1. RESPONSE TO FDA COMMENTS ON CMC DATED NOVEMBER 01, 2021

The Sponsor acknowledges FDA Comments on CMC (in **BOLD**)

CMC/Manufacturing

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We havethe following requests for additional information:

Please refer to the drug product (DP) cumulative process durations (CPD, listed in the Table below) applicable to the Catalent and Baxter DP manufacturing sites, which you indicated were qualified based on:

- **Analysis of data from manufacturing experience at Catalent and Monte Carlosimulations which predict that DP release criteria for purity (b) (4) will meet specification for (b) (4) of DP lots [Section 3.2.P.2.3.1.2.3 *Pharmaceutical development {Process Characterization}*].**
- **Hold-time qualification studies conducted as part of process performance qualification (PPQ) batches [Section 3.2.P.3.5.1.3.5 *Process Validation and/or Evaluation {Catalent}* and PPQ report VPPQ-256-100-00003-S for DP manufacture at Catalent].**

Table – DP cumulative process durations

Process Parameter	PAR	Criticality Designation
Total cumulative process duration (refrigerate 2 to 8°C, TOR 20 to 25°C)	(b) (4)	**Critical Process Parameter**
Cumulative time out of refrigeration (TOR 20 to 25°C)	(b) (4)	**Critical Process Parameter**

Abbreviations: PAR = proven acceptable range; TOR = time out of refrigeration

ITEM 1:

We have the following comments:

1. **Regarding report VPPQ-256-100-00003-S,**
   (b) (4)

(b) (4)

Sponsor Response

The Sponsor proposes to use the Proven Acceptable Ranges (PAR) for Cumulative Process duration (CPD) of (b) (4) for Time Out of Refrigeration (TOR) and (b) (4) Total CPD (TOR and 2-8°C) combination for initiation of commercial manufacture. The applicable Module 3 CTD sections have been revised as summarized in Section 2 of this response.

As discussed in the response to the information request #9 dated October 14, 2021 (included as part of this submission), a review of (b) (4) Catalent lots with varying levels of CPD (at CRT) and Total CPD (2 to 8°C and CRT) combined with the statistical analysis supports this proposal. Additionally, the Sponsor intends to conduct a Maximum CPD Hold study with samples from three representative lots and submit the data (during review or as CBE-30) to support an expansion of the CPD to (b) (4).

ITEM 2:
Regarding the hold studies to support the process durations, you indicated that the CPD at CRT (TOR 15 to 25˚C) and total CPD were challenged during PPQ toestablish the routine manufacturing hold limits with results presented for (b) (4) DPlots ((b) (4) (b) (4)) in section 3.2.P.3.5.1.3.5 *Hold Time Qualification,* Tables 26 and 27, and in the above cited PPQ report. We have the following comments regarding the validation study-

(b) (4)

Sponsor Response

Item 2a:

The Hold Study in Section 3.2.P.3.5.1.3.5 Table 26 and Table 27 (Lots (b) (4) was conducted by pulling samples of filled vials (b) (4) vials) immediately after filling/stoppering/capping and placing them aside for Hold Duration Study. The subsequent duration of exposure for Hold study vials was based upon the process duration (Elapsed process time at CRT and 2-8°C) that they had already experienced by the fill/stopper/cap step.

(b) (4) of the vials were held at CRT for an additional period of time, until their total CRT duration reached (b) (4) with (b) (4) vials being sampled at each of these timepoints. Thus, these vials represent CRT duration up to (b) (4) (but only the actual elapsed 2-8°C duration).

(b) (4) of the vials were held at CRT for an additional period of time, until the total CRT duration reached (b) (4). The vials were then moved to 2-8°C storage and held for an additional period of time until their total 2-8°C duration reached (b) (4) vials were sampled at each of these timepoints. Thus, these vials represent CRT duration to (b) (4) and a maximum 2-8°C duration of (b) (4) thus, the CRT Total is (b) (4)

The study design is illustrated below

(b) (4)

Note that the remainder bulk of the batches (b) (4) were processed per routine and experienced the CRT durations ((b) (4)) and total CPDs ((b) (4), (b) (4) as noted in Table 11.23 and Table 11.24 (VPPQ-256-100-00003-S).

Item 2b:

The Hold Study in Section 3.2.P.3.5.1.3.5 Table 26 and Table 27 (Lots (b) (4)) missing data.

Due to sample handling errors, some of the samples were lost. The primary data point missing is the (b) (4) values for (b) (4) The primary shelf-life limiting degradation pathway is (b) (4). (b) (4) or (b) (4) are not shelf-life limiting. No impact of the Hold Times is seen on the (b) (4) attributes.

As noted in response to Item 1 above. The Sponsor intends to conduct a Maximum CPD Hold study with samples from (b) (4) representative lots and to submit this data (during review or as CBE30) to supplement the Hold Study and support the expansion of CPD to (b) (4)

ITEM 3:
In addition to qualification data (as detailed in item 1.c), you may support the CPDs with data from manufacturing experience. If you choose to use data from manufactured lots, please include results for all DP manufactured at Catalent and Baxter, including lots that did not meet release specifications. Please include CPDs at refrigerated 2 to 8°C, CRT (TOR 15 to 25˚C), and total (2 to 8°C, TOR 15 to 25˚C) and results for mRNA purity at release and any other parameters thatwere measured and may be affected by process duration. Please also specify the manufacturing step at which sampling for DP release testing occurred.

Sponsor Response

As stated above (for Item 1), a review of available data combined with the statistical analysis supports the extension of PAR CPD ranges and additionally, the Sponsor intends to conduct a Maximum CPD Hold study with samples from (b) (4) representative lots to supplement the Hold Study and support the expansion of CPD to (b) (4) .

ITEM 4:
The following comment pertains to the DP stability program:

With regard to the DP stability studies and the DP shelf-life (i.e., expiry) please include the following information in stability sections 3.2.P.8.1 *Stability Summaryand Conclusion* and 3.2.P.8.2 *Post-approval Stability Protocol and Stability Commitment* as appropriate,

a. **Please describe how the sampling was performed for DP stability studies for clinical lots and PPQ lots; specifically, the DP manufacturing step when samples were taken.**
b. **Please describe how the sampling will be performed for post-approval commercial DP release and stability studies at Catalent and Baxter. If samples are taken during filling, please specify the points during the fillingstep when samples are taken and the number of samples tested. If samples are taken after labeling or packaging, please specify the labeling or packaging step when samples are taken and provide the number of samples tested.**
c. **In section 3.2.P.8.1, please include and introductory section stating theshelf-life for the commercial DP when stored at the intended conditions and specify the manufacturing step considered the DP date of manufacture.**

Sponsor Response

Item 4a:

For clinical lots produced at ModernaTX, Inc. and Scale A PPQ lots manufactured at Catalent, mRNA-1273 DP stability samples were selected at random post visual inspection, prior to labeling. For Catalent and Baxter Scale B PPQ lots, stability samples were selected at random post-packaging. Section 3.2.P.8.1 has been revised as summarized in Section 2 of this response.

Item 4b:

For post-approval commercial DP release and stability at Catalent, the following samples will be taken during filling [beginning (B), middle (M), end (E)], as unlabeled drug product, and after packaging:

- Release Sterility (b) (4)
- Release Endotoxin (b) (4)
- Particulate Matter per USP <788> (b) (4)
- Release Purity (b) (4) + CRT treatment
    - CRT treatment: At Catalent, (b) (4) .
- Remainder Release (b) (4) Random after packaging
- Stability (when required, (b) (4) tested per timepoint), Random after packaging

For post-approval commercial DP release and stability samples at Baxter, the following samples for release testing are taken during filling (beginning, middle, end), as unlabeled drug product, and after packaging.

- Release Sterility (b) (4)
- Release Endotoxin (b) (4)
- Particulate Matter per USP <788> (b) (4)
- Remainder Release (b) (4) Random after packaging
- Stability (when required (b) (4) tested per timepoint), Random after packaging

Section 3.2.P.8.2 has been revised as summarized in Section 2 of this response.

Item 4c:

Section 3.2.P.8.1 has been revised as summarized in Section 2 of this response.

ITEM 5:

The following comment pertains to the DP release testing:

In DP section 3.2.P.5.1 *Specification(s)*, please describe the release tests performed on the unlabeled vs. the labeled filled vials. In addition, please include the identity test performed as per 21 CFR 610.14 after all labeling operations are completed (i.e., vial and package labels).

Sponsor Response

The release tests are performed on labeled versus unlabeled vials as indicated in the response to Item 4b. Sterility, Endotoxin, Particulate Matter tests are all performed on unlabeled product. At

Baxter purity samples are labeled vials and Catalent purity samples are unlabeled but held to represent longest batch CRT post packaging activities. The remaining release samples at both locations are performed on labeled vials, including the identity test as per 21 CFR 610.14. Section 3.2.P.5.1 has been revised as summarized in Section 2 of this response..

2. SUMMARY OF CHANGES

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

CTD Section		Changes
3.2.P.3.3 {Catalent}	Description of Manufacturing Process and Process Controls	• Administrative revision to presentation names from "Maximum X dose." to "x.x mL Fill…" • Table 12 revised to include both the PAR Range and site qualified range for CPD- TOR from (b) (4)
3.2.P.3.3 {Baxter}	Description of Manufacturing Process and Process Controls	• Administrative revision to presentation names from "Maximum X dose." to "x.x mL Fill…" • Table 12 revised to include both the PAR Range for CPD- TOR from (b) (4) (b) (4)
3.2.P.3.4 {Catalent}	Controls of Critical Steps and Intermediates	• Revised Table 2 CPD TOR PAR from (b) (4) at 20-25°C
3.2.P.3.4 {Baxter}	Controls of Critical Steps and Intermediates	• Revised Table 2 CPD TOR PAR from at 20-25°C
3.2.P.5.1	Specifications	• Added Section 3.2.P.5.1.1 to describe release testing sampling locations
3.2.P.8.1	Stability Summary	• Added introduction stating the shelf life for commercial DP at the intended storage conditions, specified the manufacturing step considered the DP date of manufacture., and specified the manufacture step where stability samples were taken for clinical and PPQ lots. • Administrative revision to add subheading 3.2.P.8.1.1, to revise "9 month" to "the 9-month time point" (page 3). Section 3.2.P.8.1.2 to replace "temperatures" with "conditions", Table 19 and Table 21 removed abbreviations which were not applicable. • Page 5 Correction of "The 6.3 mL fill volume is considered worst case for stability purposes and is representative of the 8.0 mL fill volume, where applicable" to "an analysis of stability data for mRNA-1273 Drug Product lots with different fill volumes has been conducted which demonstrates that there are no significant differences in degradation rate as a function of fill volume.
3.2.P.8.2	Post-Approval Stability protocol and Stability commitment	• Added text to specify the manufacture step where stability samples will be taken for post-approval commercial DP lots.