. The median projected purity is (b) (4) at administration, with lower quartile (b) (4) and upper quartile (b) (4) (meaning that the mid-range 50% of doses administered in Phase 3 have projected purity between (b) (4) and (b) (4) at the time of administration).

Figure 5: Projected purity at administration for Phase 3 doses

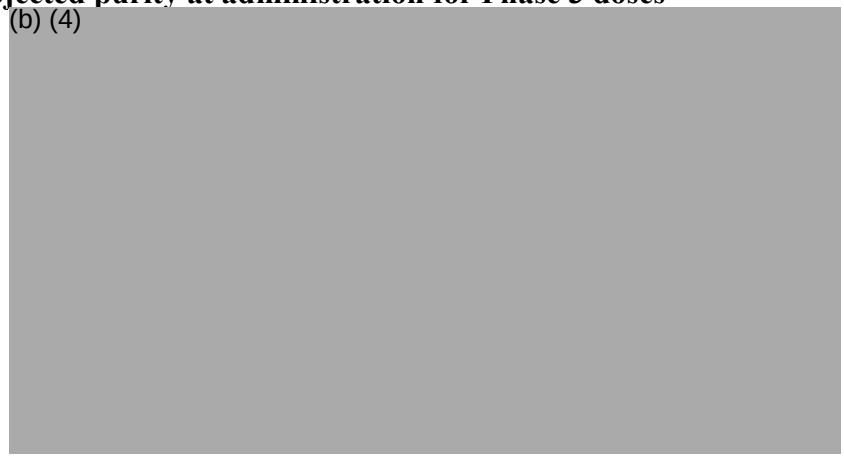


Figure 6 shows the projected purity at administration per dose based on the reported time at 5°C (Days between Shipping and Administration). Some doses were held for more than 60 days before administration, resulting in some doses below (b) (4) purity at administration.

Figure 6: Projected Purity for 29,694 Phase 3 Doses at Administration

The mRNA-1273 vaccine met its primary efficacy endpoint in the Phase 3 COVE Study. Median purity for the Phase 3 doses at administration is projected to have been (b) (4) ranging from (b) (4) (b) (4) This translates to an Effective Delivered Dose range of (b) (4) for the nominal dose level 100 µg.

The Purity of commercial doses will be consistent with the Phase 3 trial doses

In order to ensure a minimum Purity of (b) (4) through shelf life, a Minimum Release Limit for Purity will be set at (b) (4) This internal limit allows for up to 8 months of storage at -20°C, plus up to 1 month of storage at 5°C, plus up to 24 hours of use at 25°C.

The purity of doses at administration was simulated for 100,000 future doses based on these storage times, applying the same degradation rate estimates as used for simulating the purity of the Phase 3 doses, and assuming an average Purity of (b) (4) at Release based on manufacturing experience. The average and median Purity is slightly lower for the simulated commercial doses, but the minimum Purity is slightly higher because of the limits on time allowed at each temperature for commercial doses. The median purity for commercial doses is projected at (b) (4), with lower quartile (b) (4) and upper quartile (b) (4) (Figure 7).

Figure 7: Projected Purity (%) at Administration Comparing Phase 3 and Commercial Doses

ITEM 5:

Please provide information on the calculations used to estimate RNA purity release limits based on DP degradation curves, estimated degradation during storage and handling, and known assay variability. In addition, please provide report DPAD-00881 *Justification of Specifications for mRNA-1273 Purity Minimum Release Limit* submitted to EUA 27073 and updated degradation curve data for DP lots stored at the intended storage conditions.

Sponsor Response:

The Sponsor has provided DPAD-00881 as an attachment to Section 3.2.P.5.6 of BLA 125752 as part of this submission. This report provides the calculations used to derive the RNA minimum purity release limit based on the minimum purity requirement throughout shelf life, the estimated degradation rates during storage and handling, and the estimated assay variability.

The degradation rates are reassessed periodically as new stability timepoint results become available. The degradation rates are reported in DPAD-00880 which was updated using stability results available as of October 2021. The degradation rates did not change significantly compared to the previous update based on data available in April 2021.

2. SUMMARY OF CHANGES

The summary of revised Module 2 and Module 3 CTD sections that are being submitted with this quality information amendment are described in the following table.

CTD Section		Changes
3.2.S.2.6 { mRNA-1273 LNP , Comparability}	Manufacturing Process Development	• Addition of Section 3.2.S.2.6.3.3.6 for (b) (4) description and process performance
3.2.P.5.6	Justification of Specifications	• Addition of Section 3.2.P.5.6.2.18 Justification for not performing a quantitative (b) (4) test as a quality release and stability test • Addition of Attachment DPAD-00881