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Division / Office	DVP/OVRR
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Priority Review	Yes
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Review Completion Date / Stamped Date	
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Applicant	GlaxoSmithKline Biologicals SA
Established Name	Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted

(Proposed) Trade Name	AREXVY
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	A single-dose vial of lyophilized RSVPreF3 antigen component to be reconstituted with the accompanying vial of AS01 _E adjuvant
Dosage Form(s) and Route(s) of Administration	Suspension supplied as a single-dose vial for intramuscular injection only.
Dosing Regimen	A single dose of 0.5 mL contains 120 mcg of RSVPreF3 antigen adjuvanted with AS01 _E
Indication(s) and Intended Population(s)	Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults 60 years of age and older.

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BLA	biologics licensing application
RSV	respiratory syncytial virus
LRTD	lower respiratory tract disease
DS	drug substance
DP	drug product
IR	information request
TI	tolerance interval
TOST	two one sided tests
OA	older adults
IVRP	in vitro relative potency

1. EXECUTIVE SUMMARY

In this original BLA, GlaxoSmithKline Biologicals (GSK) seeks licensure for their respiratory syncytial virus (RSV) vaccine (AREXVY) for the prevention of lower respiratory tract disease caused by RSV in adults 60 years of age and older.

This statistical review focuses on the CMC information for GSK's RSVPreF3 drug substance (DS) and two drug products (DPs), RSVPreF3 Lyo and AS01_E, including validation of potency assays, justification of specifications, stability, and reference standard comparability protocols.

GSK validated their DP potency assays by assessing the accuracy, precision, and linearity over acceptable ranges. The study designs and analyses are appropriate, and all results met the pre-specified acceptance criteria.

GSK justified their (b) (4) DP potency release specifications based on a tolerance interval calculated from release and stability data from (b) (4) lots used in Phase 3 Older Adults clinical trials. While applicant's statistical approach is not appropriate because GSK included both release and stability data without accounting for the correlation between repeated measures, the CMC reviewers consider the provided scientific justification adequate to support the proposed specifications.

GSK submitted stability data from (b) (4) Process (b) (4) non-GMP lots for their (b) (4) (b) (4) Process (b) (4) lots for their RSVPreF3 Lyo DP to support the proposed 24 months shelf-lives.

GSK submitted comparability protocols for replacing several different reference standards. The comparability protocols used two one-sided-tests (TOST) of equivalence to establish comparability of the current and new reference standards, which is an appropriate method for assessing comparability.

Overall, GSK has adequately validated their DP potency assays, has proposed appropriate (b) (4) DP potency acceptance criteria for their specifications, and has submitted adequate justification for their proposed (b) (4) DP shelf-lives. GSK has proposed

comparability protocols that used an appropriate statistical approach for replacing reference standards. Therefore, I recommend approval.

2. REGULATORY BACKGROUND

GlaxoSmithKline Biologicals (GSK) seeks licensure for their respiratory syncytial virus (RSV) vaccine (AREXVY) for the prevention of lower respiratory tract disease caused by RSV in adults 60 years of age and older. AREXVY is formulated as two components in separate final containers, each referred to as DP in this memo: 120µg of the RSV recombinant fusion protein as a lyophilized powder (RSVPreF3 Lyo) and the AS01_E liquid adjuvant. The RSVPreF3 Lyo is made from the RSV recombinant fusion protein (b) (4) (RSVPreF3). AS01_E consists of two immune-enhancers: 25 µg of purified Quillaja saponin (QS-21) and 25 µg of MPL. GSK produces QS-21 in-house.

Two CMC statistics related information requests (IRs) were sent: IR #16 and IR #27. In an IR #16 (30 January 2023), CBER requested the data from the validation studies, which GSK provided in their response (BLA 125775/0.16). Their response was acceptable.

In IR #27 (13 March 2023), CBER requested GSK re-assess the release specifications for the DP in vitro relative potency and for DP RSVpreF3 content, pre-specify the equivalence margin in the reference standard comparability protocols, and describe their precision analysis methods for the validation study. In their response (BLA125775/0.27), GSK chose not to follow CBER's recommendation and instead used an alternative statistical approach and provided a scientific justification for their DP acceptance criteria. Although CBER did not agree with their statistical method, the CMC reviewers found the scientific justification acceptable. GSK adequately addressed the other two requests (i.e., equivalence margin and precision methods), and thus there are no remaining issues.

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 review.

5. SOURCES OF INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Per the CMC product reviewer's recommendation, this review focuses on:

- Validation of the RSVPreF3 Lyo in-vitro relative potency (IVRP), RSVPreF3 Lyo trimer, and AS01_E QS-21
- Specifications for the RSVPreF3 Lyo potency and content

- Stability data for the RSVPreF3 potency, RSVPreF3 Lyo potency, and AS01_E QS-21 content
- RSVPreF3 potency reference standard comparability protocol.

5.2 BLA/IND Documents that Serve as the Basis for the Review

This review refers to the following documents:

- BLA125775/0.0 (seq. 0004)
 - Module 3.2.S.2.6
 - manuf-process-dev-dev-history-rsvpref3.pdf
 - Module 3.2.S.7
 - stability-data-trend-analysis-methodology-rsvpref3.pdf
 - stability-data-longterm-stab-process-(b) (4)-nongmp-rsvpref3.pdf
 - Module 3.2.P.2
 - pharmaceutical-development-development-history-rsvpref3-lyo.pdf
 - Module 3.2.P.3.5
 - process-val-ppq-process-(b) (4)-wn-rsvpref3-lyo.pdf
 - Module 3.2.P.5.6
 - just-of-spec-rsvpref3-inviro-rel-pot-(b) (4)-rsvpref3-lyo.pdf
 - just-of-spec-rsvpref3-content-(b) (4)-rsvpref3-lyo.pdf
 - Module 3.2.P.8.3
 - stability-data-longterm-stab-pro-(b) (4)-lots-rsvpref3-lyo.pdf
 - stability-data-longterm-stab-process-(b) (4)-lots-rsvpref3-lyo.pdf
 - stability-data-longterm-stab-pro-(b) (4)-ppq-lots-wn-rsvpref3-lyo.pdf
 - Module 3.2.R
 - comp-prot-ref-stand-id-inviro-rel-potency-(b) (4)-rsvpref3.pdf
 - validation-rsvpref3-id-inviro-rel-pot-(b) (4)-rsvpref3-dp.pdf
 - validation-rsvpref3-trimer-(b) (4)-rsvpref3-dp.pdf
 - validation-qs21-content-(b) (4)-as01e-dp.pdf
- BLA125775/0.12 (seq. 0015)
 - Module 3.2.S.7
 - stability-data-longterm-stab-process-(b) (4)-nongmp-rsvpref3.pdf
- BLA125775/0.16 (seq. 0019):
 - Module 1.11.1 Quality Information Amendment
- BLA125775/0.27 (seq. 0030):
 - Module 1.11.1 Quality Information Amendment

5.3 Literature Referenced

- Francq, B. G., Lin, D., & Hoyer, W. (2019). Confidence, prediction, and tolerance in linear mixed models. *Statistics in Medicine*, 38 (30), 5603-5622.

6. DISCUSSION OF PROTOCOLS, ANALYSES, AND STUDY REPORTS

6.1 CMC Assay Validation

6.1.1 RSVPreF3 Lyo Drug Product In-vitro Relative Potency (b) (4)

(b) (4)



(b) (4)



(b) (4)



|



|



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

(b) (4)

(b) (4)

6.2 Specifications

6.2.1 RSVPreF3 Lyo Drug Product Relative Potency

GSK proposed specification limits based on a (b) (4) calculated from release and stability data from (b) (4) Phase 2/3 clinical lots or non-clinical lots made with the same manufacture process. Table 14 shows the data GSK used. Based on this data, GSK proposed release acceptance criteria of (b) (4)

(b) (4)

(b) (4)

The high variability suggests that GSK currently does not have sufficient stability data to accurately and precisely estimate the stability profile or potency change over time.

Therefore, CBER recommended that GSK propose an IVRP release acceptance criterion using only the release (Month 0) data and to update the release and end of shelf-life acceptance criteria after GSK has collected sufficient stability data to permit an accurate and precise estimate of the stability profile (IR #27; 13 March 2023). CBER also

recommended that GSK consider placing additional lots into stability studies and collect replicates at each time point, given the apparently high variability.

In BLA 125775/0.27, GSK provided the following responses to IR#27:

- GSK proposed a revised acceptance criterion of (b) (4) which will also apply at the end of shelf-life. GSK calculated this revised acceptance criterion using the release and stability data from (b) (4) lots used in Phase 3 Older Adults (OA) clinical trials (excluding (b) (4)). To address the non-independence between release and stability data, GSK calculated the TI using a random effect model (Francq et al. 2019). GSK also provided a scientific justification for their proposed acceptance criterion, based on the clinical development data.
- GSK revised the (b) (4) potency release acceptance criterion, which depends on the DP potency specification.
- GSK argued that the inclusion of the stability data is justified because stability data through 24 months (proposed shelf-life) are available and the potency loss per month is not statistically significant.
- GSK committed to continue to evaluate stability trends and update their potency acceptance criteria as needed.

Reviewer's Comment: *Inclusion of the stability data may be appropriate if the statistical model accounts for the stability trend, if one exists, and the correlation between time points within each lot. However, GSK's approach does not account for either.*

The evidence for a lack of meaningful stability trends is limited by the small sample size, and GSK's conclusion of no stability trend based on a non-significant difference test (i.e., a null hypothesis that the time slope is zero) is inappropriate. Such hypothesis tests may be non-significant because they have too small a sample size to detect meaningful stability trends. Because of this, the assumption of no stability trend may be inappropriate.

Furthermore, the proposed approach (Francq et al.) assumes a non-time-dependent correlation structure, which may not be valid in this case. Therefore, GSK's response did not address CBER's statistical concerns.

While GSK's statistical approach is not appropriate, the CMC reviewers consider the provided scientific justification adequate to support the proposed specification limits. Therefore, CBER agrees with the proposed acceptance criterion.

6.2.2 RSVPreF3 Lyo Drug Product Content

GSK proposed DP content acceptance criteria of:

120 µg/dose (b) (4),

where 120µg/dose is the target DP content (b) (4).

(b) (4)

Because GSK considered these (b) (4)

This resulted in a proposed acceptance criterion of 120 µg/dose (b) (4), that is, (b) (4).

Reviewer's Comment: *I have concerns about the method GSK used to estimate the (b) (4)*


Consequently, an IR (#27) was sent on 13 March 2023 requesting a description of the data and statistical methods used to estimate the (b) (4), including any study design information.

In the response to IR #27, GSK proposed to tighten the specification limits based on the calculation of a (b) (4), estimated using the release results from the (b) (4) Phase 3 OA clinical lots used for the DP potency acceptance criterion. The proposed acceptance criterion is (b) (4).

Reviewer's Comment: *Based on discussions with CMC reviewers, the proposed acceptance criterion is acceptable.*

6.3 Stability

(b) (4)



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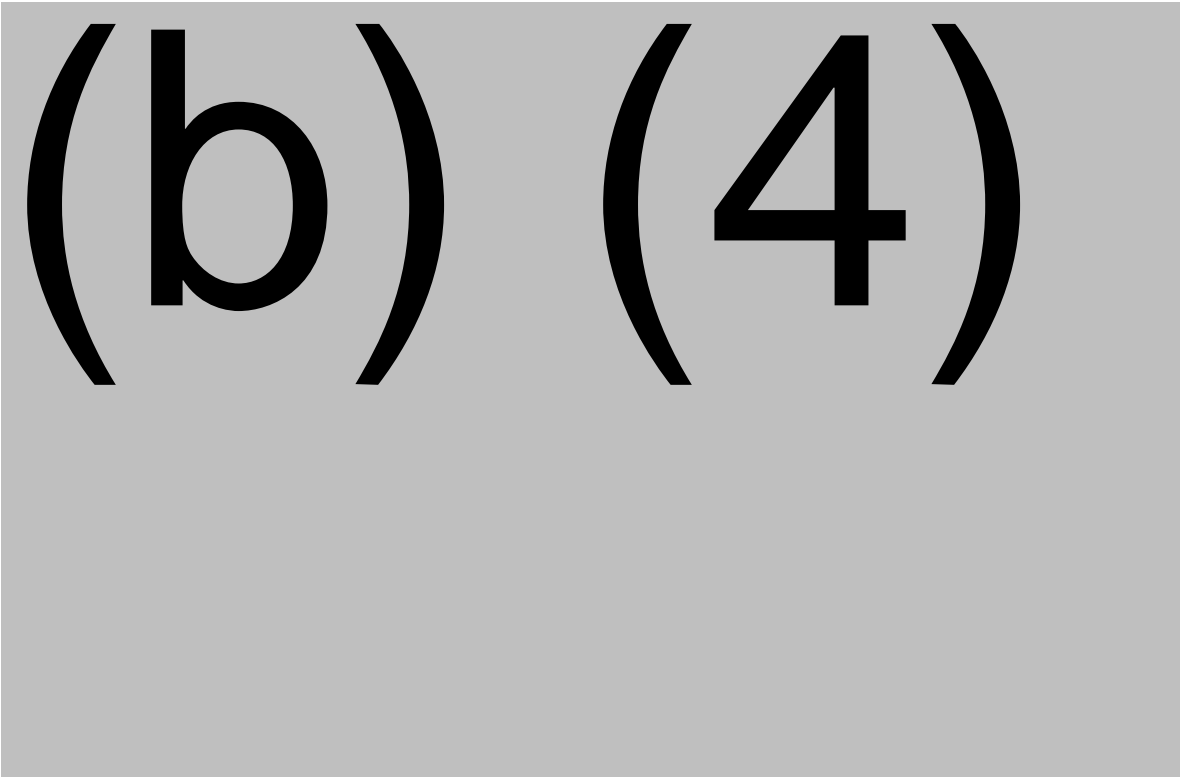
(b) (4)



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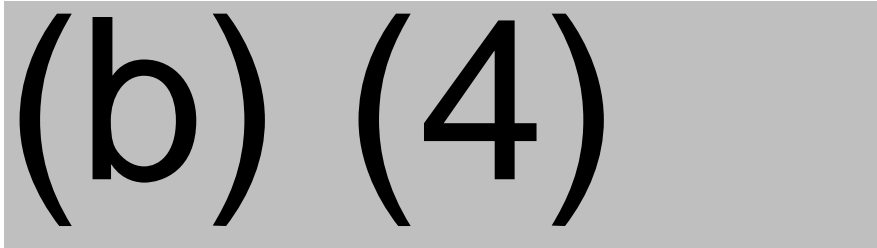





6.3.2 RSVPreF3 Lyo Drug Product

GSK has proposed a shelf-life of 24 months at 5°C for the RSVPreF3 DP in the final container based on stability data from (b) (4) Process (b) (4) older adult Phase 3 clinical lots through 18 to 24 months of storage (P3 OA and P3 OA/MAT lots in Table 7 with data through Month 24 from BLA 125775/0.12). Figure 8 shows the stability data for these lots.



(b) (4)



7. CONCLUSIONS

7.1 Statistical Issues and Collective Evidence

GSK validated their DP RSVPreF3 Lyo relative potency assay, DP RSVPreF3 Lyo content purity assay, and DP AS01_E QS-21 content potency assay by assessing the accuracy, precision, linearity and range. These three assay validation studies had appropriate designs and analyses, and all results met the pre-specified acceptance criteria over acceptable ranges. Therefore, these three assays appear acceptable for monitoring DP quality.

GSK justified their release specifications for DP RSVPreF3 Lyo relative potency based on a (b) (4) calculated from release and stability data from (b) (4) lots used in Phase 3 OA clinical trials. Based on the same (b) (4) approach, GSK also updated their specifications for (b) (4) RSVPreF3 relative potency accordingly. While GSK's statistical approach is not appropriate for reasons discussed in the body of this memo, the CMC reviewers consider the provided scientific justification adequate to support the proposed specifications. Therefore, the proposed acceptance criterion is acceptable. Similarly, GSK justified their release specifications for DP RSVPreF3 Lyo content based on the same (b) (4) approach from release data of the same (b) (4) lots used in Phase 3 OA clinical trials. Based on discussions with CMC reviewers, the proposed acceptance criterion is acceptable.

GSK submitted stability data from three Process (b) (4) non-GMP lots to support the proposed shelf-life of 24 months for their (b) (4) RSVPreF3 and (b) (4) Process (b) (4) lots to support the proposed shelf-life of 24 months for their DP RSVPreF3 Lyo. All results do not suggest that the risk of lots going out-of-specification within the proposed 24-month shelf-lives are unacceptable. Therefore, the proposed shelf-lives are acceptable.

Finally, GSK submitted comparability protocols for the qualification of reference standards used in the RSVPreF3 IVRP (b) (4), RSVPreF3 content (b) (4) and QS-21 content (b) (4). In all three comparability protocols, GSK uses two one-sided-tests (TOST) of equivalence to establish comparability of the current and new reference standards. The proposed statistical approach is appropriate, and I verified that the proposed sample size calculation is correct. Therefore, the submitted comparability protocols are acceptable.

7.2 Conclusions and Recommendations

Overall, GSK has adequately validated their DP potency assays, has proposed appropriate (b) (4) DP potency acceptance criteria for their specifications, and has submitted adequate justification for their proposed (b) (4) DP shelf-lives. GSK has proposed comparability protocols that used appropriate statistical approach for replacing reference standards. Therefore, I recommend approval.