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Chemistry, Manufacturing, and Controls Statistical Review

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1. EXECUTIVE SUMMARY

This original Biologics License Application (BLA 125869/0) seeks approval for mRNA-1010 (MFLUSIVA), an mRNA-based seasonal influenza vaccine. This review evaluates the mRNA-1010-specific quantitative assay validations, justification of specifications for purity, impurities, and effective delivered dose (EDD), and stability results.

Validation of product-specific assays for four quality attributes were reviewed: (b) (4) purity and impurities, (b) (4). For drug product, full validation of purity and impurities was based on (b) (4). Supplemental validation with mRNA-1010 was provided. The applicant adequately validated the assays.

Most of the specifications were justified based on clinical evidence or previously licensed vaccines from this platform, except for the release specification for purity/impurities which was justified based on the shelf-life establishment. The applicant proposes a 12-month refrigerated shelf life for the drug product and an (b) (4) shelf life for the RNA and LNP drug substances. Stability results from mRNA-1010 (b) (4) supported the proposed shelf lives. These results also supported the proposed release limit for purity and impurities.

During the review, CBER determined that the proposed drug product specifications may not ensure a clinically supported minimum end of shelf life (EoSL) effective delivered dose (EDD), and that batch release data combined with the minimum EoSL purity could yield an EDD (b) (4) per strain) below the applicant's clinically minimum (b) (4) per strain). In response, the applicant submitted results from a simulation of their manufacturing process that were intended to demonstrate that worst-case EDD is rare. However, these simulation results relied on unjustified assumptions and CBER was concerned that the simulations underestimated the probability of a worst-case EDD. In addition, existing batch release data from mRNA-1010 and other vaccines suggested that batches are frequently released at or near the release specifications, suggesting the worst-case EDD is unlikely to be rare, given the observed stability trends. The review team requested the applicant to add a release specification: (b) (4) to ensure an acceptable EDD. The applicant counter proposed a change in the EoSL specification changes for purity from (b) (4) and a specification for (b) (4). The review team considered this acceptable.

Overall, I recommend approval of this BLA based on the totality of evidence reviewed.

2. REGULATORY BACKGROUND AND SOURCE OF INFORMATION

This original Biologics License Application (BLA) is for mRNA-1010, a trivalent seasonal influenza vaccine. mRNA-1010 is manufactured from an RNA DS, which is combined with the lipid nanoparticle (LNP) to produce the LNP drug substance (DS) which is then used to produce drug product (DP). The LNP process used for mRNA-1010 (LNP-102) is the same platform used in several of the applicant's currently licensed vaccines,

including Spikevax (mRNA-1273), mRESVIA (mRNA-1345), and mNEXSPIKE (mRNA-1283).

The applicant leveraged assay validation results from mRNA-1273 and (b) (4) [REDACTED], for (b) (4) [REDACTED] attributes. Therefore, this review focuses on the validation of (b) (4) [REDACTED] quantitative assays. For purity and impurities, validation results from both mRNA-1010 and (b) (4) [REDACTED] are reviewed. For (b) (4) [REDACTED], this review focuses on the (b) (4) [REDACTED] (SOP-6855), the only quantitative attribute derived from this assay. The other validation reports provided are qualitative (RPT-16589, RPT-80982, RPT-83955, RPT-87940, and RPT-83955) and are not reviewed. For (b) (4) [REDACTED], this review focuses on RPT-90365, the mRNA-1010 specific validation.

Most of the specifications are justified based on clinical results or previously licensed vaccines and are not reviewed. However, the purity/impurities release limits were justified based on the stability modeling and the minimum effective dose was also justified based on analysis of manufacturing data and is reviewed.

The applicant leveraged the stability data from (b) (4) [REDACTED] to support the proposed drug product shelf life. Because (b) (4) [REDACTED], stability data from both vaccines are reviewed.

This memo refers to Modules 1 and 3 of the original BLA, along with the applicant's responses to information requests (IRs) in the amendments in Table 1. All IR responses were reviewed and found acceptable.

Table 1. Sub-Amendments and IRs Reviewed

IR #	Response Sequence	Date Response Received	Description
8	0011	3/5/2026	Confirmed (b) (4) assay implementation as quantitative with defined acceptance criteria
8	0014	3/13/2026	Submitted completed (b) (4) method validation report (RPT-99120)
13	0031	4/2/2026	Responded to CMC review team questions
16	0027	3/25/2026	Argued purity/impurity assay adequately validated by leveraging (b) (4) co-validation
19	0030	3/31/2026	Submitted (b) (4) DP purity assay validation reports and raw data (RPT-78652)
24	0037	4/22/2026	Submitted EoSL analysis details and raw data for (b) (4)
34	0052	5/13/2026	Revised linearity assessment; response about additional validation
35	0058	5/19/2026	mRNA-1010 stability data and EoSL analysis
50	0071	6/4/2026	Revised minimum strain-specific EDD
51	0073	6/8/2026	Acknowledged additional purity/impurity validation testing and submitted protocol
51	0088	6/30/2026	Submitted partial purity validation report
51	0096	7/15/2026	Full validation report for purity (SOP-5401, RPT-102661 V2)
59	0080	6/18/2026	Submitted full simulation description and script for minimum EoSL EDD assessment
60	0083	6/23/2026	Responded to questions on mRNA-1010 mRNA EoSL purity
70	0099	7/17/2026	Added additional release specification for (b) (4)
77	0105	7/24/2026	Revised assay ranges for SOP-5401

Source: BLA 125869/0

3. DISCUSSION OF PROTOCOLS, STUDIES OR ANALYSES, AND RESULTS

3.1 Drug Product (b) (4) Validation

The drug product (b) (4) is measured by (b) (4)

(b) (4). I did not review the (b) (4) assay, as the product reviewer considered it acceptable based on their review during the (b) (4)

(b) (4). The applicant conducted supplemental validation at (b) (4) for mRNA-1010, and the method was transferred to (b) (4)

(b) (4)

(b) (4)



3.2.4 mRNA-1010 DP SOP-5401 Supplemental Validation (RPT-82658)

The applicant performed supplemental validation of SOP-5401 at (b) (4) for mRNA-1010 DP. The supplemental validation assessed repeatability and IP for labeled and unlabeled DP using the same study design and AC as for the validation studies in Section 3.2.1, but with a stricter AC for (b) (4). Table 13 gives the results, all of which met the AC (purity (b) (4)).



Table 13. mRNA-1010 DP (b) (4) SOP-5401 Supplemental Precision Results

Attribute	Precision*	(b) (4) DP	(b) (4) DP
Purity	Repeatability	(b) (4)	(4)
Purity	Intermediate		
(b) (4)	Repeatability		
	Intermediate		
	Repeatability		
	Intermediate		

*Repeatability given as minimum, maximum across analysts

Source: Tables 5-10, RPT-82658, Module 3.2.R, BLA 125869/0001

Reviewer's Comment: The applicant only assessed the precision at a single purity level because SOP-5401 was fully validated for (b) (4) DP (see Section 3.2.6). The precision results are similar across the two DP types and are consistent with those found in the (b) (4) validation study.

3.2.5 mRNA-1010 DP SOP-5401 Transfer Study (RPT-92401)

To transfer the SOP-5401 method for mRNA-1010 DP from (b) (4), the applicant assessed repeatability, IP, and reproducibility. The study design was the same as for the validation studies in Section 3.2.1, except that the (b) (4) criterion was (b) (4) (stricter AC). Table 14 shows the results, all of which met the acceptance criteria (purity (b) (4))

Table 14. mRNA-1010 DP SOP-5401 Transfer Study Results

Attribute	Parameter*	(b) (4)	(4)
Purity	Mean	(b) (4)	(4)
Purity	Repeatability		
Purity	Intermediate Precision		
(b) (4)	Mean		
	Repeatability		
	Intermediate Precision		
	Mean		
	Repeatability		
	Intermediate Precision		

*Repeatability is given as minimum, maximum across analysts.

Source: Tables 8-13, RPT-92401, Module 3.2.R, BLA 125869/0001

Reviewer's Comment: The results suggest comparable means, repeatability, and IP at (b) (4) and (b) (4) although (b) (4) has lower IP for (b) (4). However, this transfer study only assessed assay performance at a single purity/impurity level.

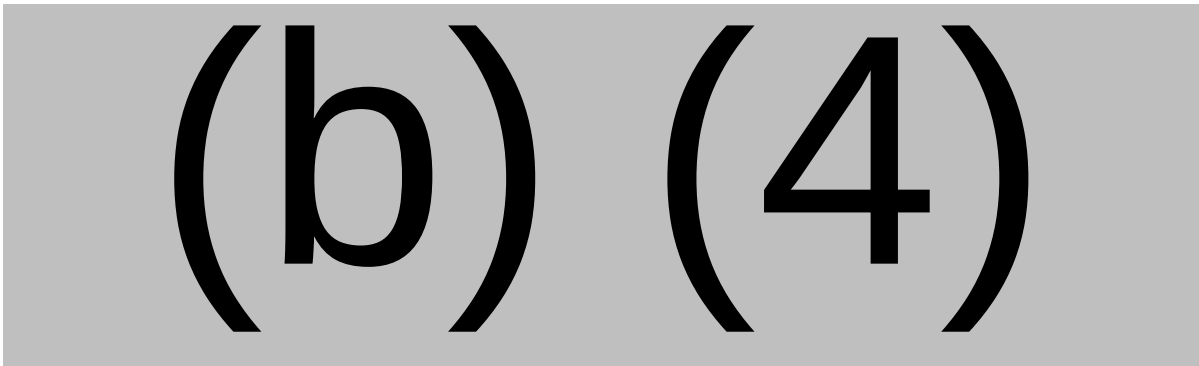
3.2.6 mRNA-1010 DP SOP-5401 Supplemental Validation (RPT-102661)

In response to CBER's comments, the applicant performed this supplemental validation of mRNA-1010 DP samples at (b) (4) and (b) (4). The applicant created defined (b) (4)

(b) (4)



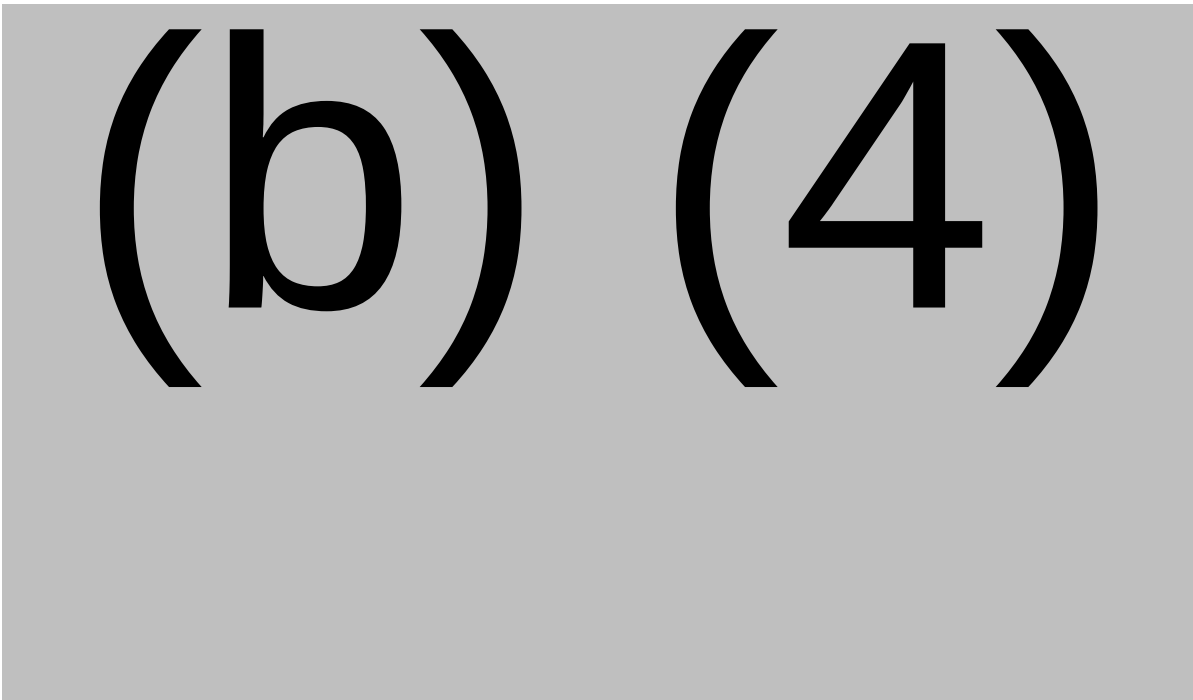
(b) (4)



Linearity was evaluated by (b) (4)

(b) (4) Linearity was considered acceptable if the (b) (4) and the slope and intercept from each model were reported. Figure 5 and Figure 6 show the linearity results for each lab, all of which meet the acceptance criteria.

Reviewer's Comment: Typically, linearity is assessed across all analysts at each site. I find similar results when calculating the linearity results combining data from all analysts at each site. I also performed a sensitivity analysis where I omitted level (b) (4) since the theoretical results of level (b) (4) are based on the observed data. I also find similar results when I omit level (b) (4). In general, the results support a conclusion of linearity, with slopes close to one and intercepts close to zero.



Accuracy was evaluated using (b) (4)



(b) (4)

Reviewer's Comment: *The applicant assessed accuracy compared to each lab's theoretical value, which gives the relative accuracy of the assay at each lab. Since each lab is testing the same batches, the combined data will give a more precise estimate of the theoretical values and allows assessment of accuracy at levels (b) (4). I conducted a sensitivity analysis where I used the theoretical values shown in Table 15. The sensitivity (b) (4) results are mostly consistent with the results given in Table 16, except for the (b) (4) level (b) (4) results, which show somewhat higher recoveries of (b) (4) for (b) (4) and (b) (4) for (b) (4). These higher (b) (4) are caused by the relatively large difference in means between the (b) (4) labs at the lowest level of (b) (4).*

Tables 17 and 18 show repeatability and IP results, respectively. IP was only assessed at Levels (b) (4). All results met the AC (purity: (b) (4)).

Table 17. mRNA-1010 DP SOP-5401 Supplementary Repeatability Results* (RPT-102661)

Attribute	Lab
Purity	(b) (4)
Purity	(b) (4)
(b) (4)	(b) (4)

(b) (4)

*Results given as minimum, maximum over analysts

Source: Tables 17-28, RPT-102661, Module 3.2.R, BLA 125869/0096

Table 18. mRNA-1010 DP SOP-5401 Supplementary IP Results (RPT-102661)

Attribute	Lab
Purity	(b) (4) (b) (4)
Purity	(b) (4) (b) (4)

Source: Tables 32-37, RPT-102661, Module 3.2.R, BLA 125869/0096

Reviewer's Comment: *The precision results are acceptable. The applicant did not calculate the IP at levels (b) (4), despite having appropriate data. I find comparable %RSDs as those shown in Table 18, suggesting acceptable precision across the range tested.*

Based on the validation results provided, the applicant proposed the ranges shown in Table 19. The applicant justified extended ranges beyond the validated ranges because purity has a mathematical upper limit of 100%. The applicant also extended the lower end of range of (b) (4) with degraded batch data that was generated during this study but not included in the range assessment.

Table 19. mRNA-1010 DP SOP-5401 Validated and Proposed Ranges (RPT-102661)

Attribute	Release Specification	EOSL Specification	Validated Range	Proposed Range
Purity	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Source: Table 38, RPT-102661, Module 3.2.R, BLA 125869/0096; Table 1, Response to BLA 125869/0: IR #77 – Quantification Limits (SOP-5401), Module 1.11, BLA 125869/0105

Reviewer's Comment: *The applicant originally proposed ranges wider than the validated ranges for all three attributes, based on the testing in RPT-78652. However, the testing in RPT-78652 does not support the extended range (see Section 3.2.6). CBER requested that the applicant define the ranges based on this study's results. In their July 24, 2026, the applicant proposed the ranges shown in Table 19. The review team considered the extension of the purity range to (b) (4) reasonable, given the mathematical limit, the greater accuracy and precision observed at higher purities, and the difficulty in producing a batch with higher purity. However, the applicant did not provide the results cited from the degraded lot to support the wider range for (b) (4). Nevertheless, the review team agreed to the proposed range because the (b) (4) validation supports a range of approximately (b) (4). Overall, the proposed ranges are acceptable.*

Comparability of accuracy and precision between the (b) (4) labs was assessed for the purity, (b) (4) using Two One-Sided Tests (TOST). For each attribute and level, the difference in means (b) (4) was calculated with 90% confidence interval (CI). Equivalence was concluded if the 90% CI was fully

contained within the AC of (b) (4). This AC was derived from (b) (4) supplemental validation data as (b) (4). The overall standard deviation was (b) (4) for purity, (b) (4) for (b) (4), and (b) (4) for (b) (4). To establish a single AC for all three attributes, the maximum standard deviation (b) (4) was used. The 90% CI for the difference in means was estimated from a fixed-effects model with effects for lab, level and their interaction. Table 20 shows the results, all of which met the AC for equivalence.

Table 20. mRNA-1010 DP SOP-5401 Comparability of Means Results (RPT-102661)

Attribute	Level	(b) (4)	(b) (4)	Difference* (90% CI)
Purity		(b) (4)	(4)	
Purity				
Purity				
Purity				
Purity				

(b) (4)

Source: Table 40, RPT-102661, Module 3.2.R, BLA 125869/0096

Reviewer's Comment: The overall approach is acceptable. However, the proposed AC for (b) (4) appears wide, since the AC is (b) (4) for (b) (4). Using a tighter AC of (b) (4), all levels except (b) (4) pass. While levels (b) (4) do not pass the AC, these levels are substantially higher than the release and EoSL specifications and the observed differences and CIs are small compared to the absolute (b) (4) levels, implying these differences will not impact the product quality. Hence the equivalence test results are acceptable.

Precision comparability was evaluated descriptively by comparing lab-specific repeatability and IP %RSD values. These results were shown in Table 18, and support a conclusion of comparable precision at the (b) (4) labs.

Reviewer's Comment: Overall, the applicant has provided evidence that the assay is accurate and precise across a range of purity and impurity levels when testing DP (b) (4).

(b) (4)

4. JUSTIFICATION OF SPECIFICATIONS

For the quantitative quality attributes, the applicant established most DP specifications based on clinical data or manufacturing experience from licensed vaccines from this mRNA platform. The purity and impurity release limits were established based on the shelf life and the corresponding clinical minimums. Their justification is reviewed in Section 5.

At CBER's request (IR #25), the applicant proposed a minimum effective delivered dose (EDD): the minimum antigen dose (μg) per strain needed to elicit the same immune response as the clinical trial batches. In their response, the applicant proposed an EDD for each strain of (b) (4), based on the (b) (4)

The applicant provided clinical trial results to support this choice of EDD. However, the product reviewer considers the clinical evidence insufficient to support the proposed EDD and the proposed EDD inconsistent with the EoSL release specifications for total RNA content and (b) (4). In response, CBER requested the sponsor re-evaluate the EDD based on the mRNA-1010 phase 3 study data.

Based on clinical study results from mRNA-1010 and (b) (4), the applicant proposed a revised EDD of (b) (4) with a tightened (b) (4) specification (b) (4). Along with the clinical study results, the applicant provided results from simulations intended to show that their commercial control strategy would reliably maintain strain-specific EDDs above (b) (4) through the EoSL. At the product reviewer's request, I reviewed these simulations.

The applicant simulated the EoSL EDD of (b) (4) mRNA-1010 DP batches based on an idealized model of their manufacturing process and the mRNA-1010 stability. Starting from the LNP DS (b) (4) (one per strain for each batch of DP), the applicant simulates the (b) (4) and uses the simulated results and a series of equations to model the total RNA content, (b) (4), and purity at release of the DP batch made from these LNP DS (b) (4), accounting for the assay variability. From these release values and the stability results (see Section 5), the applicant modeled the EoSL EDD for each simulated batch.

From the distribution of simulated EDDs, the applicant reported the (b) (4) percentile (lower one-sided 3σ bound) as the worst-case EoSL EDD, (b) (4) per strain, which is greater than the proposed EDD. Based on the simulation results, the applicant also claimed that simultaneous worst-case values for multiple quality attributes is extremely rare, the probability of an out-of-specification (OOS) RNA content occurring when other attributes have low levels is essentially (b) (4) and that the worst-case scenario of simultaneously low purity and (b) (4) only occurred in (b) (4) of simulations under the tightened (b) (4) specification. Therefore, the applicant concluded that probability of observing a batch with an EoSL EDD below (b) (4) is negligible.

Reviewer's Comment: *The applicant did not provide justification for their modeling approach, which may not reflect their manufacturing process. For example, the applicant does not model losses during each manufacturing step and assumes that the LNP (b) (4) are the only source of manufacturing variability. The applicant also did not justify their choice of input parameter values (e.g., means and standard deviations) or their choice of distributions (e.g., normal). Several parameters are bounded, making a normal distribution inappropriate. The applicant also did not justify their use of data from other mRNA products to estimate the RNA content variability, nor did they justify their assumption that certain parameters are uniformly distributed within a range. If the simulations do not accurately reflect the manufacturing process, the estimated probability of a worst-case EDD may be inaccurate. In particular, if key sources of variability are omitted, the probability may be underestimated.*

Furthermore, the CMC reviewer found that a substantial proportion of mRNA-1010 batches released so far had a (b) (4) RNA content and (b) (4) and that some mRNA-1273 batches have been released at (b) (4) with (b) (4). These release values imply an EoSL EDD of (b) (4) per strain based on the minimum purity specification of (b) (4), directly contradicting the applicant's claim that simultaneous worst-case quality parameters are rare.

In response to this, CBER proposed in IR#70 that the applicant add an additional release specification to ensure acceptable EoSL EDD: release (b) (4)

The applicant counter-proposed a release specification of (b) (4) with an increased EoSL purity specification of (b) (4)

Reviewer's Comment: *The review team considers the applicant's counter proposal acceptable.*

5. STABILITY RESULTS AND SHELF LIFE ESTABLISHMENT

5.1 Drug Product

The applicant proposed a 12-month shelf life at 2–8°C that includes up to 12 hours at 23–(b) (4)°C. To support this shelf life, the applicant provided data from mRNA-1010 LNP-102 DP and (b) (4)

5.1.1 mRNA-1010 LNP-102 DP

Table 27 shows a summary of the available stability data from commercial and development mRNA-1010 LNP-102 DP batches.

Table 27. mRNA-1010 LNP-102 Stability Data Summary

Temperature	Commercial: Sample Size	Commercial: Max Time*	Development: Sample Size	Development: Max Time*
(b) (4)	(b) (4)			
2 to 8°C				
23 to (b) (4) °C				

*Latest available time point in months; given as min, max if batches differ in available data

Source: 3.2.P.8.3 Stability Data – LNP-102 lots {DP, 37.5 PFS}, submitted in response to FDA IR #35, BLA 125869/0058.

To model the quantitative quality attributes at the EoSL, the applicant first (b) (4)

(b) (4)

. Table 28 shows the results of this modeling.

Table 28. mRNA-1010 LNP-102 DP Stability Modeling Summary

Attribute	Temperature	Change per Month: Estimated Mean	Change per Month: Standard Error	Assay Variability*
Purity (b) (4)	(b) (4)	(b) (4)		
Purity (b) (4)	2 to 8°C			
Purity (b) (4)	23 to (b) (4) °C			
(b) (4)	(b) (4)	(b) (4)		

*Assay variability was estimated once for each attribute, pooling data across temperatures

Source: Table 2, Response to BLA 125869/0: IR #35 - Stability Data and Protein Expression, Module 1.11, BLA 125869/0058.

From these estimates, the applicant predicted the quality attributes at the EoSL using the following formula, accounting for estimation error and assay variability:

(b) (4)

(b) (4)

Table 29 shows the predicted EoSL values for a batch that is released at limit with 95% prediction interval bounds (one-sided, as appropriate). All attributes remained within their respective end-of-shelf-life specifications at the proposed 12-month shelf life.

Table 29. mRNA-1010 LNP-102 DP Predicted EoSL Values

Attribute	Release Limit	EoSL Predicted Mean	95% Prediction Interval	EoSL Clinical Minimum (Stability Specification)
mRNA Purity	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Source: Table 3, Response to BLA 125869/0: IR #35 - Stability Data and Protein Expression, Module 1.11, BLA 125869/0058.

Reviewer's Comment: *In the mRNA-1010 stability analysis, it was unclear whether the assay variability for purity (b) (4) represented the assay variance or standard deviation, especially since this value is much larger than the (b) (4) assay variability. The applicant clarified that this is the assay standard deviation. I find a slightly lower prediction bound of (b) (4) with this assay standard deviation, although this value is still above the clinical minimum. I also performed another sensitivity analysis using the largest purity assay IP variability (b) (4) and found a (b) (4) prediction bound of (b) (4), which is also above the clinical minimum.*

There is some evidence that the purity slopes vary across batches. CBER requested the applicant perform a sensitivity analysis to ensure that the proposed shelf life is adequate.

To assess the sensitivity of the results to pooling slopes across batches, the applicant modeled each storage condition separately with a mixed model that included fixed intercept and slopes and per-batch (random) intercepts and slopes. For each batch, this mixed-effects model was used to predict the best linear unbiased predictor of the stability trend for the batch under each storage condition. The applicant used a parametric bootstrap conditioned on the fixed and random effects for each batch (b) (4) iterations; resampled random error) to generate simulated data. The same model was fit to the resampled data, generating a set of predictions at each timepoint (more frequent than the original stability data timepoints to ensure accurate crossing time estimation). The applicant used the (b) (4) percentile of each dataset as the (b) (4) confidence interval lower bound to establish the time at which each batch would exceed the clinical minimum.

For the 5°C analysis, batch (b) (4) was the worst case, which had a crossing time of (b) (4) months. While this lot did not have the steepest slope, it had the highest uncertainty with only (b) (4) timepoints. For the worst-case lot (b) (4), the lower confidence bound at 12 months was (b) (4), which remained above the (b) (4) AC.

For the 25°C mixed model the random-intercept variance was (b) (4), meaning all lots shared a common baseline intercept of (b) (4) mRNA Purity at (b) (4). The bootstrap predictions using the same conditional parametric approach, but predictions were made at the 12-hour time point (b) (4) months). The worst-case excursion lot was (b) (4), with a baseline purity was (b) (4) and a one-sided lower (b) (4) bootstrap confidence bound after the 12-hour 23°C to (b) (4)°C excursion was (b) (4). This lower bound corresponds to a relative decrease of (b) (4), or equivalently, (b) (4) of the fitted baseline mRNA Purity remained after the 12-hour excursion.

The applicant combined the worst-case results from both temperatures by applying the observed relative loss from the 25°C to the worst-case lower confidence bound from 5°C, yielding: (b) (4) which is above EoSL purity AC.

Reviewer's Comment: *The applicant's approach is more complicated than is usually used, although the method seems reasonable. Overall, the sensitivity results support the proposed shelf life.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6. CONCLUSIONS

The applicant has provided adequate validation of the purity/impurities, (b) (4) [REDACTED] assays. The proposed shelf lives for DP and the DS are supported by stability data, and the applicant has addressed the concerns about the worst-case EDD by establishing an additional release specification. Based on the totality of the evidence reviewed, I recommend approval of this BLA.