

Application Type	Original BLA
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Product Division/Office	DVP/OVRR
Committee Chair	Goutam Sen
CMC Reviewers	Judy Beeler, Christian Sauder
Project Managers	Paul Keller, Laura Montague, Vera Stupina
Priority Review	Yes
Reviewer Name	Hairong Shi
Review Completion Date/ Stamped Date	
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Applicant	Pfizer Inc.
Established Name	Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine
(Proposed) Trade Name	ABRYSVO
Pharmacologic Class	Vaccine

Formulation, including Adjuvants, etc.	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
Dosage Form and Route of Administration	0.5 mL dose for intramuscular injection
Indication and Intended Population	prevention of (b) (4) lower respiratory tract disease caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older by active immunization

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GLOSSARY

%RSD	Percent Relative Standard Deviation
(b) (4)	(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)
(b) (4)	(b) (4)
IP	Intermediate Precision
IR	Information Request
(b) (4)	(b) (4)
PRM	Primary Reference Material
RSV	Respiratory Syncytial Virus
(b) (4)	(b) (4)
TI	Tolerance Interval
TOST	Two One-Sided 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 acute respiratory disease and lower respiratory tract disease caused by RSV in individuals 60 years of age and older by active immunization. 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 (b) (4)

(b) (4) (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

In this original BLA, Pfizer seeks licensure for their Respiratory Syncytial virus (RSV) bivalent stabilized prefusion F subunit vaccine (ABRYSVO). ABRYSVO consists of two drug product (DP) components: a lyophilized powder and sterile water for injection. The lyophilized powder DP contains (b) (4) (b) (4)

Table 1 lists the responses to CMC statistical information requests that I reviewed. Pfizer adequately responded to all information requests.

Table 1. BLA 125769/0 Amendments: Response to Information Requests

Date IR Sent	IR Response Date	IR Response	Summary
10 January 2023	24 January 2023	BLA 125769/0.18	Request for validation study data and bridging study information; comment on DP specification tolerance intervals
13 January 2023	27 January 2023	BLA 125769/0.19	Request for stability data, clarification of stability acceptance criterion
12 April 2023	21 April 2023	BLA 125769/0.54	Comments on DP specification justification, bridging study analyses, (b) (4) validation analyses
27 April 2023	4 May 2023	BLA 125769/0.58	Request for more information about assay validation study designs

Source: Created from BLA 125769/0

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 perfusion F content specification establishment, DP shelf-life establishment, validations of the perfusion F (b) (4) and (b) (4) assay for DP (b) (4) (b) (4) (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 125769/0.0 (seq. 0001)

- 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.P.5.3 Validation of Analytical Procedures – (b) (4) VAL100155025
 - 3.2.P.6 Reference Standards or Materials
- Module 3.2.S Drug Substance (b) (4)
 - 3.2.P.6 Reference Standards or Materials
- BLA 125769/0.5 (seq. 0006)
 - Module 1.11.1 Response to 05 Dec 2022 FDA QQR4-4
- BLA 125769/0.18 (seq. 0019)
 - Module 1.11.1 Quality Information Amendment
 - Module 3.2.S Drug Substance (b) (4)
 - 3.2.P.5.3 Validation of Analytical Procedures – (b) (4) VAL 100145649
 - Module 3.2.S Drug Substance (b) (4)
 - 3.2.P.5.3 Validation of Analytical Procedures – (b) (4) VAL100155026
 - 3.2.P.5.3 Validation of Analytical Procedures – (b) (4) VAL 100146817
 - Module 3.2.R Regional Information
- BLA 125769/0.19 (seq. 0020)
 - Module 1.11.1 Quality Information Amendment
 - Module 3.2.R Regional Information
- BLA 125769/0.35 (seq. 0037)
 - Module 1.11.1 Quality Information Amendment
 - Module 3.2.R Regional Information
- BLA 125769/0.35 (seq. 0037)
 - Module 1.11.1 Response to 07 Apr 2023 FDA QQR18-10
- BLA 125769/0.50 (seq 0052)
 - Module 1.11.1 Quality Information Amendment
- BLA 125769/0.54 (seq 0056)
 - Module 1.11.1 Quality Information Amendment
 - Module 3.2.P Drug Product [RSVpreF]
 - 3.2.P.5.3 Validation of Analytical Procedures – (b) (4) VAL 100148445
- BLA 125769/0.58 (seq. 0060)
 - Module 1.11.1 Quality Information Amendment
 - Module 3.2.R Regional Information

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) (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.

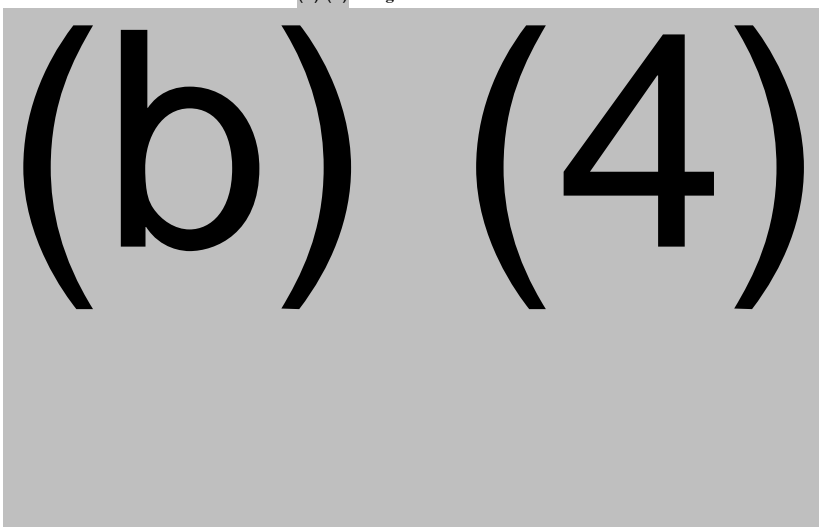
On the other hand, Pfizer's TI method assumes that the DP lots are independent, but most of the DP lots (b) (4) (b) (4) Nevertheless, this TI method is acceptable; in this case, the TI calculated under independence is likely to be wider than a TI calculated under an assumption of correlation.

6.2 Drug Product Shelf-Life

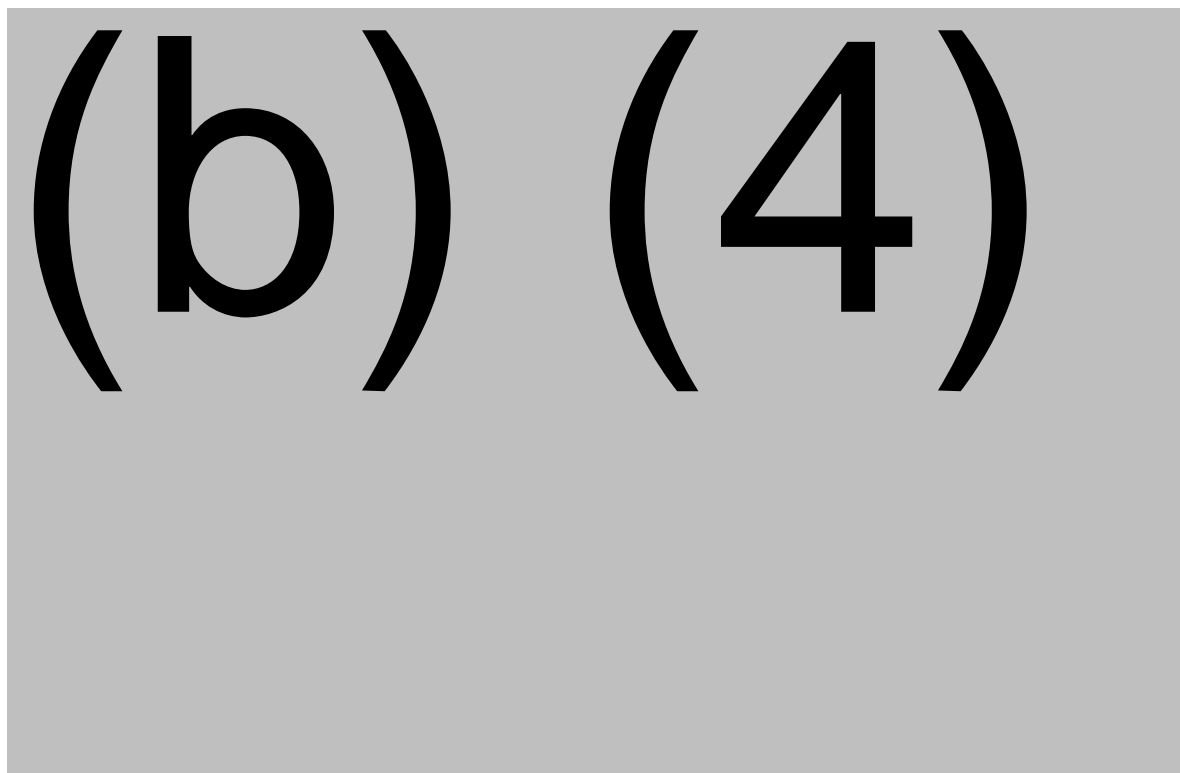
Pfizer seeks a shelf-life of 18 months for DP when stored at $5 \pm 3^\circ\text{C}$.

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).

Figure 1. Drug Product Stability Data
Prefusion F (b) (4) Long Term trend



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)

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.

12 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) 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.