

RESPONSE TO FDA COMMENTS ON CMC RECEIVED ON 06 OCTOBER 2021

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

CMC: Analytical method procedure and validation

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing.

We have the following request for additional information regarding sample availability for in-support testing:

Drug Substance (DS)

Please provide 10 aliquots (100 µL aliquots preferred) of DS from three different lots and the following documentation and reagents in sufficient quantity to perform 10 independent tests for the following DS assays:

Three lots of drug substance (CX-024414), with aliquots of 10 x 100 ul, will be submitted to the agency with delivery planned by 29Oct21:

- a. 4007921039
- b. 4007921050
- c. 4007921054

ITEM 1:

1. 5' – Cap assay

- a. (b) (4) (with COA)
- b. mRNA reference material (with COA)
- c. Cap guide
- d. Upper limit of backpressure of HPLC system during sample run
- e. Test result for each DS lot
- f. Please confirm that (b) (4) is used as the (b) (4) in sections 8.3.7.2 and 8.3.8.1 of SOP-0997.

Sponsor Response

For the 5' Cap Assay:

- a. 10 x 300µL vials of (b) (4) will be provided. Refer to Summary of Analysis document DSAD-SOA-0285.
- b. 40 x 300µL vials of CX-024414 mRNA Reference Material lot DH-03180.1 will be provided (40 vials total for all requests). Refer to certificate of analysis document COA-0483.
- c. 10 x 100µL vials of (b) (4) will be provided.
- d. Upper Limit backpressure of HPLC system during HPLC run is approximately (b) (4)
- e. Test results for each DS lot will be provided via CoAs.
 - i. 4007921039: Refer to Certificate of Analysis document COA-2908.

- ii. 4007921050: Refer to Certificate of Analysis document COA-3019.
- iii. 4007921054: Refer to Certificate of Analysis document COA-3321.
- f. We confirm that (b) (4) is used as the (b) (4) in sections 8.3.7.2 and 8.3.8.1 of SOP-0997.

ITEM 2:

2. % Poly A tail RNA

a. mRNA reference material (with COA)

b. Test result for each lot

Sponsor Response

For the % Poly A tail RNA Assay:

- a. 40 x 300µL vials of CX-024414 mRNA Reference Material lot DH-03180.1 will be provided (40 vials total for all requests). Refer to certificate of analysis document COA-0483.
- b. Test results for each DS lot will be provided via CoAs.
 - i. 4007921039: Refer to Certificate of Analysis document COA-2908.
 - ii. 4007921050: Refer to Certificate of Analysis document COA-3019.
 - iii. 4007921054: Refer to Certificate of Analysis document COA-3321.

Drug Product (DP)

Please provide 150 vials of DP per lot from three different DP lots and the following reagents and documentation for the following DP release assays:

- a. For the DP vials, 150 vials (15 cartons containing 10 vials each) are provided from the following lots below. DP vials will be submitted to the agency with delivery planned by 29Oct21:
 - i. Baxter Lot 940875 (Moderna Lot 7007621154)
 - ii. Catalent Lot 064H21A (Moderna Lot 7006521143)
 - iii. Catalent Lot 031H21A (Moderna Lot 7006521151)

ITEM 3:

Identity

a. Positive Control: (b) (4) (Lot# (b) (4))

b. Positive control primers for (b) (4) sequencing

(b) (4)

c. Primers used for (b) (4) sequencing

(b) (4)

d. COAs with concentration/dilutions for use along with temperature of storage and expiry date

Sponsor Response

For the Identity assay:

a. 10 x 25 µL vials of (b) (4) lot (b) (4) Positive Control will be provided. Refer to summary of analysis document DSAD-SOA-0212.

b. Positive control primers for (b) (4) sequencing:
(b) (4)

Refer to SOP instructions for reconstitution.

c. Primers used for (b) (4) sequencing
(b) (4)

Refer to SOP instructions for reconstitution.

d. Concentration/dilutions for use along with temperature of storage and expiry dates can be found in the provided CoA ((b) (4)) and SOP test method document.

ITEM 4:

Total RNA Content

a. mRNA reference material (with COA)

b. Test result for each DP lot

Sponsor Response

For the Total RNA Content Assay:

a. 40 x 300µL vials of CX-024414 mRNA Reference Material lot DH-03180.1 will be provided (40 vials total for all requests). Refer to certificate of analysis document COA-0483.

b. Test results for each DP lot will be provided via CoAs.

- i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
- ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
- iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.

ITEM 5:

Purity/Product-Related Impurities

a. RNA reference material

b. Test result for each DP lot

Sponsor Response

For the Purity / Product-Related Impurities Assay:

- a. 40 x 300µL vials of CX-024414 mRNA Reference Material lot DH-03180.1 will be provided (40 vials total for all requests). Refer to certificate of analysis document COA-0483.
- b. Test results for each DP lot will be provided via CoAs.
 - i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
 - ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
 - iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.

ITEM 6:

% RNA Encapsulation

a. current mRNA-1273 LNP DP Positive control (working reference material)

b. Formulation Buffer (20mM Tris, (b) (4) Sucrose, pH (b) (4) buffer), (b) (4)

(b) (4)

c. COAs with concentration/dilutions for use along with temperature of storage and expiry date

Sponsor Response

For the RNA %Encapsulation Assay:

- a. There is no positive control in-use for this testing.
- b. (b) (4) of Formulation buffer (20mM Tris, (b) (4) Sucrose, pH (b) (4) buffer) will be provided.
- c. A CoA will not be provided for (a) as this is not applicable.

ITEM 7:

Particle Size

a. Test result for each DP lot

Sponsor Response

For the Particle Size assay:

- a. Test results for each DP lot will be provided via CoAs.
 - i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
 - ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
 - iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.

ITEM 8:

Polydispersity

a. Test result for each DP lot

Sponsor Response

For the Polydispersity assay:

- a. Test results for each DP lot will be provided via CoAs.
 - i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
 - ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
 - iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.

ITEM 9:

Lipid Identification

a. Standards for the 4 different lipids

b. Test result for each DP lot

Sponsor Response

For the Lipid Identification assay:

- a. The following lipid standards will be provided (with associated CoAs)

(b) (4)



(b) (4)

- b. Test results for each DP lot will be provided via CoAs.
 - i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
 - ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
 - iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.

ITEM 10:

Lipid Content (mg/mL)

a. Test result for each DP lot

Sponsor Response

For the Lipid Content assay:

- a. Test results for each DP lot will be provided via CoAs.
 - i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
 - ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
 - iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.

ITEM 11:

pH

a. Test result for each DP lot

Sponsor Response

For the pH Assay:

- a. Test results for each DP lot will be provided via CoAs.
 - i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
 - ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
 - iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.

ITEM 12:

In Vitro Translation

- a. Current Positive controls, CX-024414 or mRNA-1273 (b) (4)**
- b. COAs with concentration/dilutions for use along with temperature of storage and expiry date**

Sponsor Response

For the IVT Assay:

- a. 40 x 300µL vials of CX-024414 mRNA Reference Material lot DH-03180.1 (used as positive control) will be provided (40 vials total for all requests). Refer to certificate of analysis document COA-0483.
- b. Concentration/dilutions for use along with temperature of storage and expiry dates can be found in the provided CoA and SOP test method document.

ITEM 13:

Bacterial Endotoxins

- a. Test result for each DP lot**

Sponsor Response

For the Bacterial Endotoxins Assay:

- a. Test results for each DP lot will be provided via CoAs.
 - i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
 - ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
 - iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.

ITEM 14:

Documentation

- 1. Please provide Certificates of Analysis for all reagents**
- 2. Please provide results of the assays listed for the DS lots and DP lots submitted to CBER**

Sponsor Response

For Documentation:

- 1. CoAs or SoAs for all reagents will be provided
- 2. Test results for each DS and DP lot will be provided via CoAs.
 - a. Drug Substance COAs
 - i. 4007921039: Refer to Certificate of Analysis document COA-2908.
 - ii. 4007921050: Refer to Certificate of Analysis document COA-3019.
 - iii. 4007921054: Refer to Certificate of Analysis document COA-3321.
 - b. Drug Product CoA

- i. Baxter Lot 940875 (Moderna Lot 7007621154): Refer to Certificate of Analysis document COA-3345.
- ii. Catalent Lot 064H21A (Moderna Lot 7006521143): Refer to Certificate of Analysis document COA-3224.
- iii. Catalent Lot 031H21A (Moderna Lot 7006521151): Refer to Certificate of Analysis document COA-3214.