RESPONSE TO FDA COMMENTS ON CMC RECEIVED ON 28 SEPTEMBER 2021

The Sponsor acknowledges FDA comments on CMC topics (in **Bold)**

Clinical: efficacy data; CMC: manufacturing processes

Our review of your August 16, 2021 submission (STN 125752/1) is ongoing.

The following are Non-Priority items requested for additional CMC information regarding your manufacturing process. A response is requested by October 8, 2021:

ITEM 1:

In the Master Specification tables provided for non-compendial raw materials used in the manufacture of CX-024414 mRNA Drug Substance (e.g., Tables 18 – 42 in section 3.2.S.2.3 *Control of Materials {CX-024414} Raw Materials*), please confirm that the tests listed in those tables are performed at the ModernaTX and Lonza manufacturing sites prior to raw material use in manufacture. In addition, please confirm that Moderna has release and quality testing in place for the raw materials used for the manufacture (b) (4) , mRNA-1273 LNP DS and mRNA-1273 DP. If Moderna is not performing additional release testing for any raw materials used in the manufacture of the products listed here, please revise the Control of Materials sections for (b) (4) DS and the DP to specify the tests performed by the respective product vendors.

Sponsor Response

Master specifications as presented in BLA 125752 are approved by the sponsor for non-compendial raw materials used in the production of (b) (4) , mRNA-1273 LNP drug substance (DS) and mRNA-1273 drug product (DP). Since non-compendial raw materials from various suppliers may have different acceptance criteria, the master specifications provide a harmonized acceptance criterion for non-compendial raw materials. The attributes and acceptance criteria listed in the master specifications must therefore be met by the vendor for their supplied raw materials. Currently, all non-compendial raw materials used in the DS or DP manufacturing process, across multiple suppliers comply with their corresponding master specifications established at Moderna. Non-compendial raw materials sourced from new suppliers will need to demonstrate compliance with the master specification attributes and limits as well prior to being introduced into the manufacturing process.

Since the vendor specifications comply with the attributes and limits specified in the master specification, re-testing of these attributes is not performed at the ModernaTX or Lonza manufacturing sites. As part of incoming raw material quality inspection, at a minimum, the (b) (4) of the raw material is tested at each manufacturing site. Additional testing may be performed as per site defined specifications for the raw materials.

Testing and associated results performed by the non-compendial raw material vendor is captured in a vendor supplied certificate of analysis (CoA). As part of incoming raw material quality inspection, a check of the vendor certificate of analysis (CoA) is performed against the vendor specifications (which are aligned as applicable with the master specification) by each manufacturing site.

The combination of the use of the master specification as a minimum acceptance criterion for a non-compendial raw material, and the check of vendor CoA against vendor specifications allows for harmonization of acceptance criteria for the non-compendial raw material across multiple vendors and sufficient control on quality of the raw material. Re-testing of these attributes is therefore not performed upon receipt at the manufacturing sites.

ITEM 2:

The linearized pDNA template was initially manufactured at the (b) (4) facility. This manufacturing step has now been transferred to Aldevron to supply the linearized pDNA template for the manufacture of EUA and commercial vaccine product. In your BLA, release data and a Certificate of Analysis were provided for pDNA batch (b) (4) manufactured at (b) (4). We acknowledge that the quality release criteria are the same at (b) (4) and Aldevron; however, please provide quality data for a representative linear pDNA batch produced at Aldevron.

Sponsor Response

Attached is a representative Certificate of Analysis of Aldevron manufactured Linear Plasmid (Aldevron GMP Plasmid Certificate of Analysis Lot (b) (4)).

ITEM 3:

Residual DNA was defined as a Critical Quality Attribute of CX-024414 mRNA in multiple sections of Module 3, and the residual DNA template test by qPCR was performed for release of CX-024414 mRNA during clinical development and validation across the process scales and sites. In addition, results from residual DNA testing were included in all the CoAs provided in section 3.2.S.4.4 *Batch Analyses*. However, we note in the BLA, that residual DNA was not listed among the CX-024414 specifications (Table 1 in section 3.2.S.4.1 *Specification*) and is no longer considered a Critical Quality Attribute (Table 1, section 3.2.S.4.5 *Justification of specification*). Please provide a justification for this change in your quality assessment of the product and for not performing the test. In addition, if you intend to omit this test, please provide product characterization data and validation data showing consistent removal of DNA below the previously specified limit.

Sponsor Response

(b) (4)

(b) (4) results are available for (b) (4) lots of CX-024414 mRNA following SOP-0491. The (b) (4) is shown in Figure 1. All results are far below the specification limit of (b) (4)

(b) (4)

Figure 1: (b) (4)

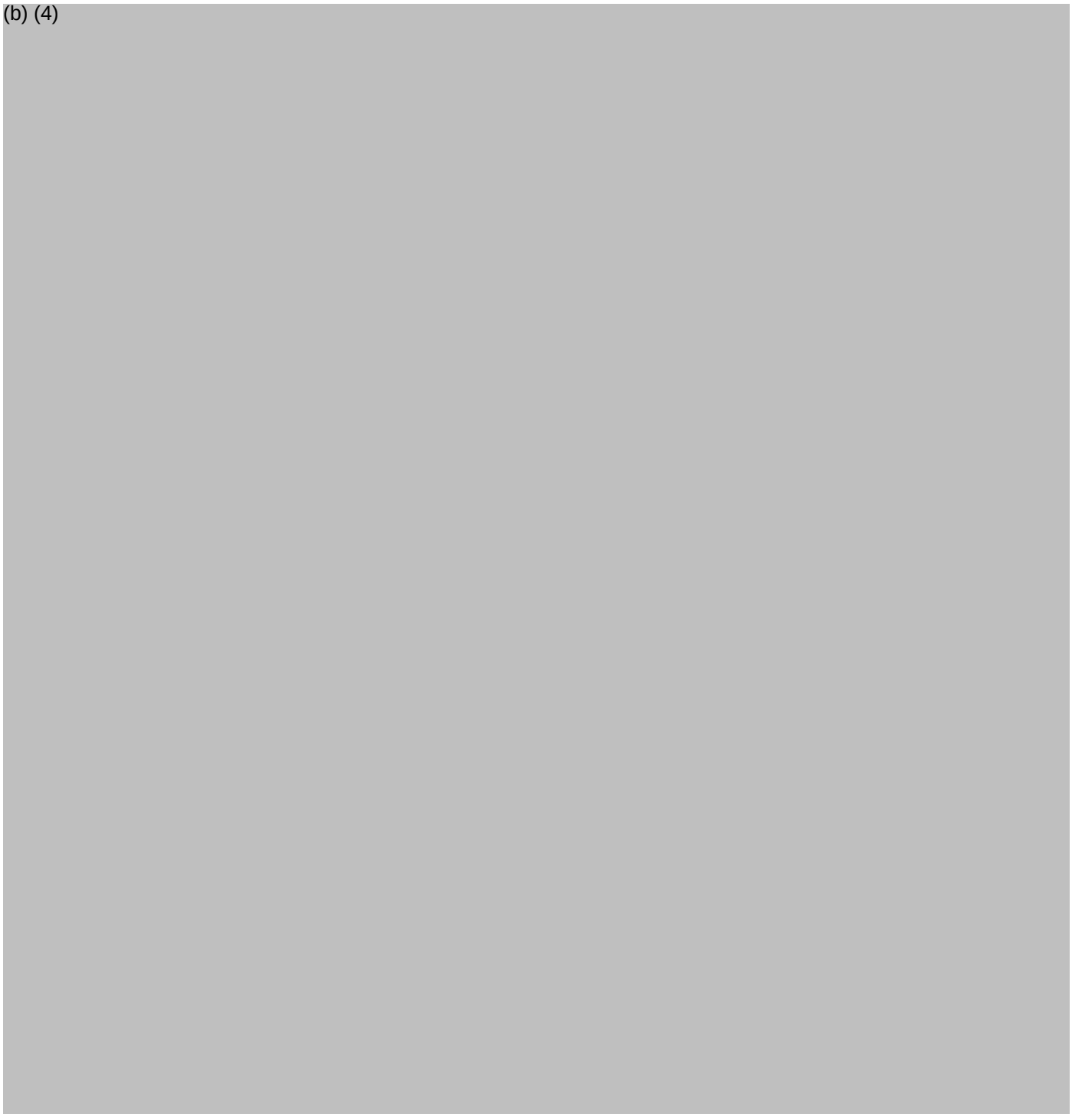

Figure 2: (b) (4)