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RESPONSE TO FDA REQUESTS FOR INFORMATION

Introduction

Information requests were sent by FDA via email to Carla Vinals on October 06, 2020 (concerning comments and questions regarding IND 19745 SN0039) and November 09, 2020 (concerning comments for IND 19745 SN0039 and SN0041). The requests are provided in bold text and are followed by the Sponsor's response.

Request for Information for IND 19745 SN0039 Dated October 6, 2020

FDA Request 1 from October 06, 2020:

Based on the information reported in this amendment, it is our understanding that there are two potency assays used, one as a characterization test and one as a release test.

For mRNA-1273 LNP (potency for characterization only), relative protein expression is assessed by cell-based bioassay in comparison with the mRNA-1273 DP reference material DHM-49621 (described in section 3.2.S.2.6.3.2.3.12). As a release test of mRNA-1273 DP, a

(b) (4)

A. Please confirm that our understanding is correct, and please provide details for both methods including SOPs and method qualification or validation reports.

Sponsor Response to FDA Feedback for Request 1, Part A

In response to FDA feedback provided on July 27, 2020 (FDA reference 19745/5) concerning a Request for CBER Feedback submitted by the Sponsor on June 23, 2020 (IND 19745 SN0006), the Sponsor is utilizing the measurement of RNA content by AEX-HPLC in conjunction with the measurement of the mRNA purity by RP-HPLC as the potency test for the mRNA-1273 Drug Product. In addition, the release specification for the mRNA-1273 Drug Product includes a qualitative test (b) (4) to confirm expression of the mRNA. Regarding the cell-based protein expression assay, the Sponsor is utilizing this assay for supplemental extended characterization during comparability assessments for the mRNA-1273 Lipid Nanoparticle (LNP). This assay is not included as a release test for the mRNA-1273 Drug Product.

The analytical procedures for the RNA Content method by AEX-HPLC ([SOP-0999](#)), the purity method by RP-HPLC ([SOP-0996](#)) and the (b) (4) method ([SOP-0937](#)) and the associated analytical method validations ([QC-MVR-0008](#), [QC-MVR-0005](#) and [QC-MVR-0020](#)) were submitted to FDA on October 16, 2020 (IND 19745 SN0053).

We notice that in IND 19745 SN 0025 (3.2.P.6 Reference Standards or Materials), CX-024414 (mRNA) (b) (4) was referred to as the reference standard for the DP potency test.

B. Please clarify which reference materials are designated as the reference standard for each, mRNA-1273 LNP and mRNA-1273 DP. In addition, please provide information on the qualification of these standards. Please introduce the corresponding changes in 3.2.P.5.6 Justification of Specifications where needed.

Sponsor Response to FDA Feedback for Request 1, Part B

The Sponsor submitted revised 3.2.S.5 Reference Standards or Materials sections for CX-024414 ([Section 3.2.S.5 {CX-024414}](#)) and the mRNA-1273 LNP ([Section 3.2.S.5 {mRNA-1273 LNP}](#)) and a revised 3.2.P.6 Reference Standards or Materials ([Section 3.2.P.6](#)) section on October 16, 2020 (IND 19745 SN0066) to correct any discrepancies concerning the use of the reference materials.

In general, the CX-024414 reference material, (b) (4), as described in [Section 3.2.S.5 {CX-024414}](#) serves:

- as the reference material for the total RNA content method by AEX-HPLC and the % purity method by RP-HPLC (system suitability) for mRNA-1273 Drug Product and the mRNA-1273 LNP
- as the reference material for the (b) (4) assay (positive control) for the mRNA-1273 Drug Product
- as the reference material for % purity method by RP-HPLC (system suitability) and % polyA tail method by RP-HPLC (system suitability) for CX-024414

The Sponsor is actively qualifying primary and working reference materials for CX-024414 for mRNA-1273 Drug Product, mRNA-1273 LNP and CX-024414 release testing as well as primary and working reference materials for mRNA-1273 Drug Product for supplemental extended characterization during comparability assessments for the mRNA-1273 Lipid Nanoparticle (LNP). This information will be submitted to IND 19745 no later than December 30, 2020.

C. Please provide information for each of the four lipid reference standards,

SM-102, cholesterol, DSPC, and PEG2000-DMG, used in the lipid identification release test, which assesses the lipid retention time. This information should include the corresponding CoAs and/or analytical qualification data.

Sponsor Response to FDA Feedback for Request 1, Part C

The Sponsor submitted revised 3.2.S.5 Reference Standards or Materials sections for (b) (4) ([Section 3.2.S.5 \(b\) \(4\)](#)) on October 16, 2020 (IND 19745 SN0066) concerning the lipid reference materials and associated CoAs.

Request for Information for IND 19745 SN0039 and SN0041 Dated November 9, 2020

FDA Request 1 from November 09, 2020:

CX-024414 mRNA Drug Substance (DS)

1. Regarding the pDNA template used in the first step of the manufacturing process:

- Please provide CMC information and identify the manufacturing site(s) where the (b) (4) pDNA and the linearized pDNA template will be manufactured for Process B. Please clarify, whether the linearized pDNA (b) (4) used for the manufacturing of Scale A (b) (4) mRNA at the Moderna site and pDNA (b) (4) used for Scale B (b) (4) mRNA manufacturing at the Lonza site were produced under cGMP using the validated manufacturing process and well-controlled qualified raw materials. Please explain, if the analytical assays for characterization and release of the linearized pDNA have been qualified or validated at the laboratory sites where the tests will be performed.***
- In addition, please provide the certificate of analysis (CoA) for the Lonza linearized pDNA (b) (4)***

Sponsor Response to FDA Feedback for Request 1 from November 09, 2020

A total of 13 linearized pDNA template lots for CX-024414 have been manufactured at ModernaTX, Inc. Plasmid (b) (4) and pDNA (b) (4) (ModernaTX, Inc. plasmid (b) (4) DNA were manufactured in a GMP manufacturing area at ModernaTX, Inc. (Norwood, MA, USA). All plasmid manufacturing steps to source the linearized pDNA template for EUA/commercial manufacturing of CX-024414 has transitioned to Aldevron (Fargo, ND, USA) also in a GMP compliant facility with appropriate quality oversight. The transition to Aldevron will enable a significantly higher manufacturing capacity and pDNA template for CX-024414 will no longer sourced from Moderna's Norwood facility. It is anticipated that this information will be submitted to IND 19745 no later than December 11, 2020.

In alignment with CBER's feedback dated August 27, 2020 (CBER Reference IND 19745.12), CMC information for linearized pDNA template is documented in [Section 3.2.S.2.3 {Starting Materials}](#). The linearized pDNA template is manufactured in GMP facilities, under GMP documentation and with appropriate quality requirements. As part of the requirements for the linearized pDNA's suitability for use a template material in mRNA manufacturing, ModernaTX, Inc. has classified plasmid identity and %linear testing by Sanger Sequencing as the critical material attribute (CMAs) ([Table 1, Section 3.2.S.2.3 {Starting Materials}](#)) as well a robust release testing panel which are described in ([Table 20, Section 3.2.S.2.3 {Starting Materials}](#)). As an example of the consistency of the measured attributes from the 13 lots of linearized pDNA produced at ModernaTX, Inc in Norwood, MA, residual RNA, genomic DNA, residual protein, endotoxin and linear DNA were below the LODs for residuals as shown in [Table 1](#) and well below release acceptance criteria.

Table 1: Release Testing for Linearized Plasmid Data from ModernaTX, Inc.

Batch	(b) (4) Concentration (b) (4)	Appearance (Clear and colorless)	Plasmid Identity, Seq (b) (4)	Linear (AGE) (b) (4)	Residual Genomic % (b) (4)	Residual Protein % (b) (4)	Residual RNA % (b) (4)	Endotoxin (b) (4)
(b) (4)								

Relating to analytical assays, characterization and release methods for linearized pDNA have been qualified by the Quality Control Unit. The specifications and acceptance criteria are set to meet the appropriate quality attributes for linearized pDNA as a template material for mRNA manufacturing. In addition, an extended characterization test panel is in-place to evaluate any significant process changes and the introduction of new suppliers.

Raw materials utilized in plasmid manufacturing are well characterized, and the quality of materials for linearized DNA production is assured through a rigorous system consisting of supplier evaluation, supplier qualification, audits, quality agreements, incoming goods testing, internal release procedure, package selection, shipping, storage conditions, expiry dates, and/or sterility requirements, based on the risk and criticality of supplier and/or material.

Raw materials are received from qualified suppliers at ModernaTX, Inc. The supplier qualification process demonstrates that the supplier has an effective and acceptable Quality Management System in place and that their supplied raw materials can meet the minimum quality requirements of the process. Qualified suppliers have been assessed and qualified using a supplier risk level review as well as audit requirements based on the materials to be sourced from the supplier. Qualification includes verification of release assay performance. Supplier performance is maintained and monitored through routine surveillance audits, periodic re-verification of release assay performance, quality agreements, and change notification agreements based on supplier risk level.

The COA for the linearized pDNA template utilized at Lonza Biologics, Inc (Portsmouth, MA, USA) (b) (4) which corresponds to ModernaTX, Inc. (b) (4) is attached.

FDA Request 2 from November 09, 2020:

Regarding the purification of the CX-024414 mRNA, please provide the report (or description and results) of the laboratory scale pilot studies performed to support the (b) (4)

(b) (4)

Sponsor Response to FDA Feedback for Request 2 from November 09, 2020

(b) (4)

FDA Request 3 from November 09, 2020:

To support consistency of performance between manufacturing sites/scales, please provide an in-process yield summary for the (b) (4) *mRNA Lonza PPQ batches, including mass yield for each operation/step and the final yield/grams of mRNA, as was reported in the Moderna PPQ summary (Table 13-1, from PPQ report* (b) (4) *for CX-024415).*

Sponsor Response to FDA Feedback for Request 3 from November 09, 2020

The mass and percent yields across the three (b) (4) PPQ batches manufactured at Lonza Biologics, Inc. demonstrates consistent performance as presented in the tables below. [Table 2](#) contains the mass yields for the PPQ data for the (b) (4) conducted at Lonza Biologics, Inc. and

[Table 3](#) includes the % yield data for the PPQ data for the (b) (4) conducted at ModernaTX, Inc. and the PPQ data for the (b) (4) conducted at Lonza Biologics, Inc.

Please note that the final cycling of both chromatography operations demonstrated reduced yield. The cycle yield is calculated based on the theoretical load of each cycle. As there are line losses during the cycles prior to the final cycle, the final cycle has a reduced load volume. Consequently, the actual yield for the final cycle is typically much lower as indicated in the table.

Final yield as determined by the mRNA Content as measured by QC (NaOH Digest Method) is provided for information. A [Summary of PPQ Step Yield Data](#) is provided as an attachment.

Table 2: Mass Yield Summary for (b) (4) CX-024414 mRNA

(b) (4)



Table 3: Percent Yield Summary for (b) (4) CX-024414 mRNA (Lonza) and (b) (4) CX-024414 mRNA (Moderna)

(b) (4)



FDA Request 4 from November 09, 2020:

(b) (4)

Regarding (b) (4) we acknowledge that you have included in your IND CoAs for the four lipids (SM-102, DSPC, PEG2000-DMG and cholesterol) used in the manufacture of your DP (b) (4). Since these lipids are integral to your DP, it is important that you evaluate whether the specifications in the CoAs regarding the lipid quality and impurities are adequate. To support your EUA or BLA, for the commercial lipids (DSPC, PEG2000-DMG and cholesterol), in addition to the CoAs, please provide the following information:

- a. Please obtain from the DSPC, PEG2000-DMG and cholesterol manufacturers an overall assessment of all the impurities from the manufacturing process that are potentially present in the lipid and information on any impurities that are not tested for release. Based on this information (b) (4) please update the DP Characterization of Impurities section of your IND or BLA. Please include an overall assessment of the impurities content and risk taking into consideration the DP dilution and tangential flow filtration steps.*
- b. Please provide a listing of the control tests (and acceptance criteria) that are performed on the lipids when received at the manufacturing facilities prior to their use in the manufacture of DS.*
- c. Please clarify how any change that the manufacturer makes in the manufacture, control and/or tests/specifications of the three lipids that are non-compendial (SM-102, DSPC and PEG2000-DMG) will be conveyed to you and explain how you will control and evaluate these changes. For post approval CMC changes to these four lipids, please report the changes that may impact final DP quality as BLA supplements (PAS, CBE-30, CBE or Annual Report), as appropriate.*

Sponsor Response to FDA Feedback for Request 4, Part a from November 09, 2020

- A. The following section provides the overall assessment of the impurities from the manufacturing process for the individual lipids that are potentially present (b) (4) information on any impurities that are not tested for release.

(b) (4)

(b) (4)



(b) (4)



Sponsor Response to FDA Feedback for Request 4, Part b from November 09, 2020

Specification for the lipids and additional testing that are performed on the lipids when received at the manufacturing facilities are provide in the following section.

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



Sponsor Response to FDA Feedback for Request 4, Part c from November 09, 2020

Moderna has quality agreements with its suppliers that require notification of significant changes through a supplier change notification process. Once changes are communicated to Moderna Quality, the change is assessed for impact and if impact is determined, the change is documented in Moderna's change management system. Change controls are evaluated by a cross functional team including manufacturing, manufacturing sciences and technology, quality and regulatory and change actions are defined for change implementation.

FDA Request 5 from November 09, 2020:

In your Catalent PPQ Final Report please provide summary data for PPQ batches, including the following attributes and parameters:

- Critical Quality Attributes,*
- Critical Process Parameters,*
- Non-critical Process Parameters,*
- In-process Controls.*

Sponsor Response to FDA Feedback for Request 5 from November 09, 2020

The initial Scale A (nominal (b) (4) multiple-dose vial scale) Catalent PPQ Summary report was included in IND 19745 Sequence 0039 (dated September 28, 2020). Subsequently, a discrepancy in mRNA concentration acceptance criteria was discovered, a change control (REC 260856) was issued, and a revised Scale A Catalent PPQ Summary report ([VPPQ-256-100-0002-S](#)) was submitted in IND 19745 Sequence 0070 (dated November 16, 2020). The Scale A PPQ summary report identifies Critical Process Parameters, Non-critical Process Parameters and In-process Controls for the mRNA-1273 Drug Product manufacturing process.

The final Scale B (nominal (b) (4) multiple-dose vial scale) Catalent PPQ Summary report will also include Critical Process Parameters, non-critical process parameters and in-process controls. The Process Control Strategy (PCS) document lists the direct correlation between the Critical Quality Attributes (CQAs) and the process parameters. Both documents will be submitted as attachments to Section 3.2.P.3.5 of IND 19745 when available.