

RESPONSE TO CBER COMMUNICATION REGARDING CMC QUESTIONS RECEIVED ON DECEMBER 08, 2020

The Sponsor acknowledges CBER's communication regarding CMC questions which were sent by FDA via email to Carla Vinals on December 08, 2020 concerning the CMC information for the Lonza Biologics, Inc. facility included in IND 19745.

This document provides the Sponsor's responses to CBER's requests (in **Bold**).

Request 1

You indicated that the Lonza facility is being modified to accommodate the manufacture of large-scale (b) (4) drug substances (DS) and that you intend to submit supporting PPQ report in January 2021. Based on the batch analyses in IND 19745/amendment 84, Lonza manufactured one batch of each DS at large scale. Please provide the following information to ensure the modifications have no impact on (b) (4) mRNA DS manufacture:

- a. *Updated floor plans of Lonza facility (HVAC zoning, flows, room classifications and pressure differentials)*
- b. *Environmental monitoring data for the period from October 20, 2020 to the present for manufacturing (b) (4) and supporting areas or a statement that no changes (including air rebalancing) to (b) (4) were made as a result of the facility modifications*

Sponsor's Response:

- a. The requested updated floor plans for the Lonza facility is provided in [Section 3.2.A.1.1.2 {Lonza Biologics, Inc}](#) and [Section 3.2.A.1.5.3 {Lonza Biologics, Inc}](#). The revised Lonza facility drawings reflect the facility modifications made for manufacture of large scale mRNA drug substances. The (b) (4) scale CX-024414 mRNA will no longer be manufactured at Lonza Portsmouth and manufacturing (b) (4) is no longer used in mRNA manufacturing activities.
- b. The requested Lonza environmental monitoring data is provided in section [3.2.A.1.2.1 {Lonza Biologics, Inc}](#) for the full scale mRNA drug substance manufacturing suites (b) (4) from release for GMP use through 30Nov20. The (b) (4) scale CX-024414 mRNA manufacturing (b) (4) is no longer used in mRNA manufacturing activities.

Request 2

Regarding your manufacturing equipment:

- a. *According to cross-referenced (b) (4), mRNA manufacturing areas are equipped with the following equipment not listed in your IND: (b) (4)*
(b) (4)
(b) (4) *Please clarify, if any of this equipment is used in mRNA manufacture (including onsite buffer preparation) and provide an updated equipment list with the qualification status.*

- b. *You stated that (b) (4), however system cleaning and storage procedures were also provided. Please explain and provide cleaning validation/verification acceptance criteria, if applicable. If cleaning validation has not been performed, please explain how you ensure the system is clean and free from cleaning/storage solution residuals prior to each use.*
- c. *Please provide cleaning validation for the (b) (4) (b) (4) or explain how you ensure the system is clean and free from cleaning/storage solution residuals prior to each use.*

Sponsor's Response:

- a. The requested updated equipment list with qualification status for the equipment used in the Lonza mRNA full scale manufacturing process is provided in [Section 3.2.A.1.7 {Lonza Biologics, Inc}](#). (b) (4) are not used in the mRNA manufacturing process. Qualification reports associated with equipment used in mRNA full scale manufacturing process is provided in [Section 3.2.A.1.7.1 {Lonza Biologics, Inc}](#).
- b. The requested clarification of verification for the (b) (4) used in the Lonza mRNA full scale manufacturing process being free from cleaning and storage solutions is provided in [Section 3.2.A.1.6.2 {Lonza Biologics, Inc}](#).
- c. The requested clarification of verification for the (b) (4) used in the Lonza mRNA full scale manufacturing process being free from cleaning and storage solutions is provided in [Section 3.2.A.1.6.2 {Lonza Biologics, Inc}](#).

Request 3

We noted that measured RNA content in PPQ lots was (b) (4) whereas RNA concentration measured during bottle fill homogeneity study was (b) (4). Please explain the discrepancy in the results.

Sponsor's Response:


The discrepancy between the measured mRNA content in the PPQ lots and the RNA concentration measured during the bottle fill homogeneity study (BFH) is attributed to the two different RNA content assays used for each collection point, as follows:

- BFH (bulk fill homogeneity) testing was performed by (b) (4) (b) (4)
- Final release testing was performed by Moderna per *SOP-0249 mRNA Concentration by NaOH Digestion*

The observed differences for the BFH (b) (4) vs sodium hydroxide (NaOH) digestion method for CX-024414 final release testing, are in line with the observed differences during method development. Specifically, the concentration of total RNA for the in-process BFH samples was determined using (b) (4)

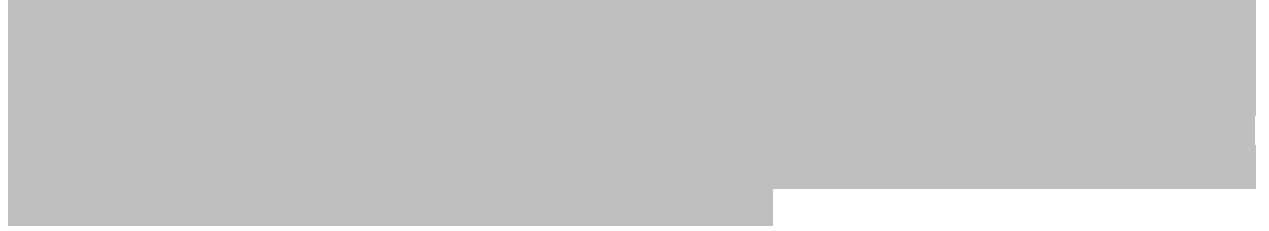
In contrast, CX-024414 mRNA final release testing is tested using sodium hydroxide digestion of the mRNA, (b) (4)

(b) (4) . The concentration of mRNA is determined using the measured UV absorbance at (b) (4) of a sodium hydroxide-digested total mRNA, and a calculated standard (b) (4)



(b) (4)

During development, a bridging study was performed to characterize the observed differences in RNA concentration that can be expected (b) (4)



(b) (4)



(b) (4)



It is important to note that the observed differences in RNA concentration values reported by (b) (4) and Moderna for the BFH and final release testing samples are in-line with the expected differences based upon the methods utilized at the different steps of analysis. The mean % difference for the two methods is (b) (4) .

(b) (4)



Request 4

Please clarify the following related to your contamination and cross- contamination controls:

- a. *For each (b) (4) in the Cell Therapy facility, please clarify supplied air makeup (e.g. fresh, recirculated, and ratios, if applicable). If recirculated air is supplied, please specify the area, from which the air is being recirculated.*
- b. *Please provide description of the gowning used in the facility and specify the areas, where different levels of gowning are required.*
- c. *Please specify the areas where degowning occurs.*
- d. *Per the provided personnel flow floor plan, personnel arriving in the facility from the (b) (4)*
Please explain.
- e. *Regarding the Q2 2020 EM trending report that you submitted, please clarify the difference between sample locations labeled in white and yellow, and between those with and without sample type labels associated with them (see p.166 for an example).*
Please explain what numbers next to each sample type represent and explain how samples shown outside of a room diagram (p.188) are related to the sample locations within the room.
- f. *Please provide a list of utilities used in mRNA DS manufacture and specify if any of them are considered product contact.*
- g. *Please clarify which disinfectants tested in the provided effectiveness study are actually used in the facility.*
- h. *You stated that Lonza Portsmouth Cell Therapy facility is a multi-product facility manufacturing autologous and allogeneic cell therapies. Please clarify if these products can be processed at risk, without donor testing results available and if so, what controls are in place to ensure no impact on mRNA DS (i.e. fully closed process, dedicated manufacturing suites, etc.).*
- i. *Please summarize your procedures for introduction of new products to the facility.*

Sponsor Response:

- a. The requested information on the Lonza Portsmouth Cell Therapy Facility (Lonza CT facility) (b) (4) supply and recirculation is provided in [Section 3.2.A.1.2.1 {Lonza Biologics, Inc}](#).
- b. The requested information on Lonza CT facility gowning requirements is provided in [Section 3.2.A.1.5.3 {Lonza Biologics, Inc}](#).
- c. The requested information on Lonza CT facility de-gowning areas is provided in [Section 3.2.A.1.5.3 {Lonza Biologics, Inc}](#).

- d. The use of (b) (4) in the Lonza CT Facility for movement of materials and equipment only is controlled procedurally through the Cell Therapy Facility Material and Equipment Movement SOP. Personnel are to only enter manufacturing areas using (b) (4). The demarcation line of a (b) (4) Personnel do not cross the demarcation line of the (b) (4) and must exit using the same door as entry. Materials/equipment placed in the (b) (4) are considered to be in a lower grade area. The materials/equipment are cleaned and retrieved from the (b) (4) from the lower grade side.

Waste is transferred from manufacturing areas in closed containers by personnel and is placed into (b) (4) then personnel return through (b) (4) into the (b) (4). This is shown on the Personnel Flow diagram as the continuous double arrow. Personnel access the dedicated (b) (4) Personnel remove the waste from the (b) (4) for transportation back to (b) (4). This is indicated by the use of the non-continuous arrow. Personnel flows do not continue through (b) (4).

- e. The primary map convention used in the Lonza Q2 2020 EM trending report is for room ID numbers to be in white, with individual samples site ID numbers within that room as yellow. The Lonza room number convention is ##### (i.e. 1334), with the individual sample site number being #####-# (i.e. 1334-1, 1334-2, etc.).

Certain maps pre-date the color-coding convention and may show both room ID number and individual site ID numbers as white. This coding is from the master P&ID maps, maintained by Engineering, and used within the QC MODA EM database to generate the report maps for visually summarizing monitoring results within the rooms. Although the color-coding convention may be different, the maps are accurate for the sample site locations and can be used for their intended purpose within the Environmental Monitoring reports.

The numbers next to each sample type symbol represent the number of samples taken for that analysis type in the given quarter. The samples outside the room diagram represent (b) (4) results (personnel in operation monitoring and routine at-rest monitoring) where the scale of the map prevents including the data within the map itself for those (b) (4).

- f. The utilities listed in [Section 3.2.A.1.2 {Lonza Biologics, Inc}](#) for the Lonza CT Facility includes only those utilities used in manufacture of mRNA drug substances. Clarification for utilities considered direct and indirect product contact is provided in [Section 3.2.A.1.2 {Lonza Biologics, Inc}](#).
- g. The requested clarification for the for the Lonza CT facility cleaning/disinfection agents used and included in the qualification report is provided in [Section 3.2.A.1.6.3 {Lonza Biologics, Inc}](#).
- h. The Lonza CT facility requires that all human sourced donor material entering the facility, whether allogeneic or autologous, be tested as defined in (b) (4). Additional information concerning control of contamination/cross-contamination of different product types is provided in [Section 3.2.A.1.5 {Lonza Biologics, Inc}](#).

- i. The requested information for the Lonza procedure for introduction of new products to the Portsmouth facility is provided in [Section 3.2.A.1.5 {Lonza Biologics, Inc}](#).

Request 5

You stated that (b) (4) supplying water to Cell Therapy facility is fed from (b) (4). Please confirm that (b) (4) is used in manufacture of US licensed products.

Sponsor Response:

The Lonza (b) (4) is qualified and used in production of drug substance for five (5) US licensed products. Additional information on Lonza manufacture of the related US licensed products can be provided directly to the agency.