

<b>Application Type</b>	Original BLA
<b>STN</b>	125768/0
<b>CBER Received Date</b>	21 December 2022
<b>PDUFA Goal Date</b>	21 August 2023
<b>Product Division/Office</b>	DVP/OVRR
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<b>Project Managers</b>	Paul Keller, Laura Montague, Vera Stupina
<b>Priority Review</b>	Yes
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<b>Review Completion Date/ Stamped Date</b>	
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<b>Applicant</b>	Pfizer Inc.
<b>Established Name</b>	Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine
<b>(Proposed) Trade Name</b>	ABRYSVO
<b>Pharmacologic Class</b>	Vaccine

<b>Formulation, including Adjuvants, etc.</b>	vial of lyophilized powder containing 120 micrograms (mcg) of RSV stabilized prefusion F protein (60 mcg A and 60 mcg B antigens) and pre-filled syringe of diluent
<b>Dosage Form and Route of Administration</b>	0.5 mL dose for intramuscular injection
<b>Indication and Intended Population</b>	Prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals.

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## GLOSSARY

%RSD	Percent Relative Standard Deviation
(b) (4)	
BLA	Biological Licensing Application
CI	Confidence Interval
CMC	Controls, Manufacturing, and Chemistry
CRM	Clinical Reference Material
DP	Drug Product
DS	Drug Substance
(b) (4)	
(b) (4)	
IP	Intermediate Precision
IR	Information Request
(b) (4)	
PRM	Primary Reference Material
RSV	Respiratory Syncytial Virus
(b) (4)	
TI	Tolerance Interval
TOST	Two One-Sided T-Tests
WRM	Working Reference Material

## 1. EXECUTIVE SUMMARY

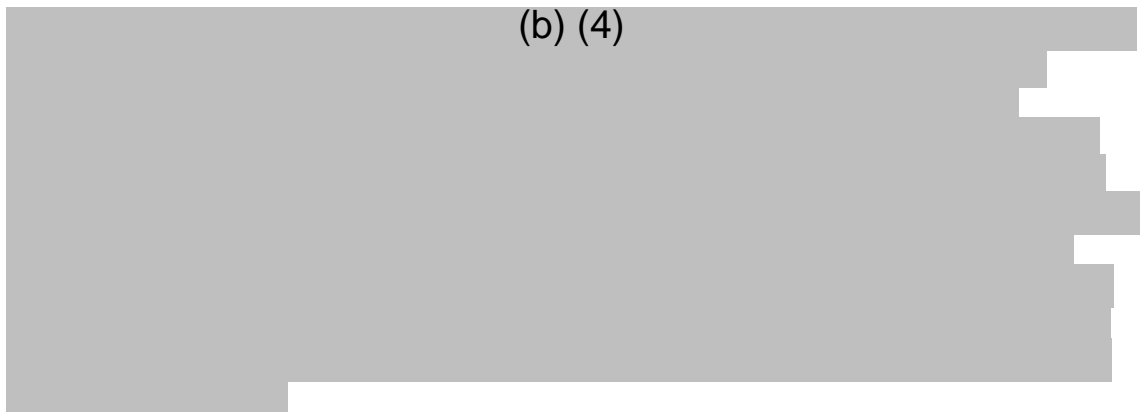
In this original BLA, Pfizer seeks licensure for their Respiratory Syncytial virus (RSV) bivalent stabilized prefusion F subunit vaccine for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals. This CMC statistical review focuses on the justification of drug product (DP) specification for the relative prefusion F content, the DP stability and shelf-life establishment, the validation of the relative prefusion F content (b) (4) and (b) (4)

assay for the DP and (b) (4)

Pfizer justified their DP relative prefusion F content (potency) acceptance criterion of (b) (4) using a (b) (4) -confidence tolerance interval (TI) calculated from the release data from (b) (4) DP lots: (b) (4). Pfizer's proposed confidence level is lower than is customary, but the coverage and confidence levels were chosen so that the TI is the mean  $\pm 3 \times$  standard deviation, which is an acceptable method. Pfizer justified using an acceptance criterion that is wider than the tolerance interval and observed data based on a scientific rationale and early phase clinical data. Therefore, the proposed DP potency acceptance criterion is acceptable.

Pfizer provided validation reports for the DP (b) (4) relative prefusion F content (b) (4) and (b) (4). However, the validation study designs had small sample sizes at the routine (b) (4) DP testing labs, did not include assessments of accuracy, linearity, repeatability, or intermediate precision at the routine testing, and the (b) (4) validation data was normalized, even though normalization is not a part of routine testing. Ideally, Pfizer would perform additional validation studies at the routine testing labs. Despite these limitations, CBER's analyses of the validation data collected at the routine testing labs do not suggest that the (b) (4) and (b) (4) have unacceptable performance over the proposed assay ranges.

(b) (4)



Overall, Pfizer has adequately justified their DP potency specification and demonstrated equivalence of their PRM to their CRM for the DP (b) (4). The assay validation study designs for the DP (b) (4) relative prefusion F content (b) (4) had significant limitations, and Pfizer would ideally perform additional validation studies at the routine testing labs for these assays to confirm these results. However, the assay validation results do not suggest that the DP (b) (4) assays are unacceptably biased or imprecise for monitoring product quality. Therefore, I recommend approval of this original BLA.

## 2. REGULATORY BACKGROUND

Pfizer's respiratory syncytial virus (RSV) stabilized prefusion F subunit vaccine (RSVpreF) was approved on 31 May 2023 for use in individuals 60 years of age and older under BLA 125769/0. In this original BLA, Pfizer seeks licensure indication for their Respiratory Syncytial virus (RSV) bivalent stabilized prefusion F subunit vaccine (ABRYSVO) used in infant from birth through 6 months of age by active immunization of pregnant individuals. The CMC information in Modules 3 of BLAs 125768/0 and 125769/0 is the same, although the organization differs between the two files. ABRYSVO consists of two drug product (DP) components: a lyophilized powder and sterile water for injection. The lyophilized powder DP contains (b) (4).

CBER sent IRs #26 on 13 June 2023 and #30 on 28 June 2023 requesting that Pfizer update Module 3 of BLA 125768/0 to match that of BLA 125769/0, list all IR responses submitted to BLA 125769/0 in Module 1 of BLA 125768/0, and confirm that the CMC information in Module 3 of BLAs 125768 and 125769 is identical or intended to be so. Pfizer adequately responded to all information requests in Amendment 30 dated 23 June 2023 and Amendment 35 dated 6 July 2023.

### 3. SUBMISSION QUALITY

The submission was adequately organized for conducting a complete CMC statistical review without unreasonable difficulty.

### 4. SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES

#### 4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC reviews.

### 5. SOURCES OF INFORMATION CONSIDERED IN THE REVIEW

#### 5.1 Review Strategy

At the product reviewer's request, this review focuses on the DP relative prefusion F content specification establishment, DP shelf-life establishment, validations of the prefusion F (b) (4) and (b) (4) assay for DP (b) (4).

#### 5.2 BLA/IND Documents That Serve as the Basis for the Review

This review refers to the following modules and documents:

- BLA 125768/0.0 (seq. 0001)
  - Module 1.11.1 Quality Information Amendment
  - Module 3.2.P Drug Product [RSVpreF]
    - 3.2.P.5.3 Validation of Analytical Procedures – Prefusion F (b) (4); VAL100148446
    - 3.2.P.5.6 Justification of Specifications
    - 3.2.P.6 Reference Standards or Materials
    - 3.2.P.8 Stability
  - Module 3.2.S Drug Substance [(b) (4)]
    - 3.2.S.4.3 Validation of Analytical Procedures – Prefusion F (b) (4); VAL100155025
    - 3.2.S.5 Reference Standards or Materials
  - Module 3.2.S Drug Substance [(b) (4)]
    - 3.2.S.4.3 Validation of Analytical Procedures – Prefusion F (b) (4); VAL100155026
    - 3.2.S.5 Reference Standards or Materials
  - Module 3.2.R Regional Information
- BLA 125768/0.30 (seq. 0029)

- Module 3 sections, as described for seq. 0001
- BLA 125768/0.35 (seq. 0037)
  - Module 1.11.1 Quality Information Amendment

## 6. DISCUSSION OF PROTOCOLS, ANALYSES, AND STUDY REPORTS

### 6.1 Drug Product Relative Prefusion F Content Specification

For lot release and end-of-shelf-life acceptance criterion, Pfizer first calculated the two-sided (b) (4) -confidence tolerance intervals (TIs) of (b) (4), using release data on (b) (4) DP batches (mean: (b) (4); standard deviation: (b) (4); range: (b) (4)). Then, Pfizer proposed a wider range, (b) (4), for final acceptance criteria based on the early phase clinical study immunogenicity results, which included doses of (b) (4).

**Reviewer's Comment:** Pfizer chose to fix the coverage at (b) (4) and vary the confidence level. A fixed confidence level, usually 95%, is standard, but in some cases, a lower confidence level may be acceptable. An IR about this was sent to Pfizer on 10 January 2023 requesting Pfizer use a higher confidence level and to comment on the choice of confidence and coverage.

In their response to the 10 January 2023 IR, Pfizer argued that fixing the coverage level and adjusting the confidence based on the sample size is more appropriate in this setting; a (b) (4) -confidence TI was chosen so that the TI is the mean  $\pm 3 \times$  standard deviation. For a fixed coverage and sample size, increasing the confidence would widen the TI. Moreover, the 99%-coverage/95%-confidence TI ((b) (4)) is very similar to the proposed interval.

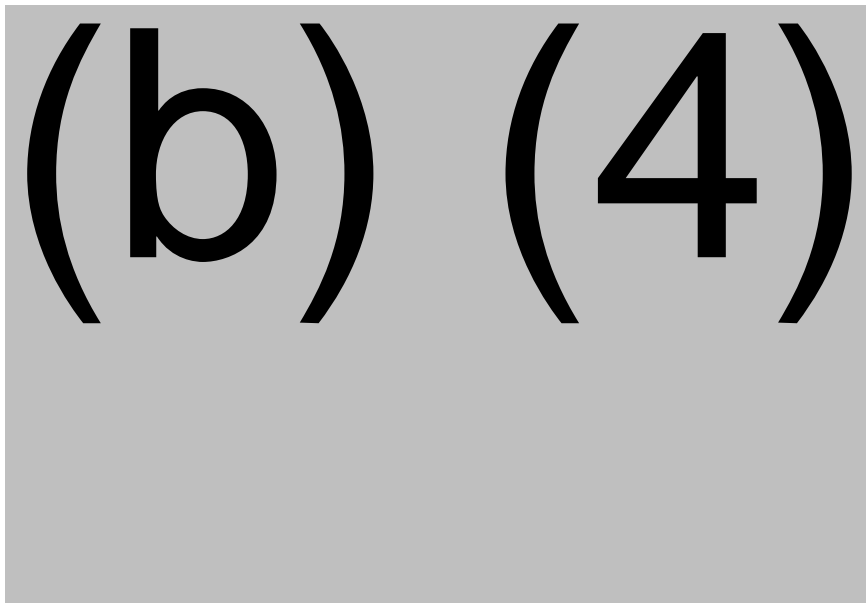
It is noted the mean  $\pm 3 \times$  standard deviation gives a range of (b) (4) which is narrower than the TI. In addition, the final proposal is even wider: (b) (4). The proposal is also much wider than the prefusion F contents for the clinical lots (range: (b) (4)). Therefore, the proposed acceptance criterion does not have solid statistical justification. However, the product reviewer found the wider interval acceptable based on early phase clinical study immunogenicity results.

On the other hand, Pfizer's TI method assumes that the DP lots are independent, but most of the DP lots (b) (4). Nevertheless, this TI method is acceptable; in this case, the TI calculated under independence is likely to be wider than a TI calculated under an assumption of correlation.

### 6.2 Drug Product Shelf-Life

Pfizer seeks a shelf-life of 18 months for DP when stored at  $5 \pm 3^\circ\text{C}$ .

Stability data at  $5 \pm 3^{\circ}\text{C}$  is available through 15 months for (b) (4) clinical lots, 18 months for (b) (4) clinical lots, (b) (4) months for (b) (4) lots, (b) (4) months for (b) (4) clinical lot, 9 months for (b) (4) process validation lots, and 6 months for (b) (4) confirmatory lots. Because all lots met the stability study acceptance criteria of (b) (4), Pfizer concluded that the results support the proposed shelf-life (Figure 1).



**Reviewer's Comment:** *The stability study acceptance criterion is wider than the proposed commercial DP acceptance criterion ( (b) (4) ). Pfizer clarified that the commercial DP acceptance criterion had not been established when the stability studies started, and that future stability studies would use the commercial DP acceptance criterion. I verified that relative prefusion F content from ongoing stability study results were within the commercial DP acceptance criteria. This is acceptable.*

(b) (4)

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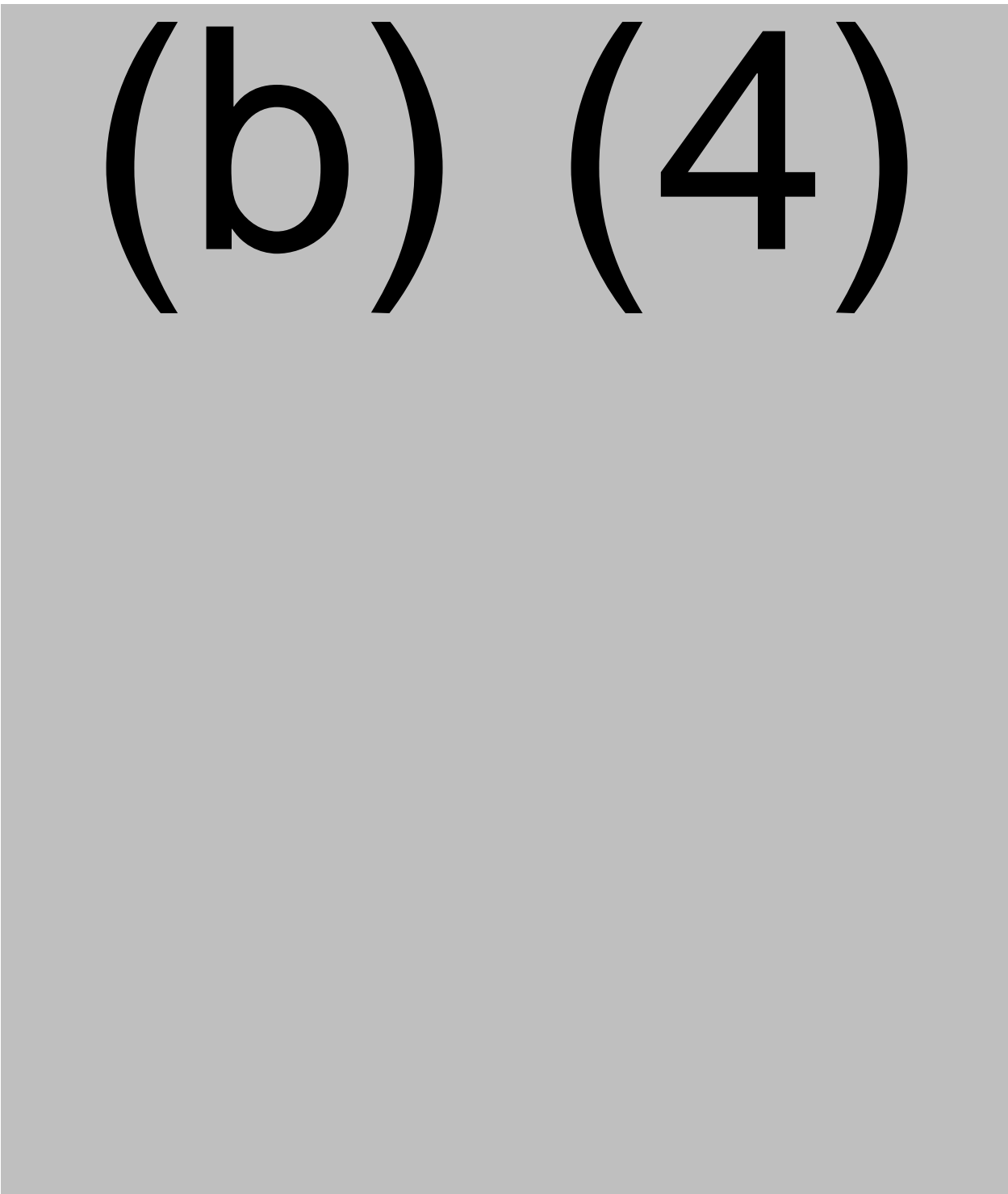


(b) (4)

*Therefore, the proposed shelf-life is acceptable. Given the additional uncertainty introduced by the apparent non-linear trend and wide range of available data for lots, a*

*comment was sent to Pfizer recommending they reassess their release and end-of-shelf-life specifications (currently the same) in light of any stability trends, as they collect more stability data.*

### 6.3 Assay Validation



11 pages have been determined to be not releasable: (b)(4)


## 7. CONCLUSIONS

### 7.1 Statistical Issues and Collective Evidence

Pfizer justified their DP potency acceptance criterion of (b) (4) using a (b) (4) TI calculated from the release data from (b) (4) DP lots: (b) (4). Pfizer's proposed confidence level is lower than is customary, but the coverage and confidence levels were arbitrarily chosen so that the TI is the mean  $\pm$  3 $\times$ standard deviation, which is an acceptable method. Pfizer justified the wider acceptance criterion based on a scientific rationale. Therefore, the proposed DP potency acceptance criterion is acceptable.

Pfizer provided validation reports for the DP (b) (4) relative prefusion F content (b) (4) and (b) (4). However, the validation study designs had smaller sample sizes than are customary, did not include assessments of accuracy, linearity, repeatability, or intermediate precision at the labs that will perform routine (b) (4) DP testing, and the (b) (4) data was normalized before assessing the validation parameters, even though normalization is not performed during routine testing. Despite these limitations, CBER's analyses of the validation data collected at the routine testing labs did not suggest that the (b) (4) have unacceptable performance over the proposed assay ranges. The assay validation results are adequate but Pfizer would ideally perform additional validation studies at the routine testing labs to confirm these results, given the study design limitations.

(b) (4)



### 7.2 Conclusions and Recommendations

Overall, Pfizer has adequately justified their DP potency specification and demonstrated equivalence of their Primary Reference Material to their Clinical Reference Material for the DP (b) (4). The assay validation study designs for the DP (b) (4) relative prefusion F content (b) (4) and (b) (4) had significant limitations. Pfizer would ideally perform additional validation studies at the routine testing labs for these assays to confirm these results. However, the assay validation results do not suggest that the DP (b) (4) assays are unacceptably biased or imprecise for monitoring product quality. Therefore, I recommend approval of this original BLA.