RESPONSE TO FDA COMMENTS ON CMC RECEIVED ON 14 OCTOBER 2021

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

CMC: TOR and CPD limits
Our review of your August 24, 2021 submission (STN 125752/2) is ongoing.

ITEM 1:

We have reviewed the information submitted in BLA Amendment 125752.1 regarding revision of the time out of refrigeration (TOR) and cumulative process duration (CPD) limits. We find that the proposed increase of the cumulative process TOR (15 – 25°C) from (b) (4) and cumulative process duration (2 to 8°C) and TOR (15˚C to 25˚C) from (b) (4) has not been adequately supported by quality data that you provided in section 3.2.P.2 Manufacturing Process Development {Comparability} and, therefore, is not acceptable.

Please note that the proposed cumulative TOR and cumulative process duration upper limits (e.g., cumulative TORs of about (b) (4) and cumulative process durations of about (b) (4)) may impact overall product consistency over the life-cycle of the product and increase the risk of releasing vaccine with RNA purity and impurity levels which are not representative of those of the clinical lots used to demonstrate effectiveness. Any changes in the specification for the cumulative TOR and/or the cumulative process duration should be supported with data from at least three lots manufactured at the most extreme time requested. Until supportive data are available, the manufacturing process should be controlled such that the proposed limits for cumulative TOR and cumulative process duration are within the PARs used for the initial Scale B PPQ and the Phase 3 clinical lots to ensure consistent DP purity levels for registered commercial lots.

Sponsor Response

A review of (b) (4) Catalent lots manufactured into July 2021 for both US and OUS markets (Table 1) demonstrates that all lots had acceptable % purity release testing results even though (b) (4) lots exceeded the PAR (b) (4) for CPD and (b) (4) lots exceeded the PAR (b) (4) for TOR. As described in Section 3.2.P.2.3.1.2.3 {Process Characterization}, DP purity is tested at release and the Release Purity already includes any impact of processing durations at each temperature prior to packaging. The minimum Release purity Limit (MRL) ensures purity will remain above the shelf life purity limit through the end of shelf life. Thus, the extended PARs for CPD and TOR prior to release testing do not increase the risk of DP lots failing during shelf life. As discussed in Section 3.2.P.5.6.2.4, the projected purity ranged from (b) (4) at the point of administration in the Phase 3 trial which delivered 94% efficacy, so the lots manufactured with longer process durations remain representative of the clinical lots used to demonstrate effectiveness.

The Sponsor would like to clarify that the extension of the current proven acceptable range (PAR) for cumulative process duration (CPD) and Time Out of Refrigeration (TOR) is based on the completion of the hold study performed with three lots as part of Scale B PPQs (Section 3.2.P.3.5.1.3.5, PPQ Final Summary report VPPQ-256-100-00003-S) as well as significant supportive data from actual manufacturing experience with (b) (4) lots at Catalent (Section 3.2.P.2.3.1.2.3 {Process Characterization}). The (b) (4) PPQ lots presented in the Section 3.2.P.2.3.3.3.1.1 {Comparability} comparability comparison do not represent the totality of lots manufactured at Catalent which have exceeded the proven acceptable range (PAR) for cumulative process duration (CPD) of (b) (4) and Time Out of Refrigeration (TOR) of (b) (4) (b) (4) but only represent PPQ lots used for comparability assessment of process changes. As provided in Table 1 of this response, a high percentage of lots manufactured into July 2021 have exceeded the initial PAR for CPD and TOR.

As background, development, scale-up and commercial production operations were performed in parallel for mRNA-1273 Drug Product due to the urgent nature of the COVID-19 pandemic. The initial PARs for the CPPs: CPD (2 – 8˚C and 20 – 25˚C) and TOR (20 – 25˚C), were established based on extrapolation from Scale A manufacture and shorter duration hold studies, along with an early stage degradation model based on limited stability data. With additional manufacturing experience at final Scale B, data from hold studies performed as part of Scale B PPQs (Section 3.2.P.3.5.1.3.5 {Catalent}), and more precise characterization of mRNA-1273 degradation rates at 2 - 8˚C and 15 - 25˚C, it has become evident that the initial PAR for CPD and TOR were conservative.

Because of the known purity degradation during product storage and administration, a separate and higher limit for purity is applied at the time of product release. This release limit ensures that even after the anticipated degradation of purity during shelf life and clinical use, doses administered will have (b) (4) purity.

Table 1: Analysis of mRNA-1273 Drug Product lots CPD, TOR and %Purity

(b) (4)

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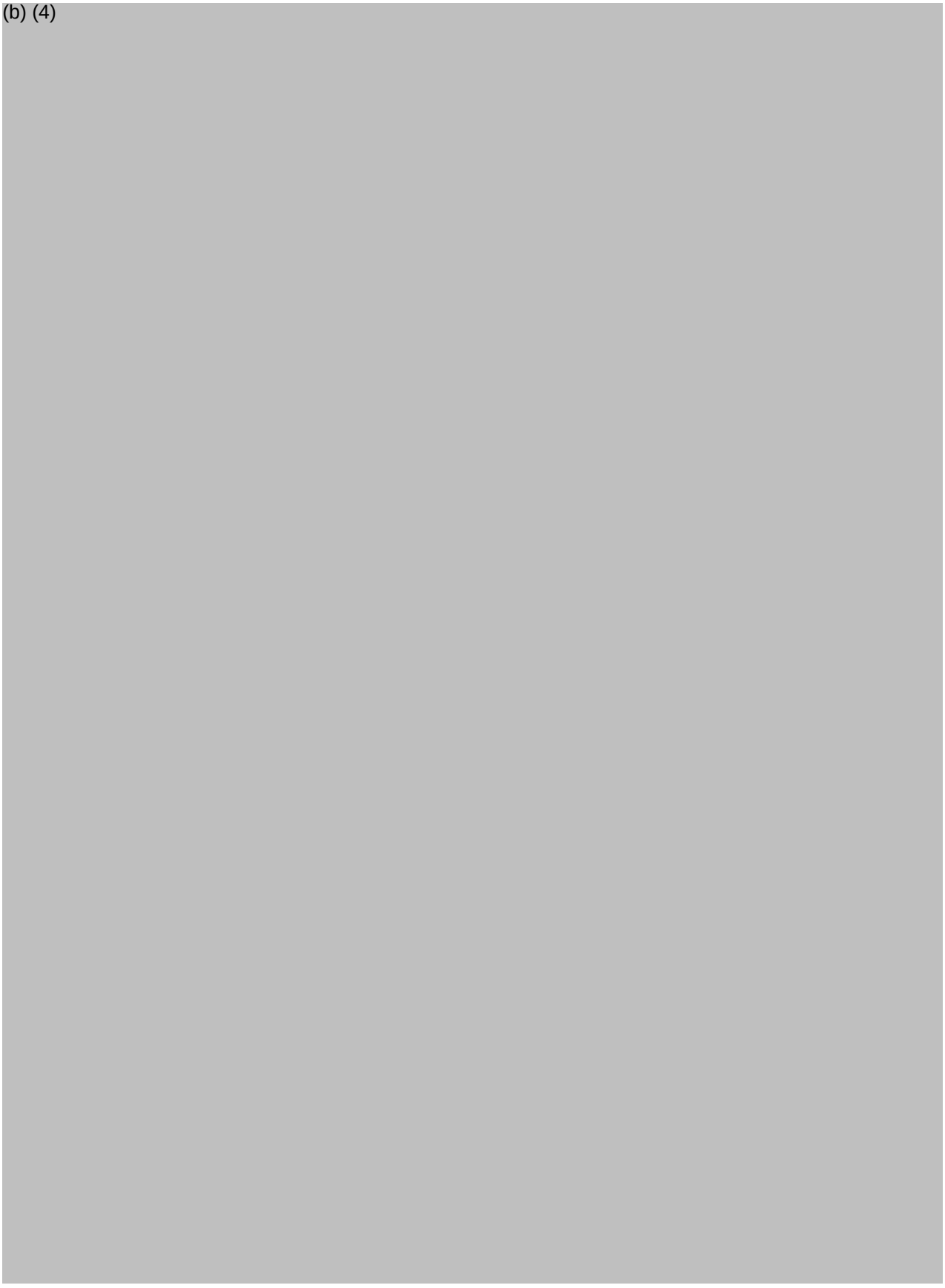
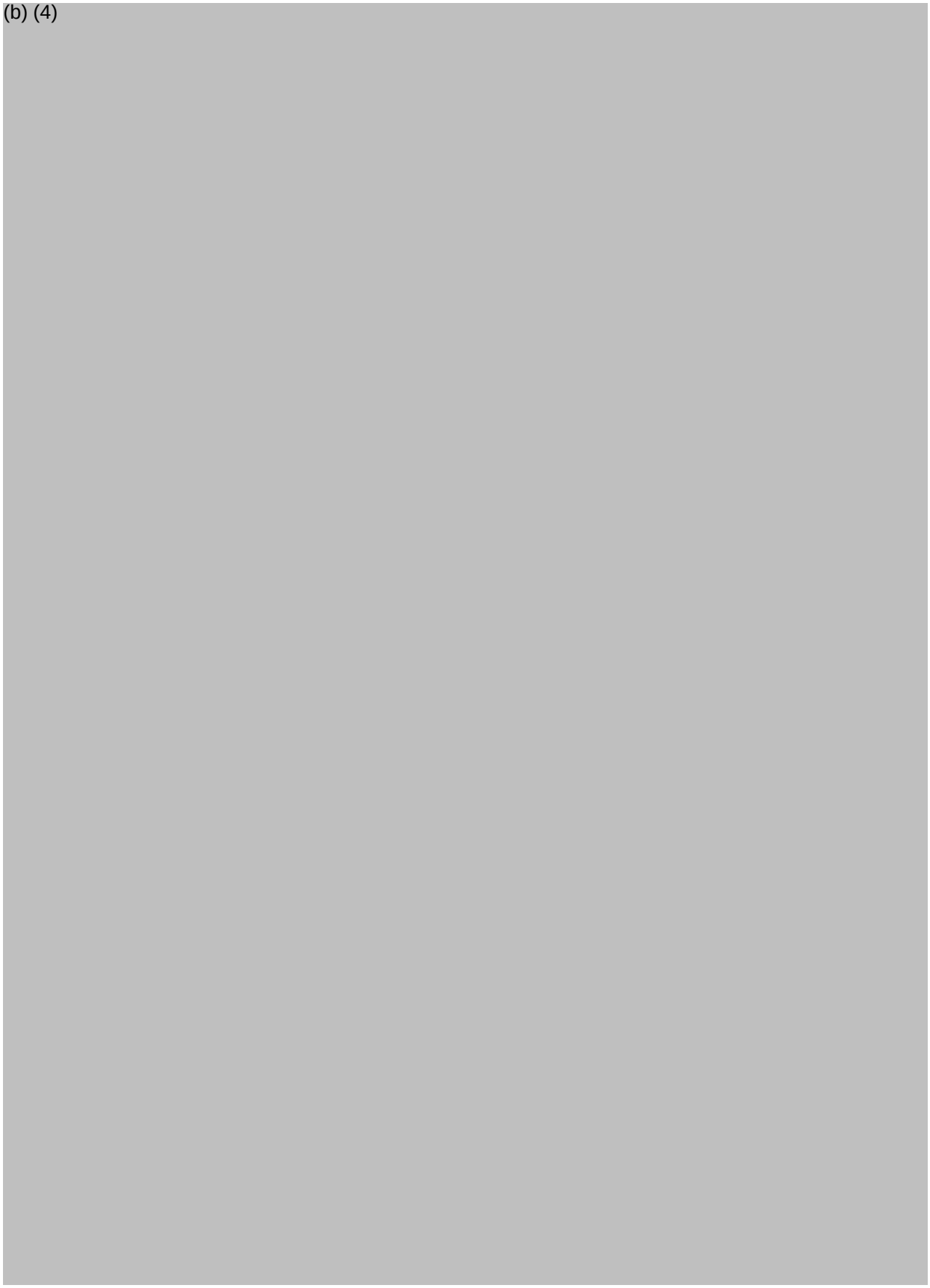
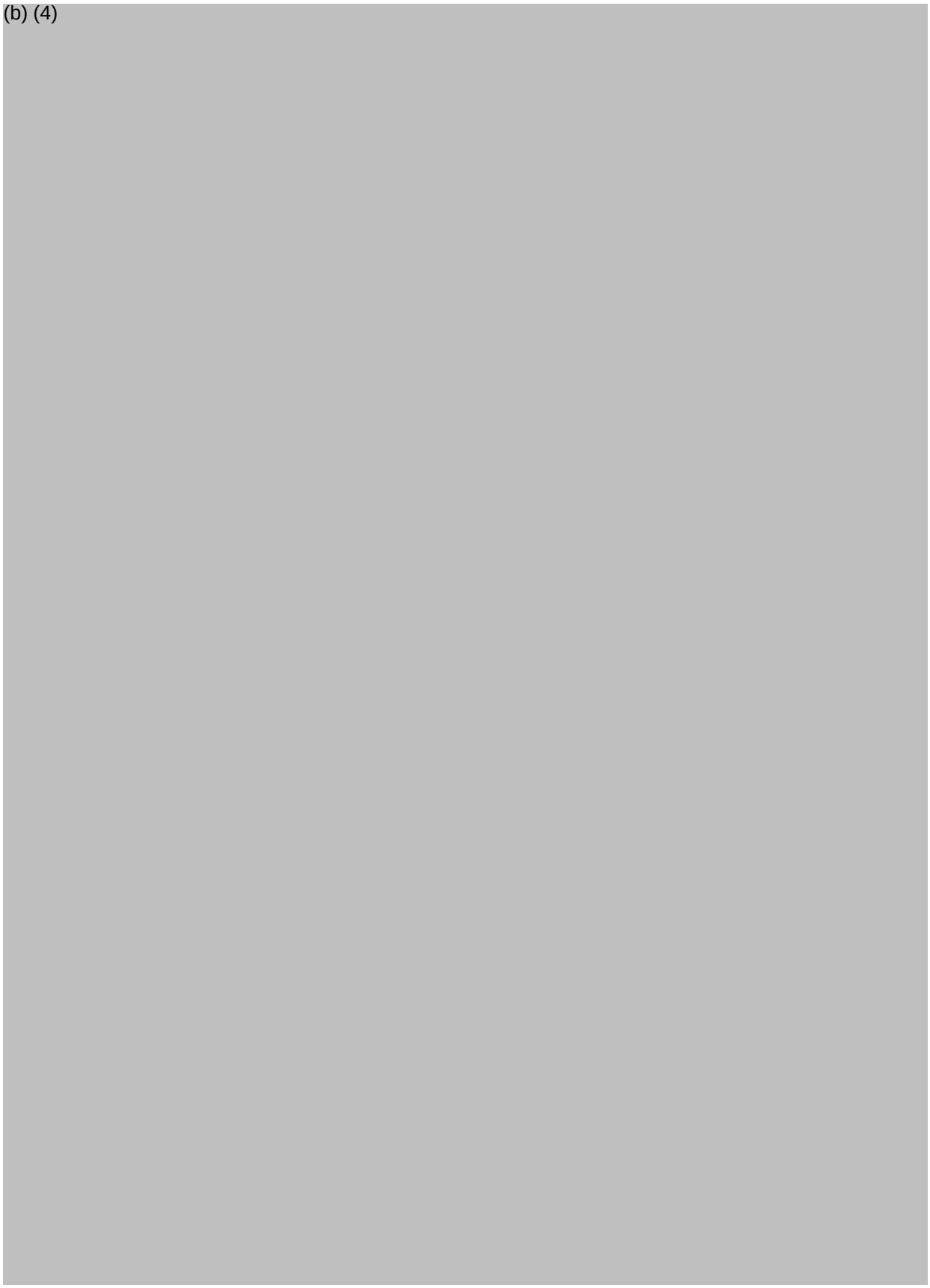


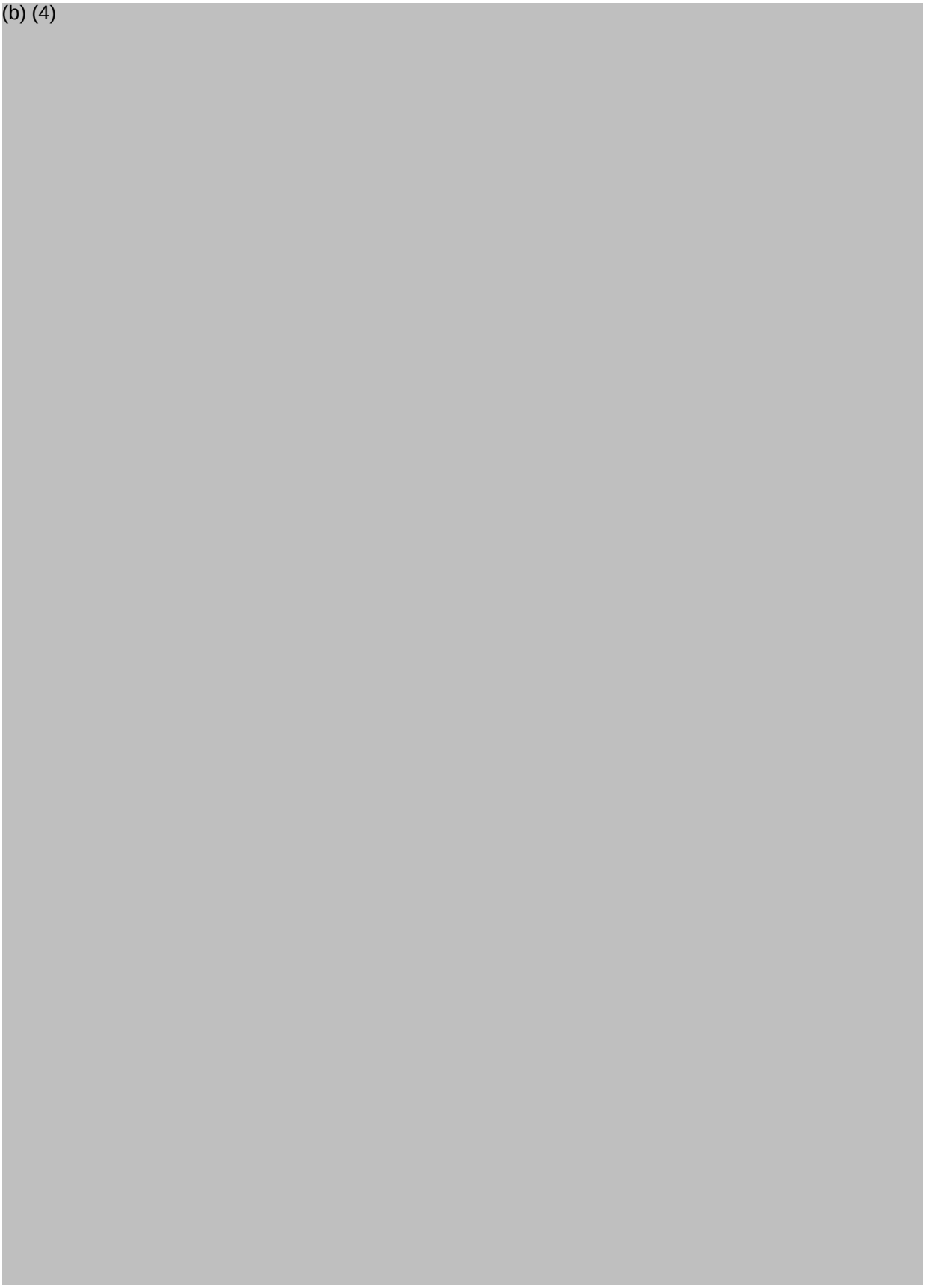
(b) (4)



(b) (4)



(b) (4)



(b) (4)

The degradation rates are independent of the starting purity per lot and the established MRL is applied to provide a high level of assurance that the product meets its shelf life specification throughout the shelf life claim. The release % Purity already includes any impact of processing durations at each temperature prior to sampling. Since the Release Purity with those impacts built in, is required to be above the minimum release limit to ensure purity through end of shelf life, processing durations prior to release testing do not increase the risk of DP lots failing during shelf life. The combination of maximum allowed times at -20°C, 5°C and 25°C is supported by a MRL of (b) (4) Note that the allowable times are additive: for example, DP having a total shelf life of 9 months means it can be held for 8 months at -20°C plus 1 month at 5°C plus 24 hours at 25°C. The shelf life totals 9 months but with no more than 1 of those months at 5°C and 24 hours at 25°C.

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 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) in the BLA STN 125752.

The summary of revised Module 3 CTD sections that are being submitted in support of 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