

<b>Application Type</b>	Original BLA
<b>STN</b>	125777/0
<b>CBER Received Date</b>	December 22, 2022
<b>PDUFA Goal Date</b>	November 22, 2023
<b>Division / Office</b>	DVRPA/OVRR
<b>Committee Chair</b>	Sudhakar Agnihothram
<b>CMC Reviewers</b>	Shufeng Liu Alicia Howard Karla Garcia Tao Pan
<b>Project Managers</b>	Konstantin Virnik Georgeta Crivat
<b>Priority Review</b>	Yes
<b>Reviewer Name</b>	Ho-Hsiang Wu
<b>Review Completion Date / Stamped Date</b>	
<b>Supervisory Concurrence</b>	Jennifer L. Kirk Team Lead, Vaccine and Related Products Team, DNCE, DB
	Chunrong Cheng Branch Chief, Device and Non-Clinical Evaluation Branch, DB
	John Scott Division Director, Division of Biostatistics, OBPV
<b>Applicant</b>	Valneva Austria GmbH
<b>Established Name</b>	Chikungunya Vaccine, Live-Attenuated

(Proposed) Trade Name	IXCHIQ
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Lyophilized drug product vial to be reconstituted with diluent (sterile water)
Dosage Form(s) and Route(s) of Administration	Solution supplied as a lyophilized powder to be reconstituted with the supplied diluent, for intramuscular injection only.
Dosing Regimen	One single dose, which is 0.5 mL after reconstitution.
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by Chikungunya virus (CHIKV) in individuals 18 years and older.

## Table of Contents

<b>1. Executive Summary .....</b>	<b>4</b>
<b>2. Regulatory Background .....</b>	<b>4</b>
<b>3. Submission Quality .....</b>	<b>5</b>
<b>4. Significant Issues Related to Other Review Disciplines .....</b>	<b>5</b>
4.1 Chemistry, Manufacturing, and Controls .....	5
<b>5. Sources of Information Considered in the Review .....</b>	<b>6</b>
5.1 Review Strategy .....	6
5.2 BLA/IND Documents that Serve as the Basis for the Review .....	6
5.3 Literature Referenced .....	7
<b>6. Discussion of Protocols, Analyses, and Study Reports .....</b>	<b>7</b>
6.1 TCID <sub>50</sub> for Infectious Virus Concentration Validation .....	7
6.1.1 Drug Product Validation Study .....	7
6.1.2 Drug Substance Validation .....	12
6.2 (b) (4) for CHIKV Identity and Quantification .....	15
6.2.1 Drug Product Validation Study .....	15
6.2.2 Drug Substance Validation Study .....	19
6.3 Stability and Expiry .....	22
6.3.1 Drug Substance .....	22
6.3.2 Drug Product .....	24
<b>7. Conclusions .....</b>	<b>25</b>
7.1 Statistical Issues and Collective Evidence .....	25
7.2 Conclusions and Recommendations .....	26

BLA	biologics licensing application
CHIKV	Chikungunya virus
DS	drug substance
DP	drug product
IR	information request

## 1. EXECUTIVE SUMMARY

In this original BLA, Valneva seeks licensure for their live attenuated Chikungunya vaccine (IXCHIQ) for active immunization for the prevention of disease caused by Chikungunya virus (CHIKV) in individuals 18 years and older.

This statistical review focuses on the CMC and related materials for the drug substance (DS) and drug product (DP), VLA1553, including validation of the two potency assays (TCID<sub>50</sub> and (b) (4) DP and the shelf-lives for (b) (4) DP.

Valneva validated their TCID<sub>50</sub> and (b) (4) assays for (b) (4) DP by assessing the accuracy, precision, linearity, and range. The design and results of the TCID<sub>50</sub> (b) (4) validation study and the (b) (4) validation studies for (b) (4) DP were appropriate and met their acceptance criteria. The TCID<sub>50</sub> DP validation study design did not allow assessment of the precision at high concentrations and lacked sufficient sample size at high concentrations. While the totality of evidence, including the accuracy results from the DP positive control lot (high concentration lot), indicates the assay is likely to have acceptable performance, CBER recommended Valneva provide additional data in a post-approval supplemental to validate performance at high concentrations. In the response to CBER recommendation, Valneva committed to submit the requested study in a post-approval supplement.

Valneva submitted stability data from (b) (4) phase 1 DS lot, (b) (4) phase 3 DS lot, and (b) (4) consistency lots to support a (b) (4) shelf-life at (b) (4) for DS, and stability data from (b) (4) clinical lot and (b) (4) process qualification lots to support a shelf-life of 24 months at 5°C for DP. The stability results do not suggest a concerning level risk of lots going out-of-specification within the proposed shelf-lives. Therefore, the proposed shelf-lives are acceptable.

Overall, Valneva has adequately validated their (b) (4) potency assays, has adequately validated their DP potency assays up to normal concentrations, has committed to submit additional evidence to validate performance at high concentrations, and has submitted adequate justification for their proposed shelf-lives. Therefore, I recommend approval.

## 2. REGULATORY BACKGROUND

Valneva seeks licensure for their live attenuated Chikungunya vaccine (IXCHIQ) for active immunization for the prevention of disease caused by Chikungunya virus (CHIKV) in individuals 18 years and older. IXCHIQ is formulated as a single dose

lyophilized vial of DP VLA1553 to be reconstituted with 0.5 mL diluent (sterile water) in a prefilled syringe.

Three CMC statistics related information requests (IR) were sent: IRs #48, #51, and #56.

In IR #48 (1 June 2023), CBER requested re-analysis of the (b) (4) validation data using an appropriate statistical approach, which Valneva provided in their response (BLA 125777/0.51). Valneva's response was acceptable.

In IR#51 (14 June 2023), CBER requested re-analysis of the TCID<sub>50</sub> precision results using correct formula and update of acceptance criteria, which Valneva provided in their response (BLA 125777/0.54). Although Valneva provided revised results based on the formula CBER provided, CBER could not reproduce the results.

In IR#56 (23 June 2023), CBER requested clarification for discrepancy in precision results in the response to IR#51 (BLA 125777/0.59) and requested additional stability analyses that considered the worst-case scenario. Valneva's responses were acceptable.

In IR#71 (25 July 2023), CBER recommended that in future validation studies, Valneva provide a more detailed description of the data used to establish the validation acceptance criteria, justify their choice of precision acceptance criteria in light of the assay's format, and provide estimates of the precision of the assay's reportable value. CBER also recommended that Valneva use statistical methods to predict the stability of a lot with a low release titer that do not obscure differences between lots or change the variability of the data. Finally, CBER requested clarification about the units used in validation study. Valneva committed to taking CBER's advice for future validation studies and clarified that the units in the validation study were correct. Valneva's responses were acceptable.

In IR#75 (2 August 2023), CBER recommended Valneva perform an additional validation of the TCID<sub>50</sub> method covering the upper range of the release specification (at least (b) (4) log<sub>10</sub> [TCID<sub>50</sub>/0.5mL]) in a post-approval supplement. Valneva committed to follow CBER's recommendation and 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 for details.

## 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 TCID50 for infectious virus concentration in DP samples
- Validation of (b) (4) for identity and quantification in DP samples
- Potency stability.

The DS and DP potency specifications were justified based on the clinical and immunological experience in the phase 1 study, accounting for the stability, and were not based on any statistical analyses. Therefore, these specifications are not discussed in this review.

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

This review refers to the following documents:

- BLA125777/0.2 (seq. 0002)
  - Module 3.2.S.4.3
    - 32s43-appendix-4.pdf
    - 32s43-appendix-5.pdf
  - Module 3.2.S.4.5
    - justification-of-specification.pdf
  - Module 3.2.S.7.1
    - stability-summary.pdf
  - Module 3.2.P.5.3
    - 32p53-appendix-5.pdf
    - 32p53-appendix-6.pdf
  - Module 3.2.P.5.6
    - justification-of-specifications.pdf
  - Module 3.2.P.8.1
    - stability-summary.pdf
- BLA125777/0.51 (seq. 0050)
  - Module 1.11
    - ir-response-file.pdf
  - Module 3.2.S.4.3
    - 32s43-appendix-4.pdf
  - Module 3.2.P.5.3
    - 32p53-appendix-5.pdf
- BLA125777/0.54 (seq. 0053)
  - Module 1.11
    - ir-response-file.pdf

- BLA125777/0.59 (seq. 0058)
  - Module 1.11
    - ir-response-file-56.pdf
  - Module 3.2.S.4.3
    - 32s43-appendix-5.pdf
  - Module 3.2.P.5.3
    - 32p53-appendix-6.pdf
- BLA125777/0.73 (seq. 0071)
  - Module 1.11
    - ir-response-file.pdf
- BLA125777/0.79 (seq. 0077)
  - Module 1.11
    - ir-response-file.pdf




### 5.3 Literature Referenced

Tan, C. Y. (2005). RSD and other variability measures of the lognormal distribution. *Pharmaceutical Forum* 31, 653-655.

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

### 6.1 TCID<sub>50</sub> for Infectious Virus Concentration Validation

(b) (4)





14 pages determined to be not releasable: (b)(4)

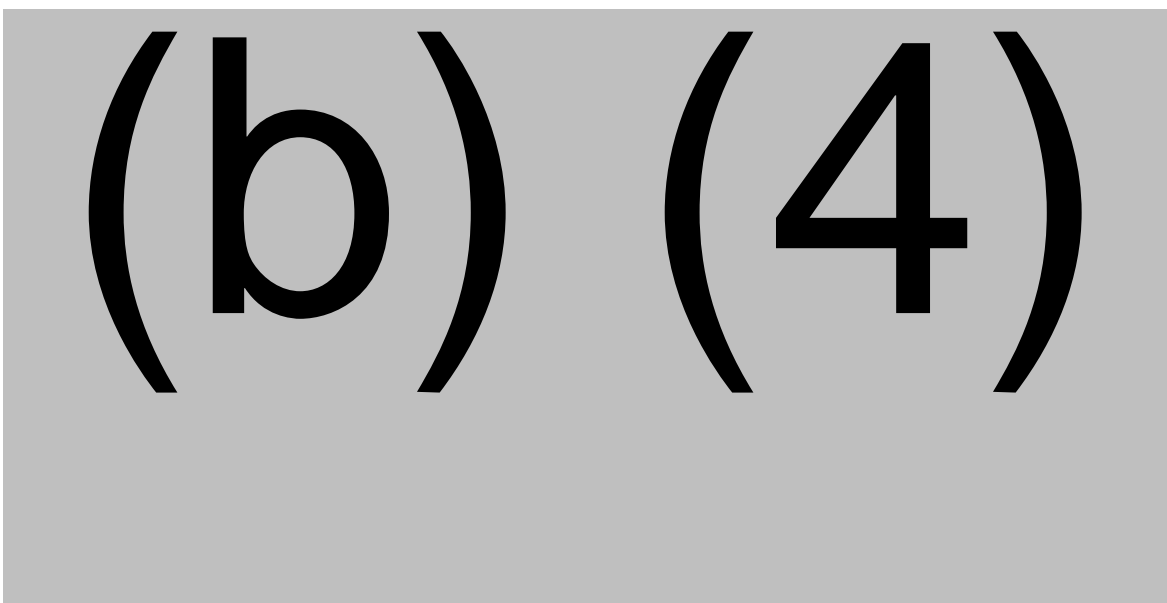


### 6.3 Stability and Expiry

(b) (4)



(b) (4)



(b) (4)





### 6.3.2 Drug Product

Valneva has proposed a shelf-life of 24 months at 2 to 8°C for DP, based on long-term stability data from (b) (4) clinical lot and (b) (4) process qualification lots in which all lots meet the end-of-shelf-life specification through (b) (4) months (Figure 10).

(b) (4)

**Reviewer's Comment:** *Despite a decrease in stability over time, Valneva did not conduct a statistical analysis to demonstrate, with adequate statistical confidence, that the DP with the minimum allowable release potency (b) (4)  $\log_{10}$  TCID/0.5mL) will maintain acceptable potency ( $\geq 3.0 \log_{10}$  TCID/0.5mL) within the proposed shelf-life. CBER requested Valneva provide additional analyses in IR #56 (BLA 125777/0.59)*

In the response to IR#56, Valneva submitted several additional statistical analyses of the worst-case scenario to support the proposed shelf-life. For each lot, Valneva (b) (4)

(b) (4) The per-lot intercepts, individual differences, and normalized data were summarized in Table 13.

(b) (4)

(b) (4)

**Reviewer's Comment:** *Valneva's per-lot analysis is equivalent to the conventional approach of using each lot's linear model slope to predict the potency after (b) (4) months of a lot with a release potency of (b) (4)*

(b) (4)

*By using the overall difference to normalize data, I obtained a lower 95% CI at 24 months of (b) (4), which is consistent with Valneva's results and supports the proposed shelf-life of 24 months. CBER issued an advisory comment stating that for future stability studies the proposed normalization may not be acceptable.*

## 7. CONCLUSIONS

### 7.1 Statistical Issues and Collective Evidence

Valneva validated their TCID<sub>50</sub> and (b) (4) assays for (b) (4) DP by assessing the accuracy, precision, linearity, and range. The design and results of the TCID<sub>50</sub> (b) (4) validation study and the (b) (4) validation studies for (b) (4) DP were appropriate and met their acceptance criteria. The TCID<sub>50</sub> DP validation study design did not allow assessment of the precision across the full assay range and lacked sufficient sample size at high concentrations. While the totality of evidence, including accuracy results from the DP positive control lot (high concentration sample), indicates the assay is likely to have acceptable performance across the entire specification, CBER recommended Valneva provide additional data in a post-approval supplemental to support the validation

performance at high concentrations. In the response to CBER's recommendation, Valneva committed to submit the requested study in a post-approval supplement. Valneva submitted stability data from (b) (4) phase 1 DS lot, (b) (4) phase 3 DS lot, and (b) (4) consistency lots to support a (b) (4)-month shelf-life at (b) (4), and stability data from (b) (4) clinical lot and (b) (4) process qualification lots to support a shelf-life of 24 months at 5°C for DP. The stability results do not suggest a concerning level of risk of lots going out-of-specification within the proposed shelf-lives. Therefore, the proposed shelf-lives are acceptable.

## 7.2 Conclusions and Recommendations

Overall, Valneva has adequately validated their (b) (4) potency assays, has adequately validated their DP potency assays up to normal concentrations, has committed to submit additional evidence to validate performance of their DP potency assay at high concentrations, and has submitted adequate justification for their proposed (b) (4) DP shelf-lives. Therefore, I recommend approval.