Summary Basis of Regulatory Action

Date: April 12, 2018
From: Richard Daemer, PhD, Chair of the Review Committee
BLA/ STN#: 125280/235

Applicant Name: Valneva Austria GmbH

Date of Submission: June 16, 2017
PDUFA Goal Date: April 16, 2018

Proprietary Name: IXIARO® (also referred to as IC51)
Established Name: Japanese Encephalitis Vaccine, Inactivated, Adsorbed

Indication: For Active Immunization for the prevention of disease caused by Japanese Encephalitis Virus (JEV) in persons 2 months of age and older

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: **Wellington Sun, M.D., Director, DVRPA**

□ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA.

Document title	**Reviewer name, Document date**
Clinical Review	Madan Kumar, DO, 4/11/2018
Statistical Review	Mridul Chowdhury, PhD, 03/09/2018
Bioresearch Monitoring Review	Anthony Hawkins, 11/16/2017
Labeling – Advertising, Promotion and Labeling Branch (APLB) review	Michael Brony, 03/07/2018
Product Review	Lewis Markoff, MD, 11/09/2017
Assay Review	Charles Cheung, PhD, 12/11/2017
Pharmacovigilance Review	Shaokui Wei, MD, MPH, 4/12/2018

1. INTRODUCTION

IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) is a formalin-inactivated, aluminum-adsorbed vaccine produced in Vero cells using the attenuated Japanese encephalitis virus strain, SA14-14-2. It currently licensed in the U.S. for prevention of disease caused by

Japanese encephalitis virus (JEV) in persons 2 months of age and older. The primary immunization series consists of two 0.5 mL doses administered intramuscularly 28 days apart for persons 3 years of age and two 0.25 mL doses administered intramuscularly 28 days apart for infants and children 2 months to <3 years of age. Additionally, a booster dose is approved in for persons 17 years of age and older who are at risk for exposure to JEV more than 1 year after completion of the primary immunization series.

In this submission, Valneva Austria GmbH proposes to update the package insert with immunogenicity and safety data from long-term pediatric studies IC51-324 and IC51-325. In addition, the sponsor has also included data supporting a booster dose in the pediatric population in the package insert. The inclusion of this booster dose is based on data from study IC51-325 that compared the safety and immunogenicity of IXIARO with or without the administration of a booster dose in a pediatric endemic population. Study IC51-325 was done as a postmarketing requirement under the Pediatric Research Equity Act (PREA), as established during the approval for the use of the booster dose of IXIARO (STN 125280/19) in individuals 17 years of age or older. In addition, the sponsor has also included the final study report from pediatric study IC51-322 (pivotal safety and immunogenicity conducted in a non-endemic population). The interim data from study IC51-322 was reviewed by CBER as a part of the approval of a supplement for the pediatric indication in 2013, and the final study report is included in this submission for completion, and was reviewed as a part of this supplement. Finally, the sponsor has also revised the package insert (PI) to comply with the Pregnancy, Lactation and Labeling Rule (PLLR) requirements.

2. BACKGROUND

Japanese encephalitis virus (JEV) a mosquito-borne flavivirus causes viral encephalitis, with a case fatality rates for clinical disease 20-30%, and 30-50% of survivors have serious neurological sequelae. No licensed antivirals are available, and current clinical intervention is limited to supportive measures for reducing intracerebral pressure and prevention of secondary infections. In Asia, JEV remains the most common cause of viral encephalitis with pediatric incidence of 5-50 cases/100, 000 children per year. Although JEV infections remain absent in North America, children in the United States (U.S) are amenable to the risk of infection when travelling to endemic regions. Consistent with this, the Centers for Disease Control (CDC) and Prevention records indicate 12 cases of travel-related infection from the United States between 1993-2017. Sixty seven percent of the cases occurred during travel greater than 1 month during the summer season, which is considered the season for transmission of JEV.

Two vaccines for prevention of Japanese encepahlitis, IXIARO and JE-VAX, have been licensed for use in the U.S. and protection against JEV by these vaccines is based on induction of neutralizing antibodies as indicated by a Plaque Reduction Neutralization Test ($PRNT_{50}$) titer of ≥1:10. JE-VAX, licensed for use in individuals of age one year and older, is no longer manufactured, and all remaining stocks expired in February 2011.

Regulatory History

Approval of IXIARO by the U.S. FDA (March 30, 2009) was based on demonstration of non-inferiority to JE-VAX, with respect to two immunogenicity endpoints measured 28 days post completion of the primary series. The initial indication was for use in individuals 17 years of

age and older. The inclusion of the long-term immunogenicity data in the package insert and the use of a booster dose (in persons 17 years of age and older) following the primary vaccination series was approved under the efficacy supplement STN 125280/19 on October 14, 2010. The extension of age range to include infants, children, adolescents two months to less than 17 years of age for active immunization for the prevention of disease caused by JEV, was approved under the efficacy supplement STN 125280/125 on May 17, 2013.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

No new manufacturing changes were submitted to this supplement.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new nonclinical pharmacology/toxicology studies were performed in support of this supplement.

5. CLINICAL PHARMACOLOGY

No new clinical pharmacology information was provided in this supplement.

6. CLINICAL/ STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The clinical studies submitted in this efficacy supplement were conducted under IND 8589. Details of the study are summarized in Table 1 (below).

Table 1: Clinical Studies in the Submission

Study ID	IC51-325	IC51 -324	IC51-322
NCT Number	NCT01296360	NCT01246479	NCT01047839
Phase	3	3	3
IND study	Yes	Yes	Yes
Trial Dates	12/08/2010 to 10/14/2013	10/20/2010 to 9/15/2014	2/24/2010 to 8/9/2013
Study Location	Philippines	U.S., Europe, Australia	U.S., Europe, Australia
Total Participants	298	23	100
Age Range	Nine months to < 17 years and 7 months of age	Nine months to < 21 years of age	Two months to <18 years
IXIARO Regimen	IXIARO booster dose at 11 months after completion of primary series	None	Two IXIARO IM doses 28 days apart
Comparator Regimen	No IXIARO booster dose	None	None
Follow up Duration	36 months	36 months	7 months
Primary endpoints	% of subjects with $PRNT_{50}$ ≥ 1:10 at 1 month after the booster dose	% of subjects with $PRNT_{50}$ ≥1:10 at 12 months after primary series	SAEs and medically attended AEs through Day 56 (1 month post-dose 2)
Non-primary immunogenicity endpoints	$PRNT_{50}$ GMT at 1 month after booster dose, $PRNT_{50}$ GMT and % of subjects with $PRNT_{50}$ ≥ 1:10 at 12, 24, 36 months after primary series	$PRNT_{50}$ GMT at 12 months after primary series, $PRNT_{50}$ GMT and % of subjects with $PRNT_{50}$ ≥ 1:10 at 24, and 36 months after primary series	$PRNT_{50}$ GMT and % of subjects with $PRNT_{50}$ ≥ 1:10 at Day 56 and Month 7

Study ID	IC51-325	IC51 -324	IC51-322
Non-primary safety endpoints	Solicited AEs within 7 days after booster dose; unsolicited AEs, medically attended AEs and SAEs through 1 month after booster dose and through Month 36 after primary series	Unsolicited AEs, medically attended AEs, and SAEs through Month 36 after primary series	Solicited AEs within 7 days after each dose; unsolicited AEs, medically attended AEs, and SAEs through Month 7

Source: Adapted from the Clinical Reviewer`s Memorandum

IC51-325

IC51-325 was the pivotal study conducted to support the booster dose in the pediatric population in a JEV endemic country, and was a postmarketing requirement under the Pediatric Research Equity Act (PREA), as indicated during the approval for the use of the booster dose of IXIARO (STN 125280/19) in individuals 17 years of age or older. It was an open-label, randomized Phase 3 study designed to evaluate long-term immunogenicity over 36 months after primary immunization, as well as safety and immunogenicity for a booster dose administered 12 months after completion of the primary immunization series. Two booster dose levels (0.25 mL and 0.5 mL) were tested for ages <3 years and 3 years and older, respectively. The study population included a total of 300 children 9 months to <17 years and 7 months of age, who had previously been vaccinated with IXIARO in study IC51-323. One hundred and fifty children were followed for three years without a booster dose, whereas the other 150 children received the booster dose one year after the primary immunization series.

The primary objective of the study was to assess the immune response (JEV-neutralizing antibody GMTs and seroconversion rates [SCRs]) at 28 days after a booster vaccination with IXIARO administered at 12 months after primary immunization in a pediatric population from JEV endemic regions.

Secondary objectives of the study were were:

- To assess persistence of immunity (GMTs and proportions of subjects with $PRNT_{50}$ titers of ≥ 1:10) following primary vaccination with IXIARO in a pediatric population from JEV endemic regions (without booster)
- To assess persistence of immunity (GMTs and proportion of subjects with $PRNT_{50}$ titers of ≥ 1:10) following a booster vaccination with IXIARO in a pediatric population from JEV endemic regions
- To assess the long-term safety profile of IXIARO and the safety profile of a booster Dose of IXIARO in a pediatric population from JEV endemic regions
- To assess age-dependent differences in the persistence of the immunity, immune response to a booster dose and the safety profile of IXIARO

End Points and Success Criteria

Two primary endpoints were used to assess the immune response to IXIARO:

a. The GMT for neutralizing antibodies against JEV
b. The proportion of subjects with neutralizing antibody titer ≥ 1:10 at one month after the booster dose

JEV neutralizing antibody titers were measured by a validated plaque reduction neutralization assay using a 50% plaque reduction endpoint ($PRNT_{50}$). No statistical success criteria were specified for the immunogenicity endpoints, since no formal hypothesis testing was involved.

Secondary endpoints used to assess the immune response to IXIARO included the following:

a. Pre-booster dose $PRNT_{50}$ titers to evaluate antibody persistence after primary immunization
b. Geometric mean increases in individual titers after the booster dose
c. Serologic evaluations for antibody persistence performed at months 12, 24 and 36 for all subjects

Analysis of Primary Endpoints (Efficacy)

Efficacy in this study was assessed by the analysis of primary immunogenicity endpoints. The primary immunogenicity analysis for the Intent-to-Treat (ITT) population is summarized in the following table, which shows the proportion of subjects with $PRNT_{50}$ titers $\geq$ 1:10.

Table 2: Proportion of subjects with JEV antibody $PRNT_{50}$ titers $\geq$ 1:10 by treatment group

Treatment Group	**0.25 mL booster dose** n/N (%)	**0.5 mL booster dose** n/N (%)	**All Booster recipients** n/N (%)	**Non-booster** n/N (%)
Visit 1 (Month 7)	75/81 (93%)	57/67 (85.1%)	132/148 (89.1%)	129/150 (86%)
Visit 2 (Month 12)	79/81 (97.5%)	60/67 (89.6%)	139/148 (93.9%)	134/149 (89.9%)
Visit 2a (Month 13)	81/81 (100%)	67/67 (100%)	148/148 (100%)	NA*
Visit 3 (Month 24)	80/80 (100%)	67/67 (100%)	147/147 (100%)	130/146 (89%)
Visit 4 (Month 36)	76/76 (100%)	67/67 (100%)	143/143 (100%)	128/142 (90.1%)

NA* = Not Assessed

90.1% of subjects in the non-booster group in population endemic to JEV, had a $PRNT_{50}$ titer of $\geq$ 1:10 at Month 36, while 100% of subjects in the group that received the booster dose achieved $PRNT_{50}$ titers of $\geq$ 1:10, from 1 month post-booster through the end of the study. It should be noted that 92% of all subjects (from booster and non-booster group) maintained seroprotective titers at 11 months after the completion of the primary immunization, which may be attributed to natural boosting from exposure to JEV in these pediatric subjects living in endemic areas. The proportion of subjects with a $PRNT_{50}$ titer $\geq$ 1:10 following the booster dose was 100% across all age subgroups for the duration of the study. GMTs waned over time but remained notably above pre-booster GMTs through 24 months after booster dosing.

Analyses of Secondary Endpoints

Persistence of antibody response up to 36 months after primary immunization series was noted, as demonstrated by the GMT value of 59.36 (at Month 36) in the non-booster group population. An 8.6 fold increase (GMT=427.73) in GMTs at Month 24 and a six fold increase (GMT=350.40) in GMTs at Month 36 after primary vaccination was observed due to the effect of booster vaccination at Month 12 following primary immunization. The persistence of higher GMTs over time in the booster group indicated that the addition of booster dose results

in increased durability of the antibody response. The magnitude of the booster response was found to be lower with increasing age, similar to antibody responses with primary vaccination.

No review issues were identified in this study, and the results were found to support the changes proposed to the package insert.

IC51-324
This study was an uncontrolled, open-label Phase 3 follow up study to IC51-322 to assess long-term safety and immunogenicity following vaccination with the primary series in a pediatric population (infants, children, and adolescents 9 months to <21 years of age) in non-endemic areas. Subjects previously enrolled in IC51-322, who received two doses of IXIARO at the now licensed primary series dosage, were followed up for four visits including the initial visit for vaccination (Months 7, 12, 24 and 36, ± 1 month) prior to travel to JEV endemic areas. Each visit included collection of blood samples for determination of JEV antibodies, updates on medical histories, and recording of AEs. Safety monitoring during the study IC51-324 was conducted as a review at each follow up visit. Blacks were underrepresented in this study compared to the U.S. population, and no Hispanics were enrolled.

Objectives of the Study
The primary objective was to assess immunogenicity of IXIARO by JEV $PRNT_{50}$ GMT and proportion of participants with $PRNT_{50}$ titer ≥ 1:10.

The secondary objectives included assessing the long-term safety of IXIARO in a pediatric population and evaluating for age-dependent differences on persistence of immunity.

Endpoints
The primary endpoint for this study was the proportion of subjects with $PRNT_{50}$ titer ≥ 1:10 at Month 12 (11 months after the completion of the primary series).

Secondary endpoints included:
- GMT for JEV neutralizing antibodies using $PRNT_{50}$ at Month 12
- GMT for JEV neutralizing antibodies using $PRNT_{50}$ and proportion of subjects with $PRNT_{50}$ titer ≥ 1:10 at Months 24 and 36
- Rates of subjects with AEs, SAEs, and medically-attended AEs throughout the study period

The statistical analysis was descriptive, and no formal sample size calculations were performed, and no statistical success criteria were specified. The safety and the ITT population were identical and included all subjects who entered into the study. As previously discussed, no efficacy analyses were performed for this study, since IXIARO effectiveness was based on JEV-neutralizing antibody responses.

Analysis of Primary and Secondary Endpoints
Although the sample size was limited, overall, approximately 90% of subjects maintained protective JEV $PRNT_{50}$ titers (≥ 1:10) 12 to 36 Months after primary immunization.

GMT titers by age group over the study period was evaluated as a secondary endpoint. A small increase in GMT between Month 12-24 in the age group between 12 to 18 years was noted and was possibly related to travel to the JEV endemic areas. Review of the travel data indicated that eighteen out of twenty-three subjects travelled to endemic countries, and two subjects had notably higher titers on Month 24 after interim visits to Manila and Borneo for seven and thirty days, respectively. The increase in antibody titers could be due to natural boosting through exposure to JEV or any other related flavivirus. An alternative explanation is that subjects in study IC51-324 or IC51-325 did not experience boosting due to natural exposure, and the vaccine-attributable seropositive rate through thirty six months following primary vaccination is indeed 90% in the pediatric population. Although there was a limitation in the sample size, the general trend demonstrated stable GMTs over time. Immunogenicity analyses indicated that subjects with available immunogenicity data demonstrated high rates of continued seroprotection ($PRNT_{50}$ titer $\geq$ 1:10) from 12 to 36 months after primary immunization.

No review issues were identified in this study, and the results were found to support the changes proposed to the package insert.

IC51-322

IC51-322 was a Phase 3 study to assess the safety and immunogenicity of IXIARO primary series in individuals 2 months to < 18 years of age in regions non-endemic for JEV. This was a multicenter study conducted in the U.S., Europe and Australia in healthy male and female subjects planning to travel to JEV endemic countries and where JEV vaccination was recommended. A total of 100 subjects (children and adolescents) were enrolled in this study and analyzed for safety. A subgroup of 64 subjects were analyzed for immunogenicity.

The interim study report that consisted of safety and immunogenicity analyses through Month 7 from 60 of the 100 planned subjects, was previously submitted to STN 125280/125 in support of the pediatric licensure for the primary vaccination series of IXIARO. The clinical review of this interim report was performed under this supplement STN 125280/125. Analysis of forty additional subjects are included in the final report that is submitted in this efficacy supplement, STN 125280/235.

Immunogenicity Analysis

The immunogenicity data from the final analysis includes 10 additional subjects overall compared to the interim analysis. Analysis of the data indicated that the rate of subjects with a $PRNT_{50}$ titer $\geq$ 1:10 was slightly reduced to 91.2% of subjects (as opposed to 100% of subjects) for those with a $PRNT_{50}$ titer result available at Month 7. Version 10 of the clinical protocol included the change of “Primary Objective” to “Safety” alone, which resulted in immunogenicity assessments being discontinued, thereby leading to the availability of immunogenicity data from only 10 subjects.

The final analysis of IC51-322 does not alter the existing profile of the safety and immunogenicity of the IXIARO primary series. The clinical reviewer had a similar recommendation for this analysis, and no outstanding concerns were identified.

No review issues were identified in this study, and the results were found to support the changes proposed to the package insert.

Clinical Assay Review
The SOP and validation report for the PRNT were not submitted to the supplement and were requested via an information request. The SOP and validation report weresubmitted in Amendment 2. Since the sponsor transferred the assay from (b) (4) , re-validation was performed to show there was no effect on results. Changes due to (b) (4) and these were mentioned in the revalidation report. The information submitted in Amendment 2 was reviewed and found to be acceptable.

b) Pediatrics
The results of the PREA postmarketing requirement (PMR) pediatric study, IC51-325, were presented at the Pediatric Review Committee (PeRC) on March 14, 2018. The PeRC concurred with the review committee`s recommendation that the available data from this study satisfied the PMR (issued during approval of STN 125280/19) for assessing the safety and immunogenicity of a booster dose in a pediatric population (≥ 2 months to 17 years) in an area where JEV is endemic.

c) Special Populations
N/A

d) BiMo (Bioresearch Monitoring Review)
The BLA review committee proposed bioresearch monitoring (BiMo) inspections at two of the three clinical investigator study sites conducting the Phase 3 study IC51-325; all three study sites are located within the Philippines. Subsequently, the Office of Regulatory Affairs Office of Bioresearch Monitoring Operations informed CBER of a U.S. State Department travel warning involving the Philippines, citing safety issues due to terrorist activity. Considering the fact that two of the three study sites were previously BiMo-inspected for a related supplement (STN 125280/125) with no inspectional issues identified, the BLA clinical review team decided no BiMo inspections would be conducted for protocol IC51-325 while the Philippines travel warning conditions remained in effect. Therefore no BiMo inspections were conducted for this application.

7. SAFETY

IC51-325
The safety population for analyses consisted of all subjects randomized to the treatment groups. Daily temperatures and solicited AEs were recorded seven days post booster dose vaccination. Solicited AEs included injection site reactions (pain, itching, tenderness, hardening, swelling and redness), as well as systemic symptoms (irritability, nausea, vomiting, diarrhea, flu-like symptoms, excessive fatigue, muscle pain, rash, headache, loss of appetite and fever). Unsolicited AEs were collected during a 1-hour observation period following study vaccination and at clinic follow-up visits.

The overall reactogenicity profile of the booster dose was milder when compared to data presented in study IC51-323, which supported licensure of the primary series. Eleven out of twelve episodes for the reported fevers were Grade 1, and no febrile seizures were reported. Furthermore, the rates of solicited and unsolicited AEs were nominally reduced from those in the primary series, and no new safety signals were seen. No safety issues were identified. There were no deaths reported in the study. None of the reported Serious Adverse Events (SAEs) were related to administration of IXIARO.

IC51-324
The safety population included all participants in the study (identical to the ITT population). Safety data collection was performed at interval follow up visits given the absence of new investigational product administration. Eight subjects reported AEs (35 total) throughout the study period, none of which were considered related to the study vaccine by the investigator. Furthermore, no deaths were reported, and the two non-fatal SAEs reported were found to be unrelated to the IXIARO vaccine.

Study IC51-322
Safety analysis in study IC51-322 indicated that very few SAEs and medically attended AEs were reported. Review of these events indicated that none of these were likely related to IXIARO. The analysis further indicated that the local and systemic reactogenicity was mild, and rates of solicited adverse reactions were similar to those reported in the interim analysis, and considerably less frequent than those observed in study IC51-323. The final analysis included 37 more solicited or unsolicited AEs and two additional SAEs (Type 1 diabetes mellitus with complications, and self-harm behavior). None of these were judged to be related to the study vaccine.

Overall, no safety issues were identified from all the three studies submitted that would affect the approval of this supplement.

8. ADVISORY COMMITTEE MEETING

CBER did not present these data to an Advisory Committee because the review of information submitted in this submission did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

None.

10. LABELING

The APLB reviewer found the prescribing information to be acceptable from a promotional and comprehension perspective. The PI submitted to the supplement included the following major changes:

A. Highlights and Section 2 – Inclusion of the following language regarding use of a booster dose: “A booster dose (third dose) may be given at least 11 months after completion of the primary immunization series if ongoing exposure or re-exposure to JEV is expected.”
B. Section 2 – Dosing instructions added regarding use of a pediatric booster dose.

C. Section 6 – Safety data included in the final CSR for IC51-322 was updated. Safety data derived from study IC51-325 was added.
D. Section 8 – Updated to comply with the PLLR. The sponsor accepted the recommended revisions to this section provided by the toxicology and clinical reviewers by. Available clinical data was noted to be insufficient to establish the presence or absence of drug associated risk during pregnancy, and therefore no human data is included in the label.
E. Section 14 – Immunogenicity data from IC51-325 was added in a Table combining Table 6 and Table 9 of this review. Immunogenicity data from IC51-324 was added in textual format.

Revised changes to the PI were agreed upon after labeling negotiations with the sponsor. The PI that was submitted via Amendment 10 on April 3, 2018, was found to be acceptable.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

a) Recommended Regulatory Action

It is the consensus of the review committee to recommend approval of this efficacy supplement to include the recommendation of a booster dose of IXIARO in the pediatric population in the PI and the proposed change to update the PI with immunogenicity and safety data from long-term pediatric studies IC51-324 and IC51-325.

b) Risk Benefit Assessment

The data submitted in this efficacy supplement support the clinical benefit of an IXIARO booster dose at 11 months or longer after completion of the primary series (based on serostatus) in infants, children and adolescents (14 months to < 17 years of age) who may be at continued risk of JEV exposure. The clinical benefit is clearly demonstrated, as 100% of subjects in study IC51-325 had a JEV neutralizing antibody titer of ≥ 1:10 at one month through two years after the booster dose.

An increase in $PRNT_{50}$ GMTs from pre-booster values was observed after the administration of the booster dose, and the increased titers were maintained for up to two years after the booster dose, suggesting the enhanced durability of the antibody responses elicited by the administration of a booster dose. The risk profile associated with a JEV booster dose was favorable compared to the age associated safety profile seen with primary immunization.

IXIARO is the only licensed vaccine currently available in the U.S. for the prevention of Japanese encephalitis, and there is no available therapy for JEV disease. The risks of JEV disease are significant enough to necessitate the option for a booster dose if the risk of continued exposure to JEV exists.

c) Recommendation for Postmarketing Risk Management Activities

No safety issues were identified during the review of this supplement. Therefore, no Risk Evaluation and Mitigation Strategy (REMS) or new postmarketing study is required.

d) Recommendation for Postmarketing Activities

Based on the information contained in this application, no changes to the submitted pharmacovigilance plan for IXIARO are recommended.

e) Pharmacovigilance Plan

Since no pharmacovigilance plan (PVP) was submitted to this efficacy supplement, in an information request dated August 02, 2017, CBER requested that Valneva submit a revised PVP, if applicable. On September 4, 2017, Valneva responded via Amendment 1 that the current version of the risk management plan which was submitted to the original BLA on January 26, 2015, included a risk assessment of the data from the pediatric study IC51-325. Since the safety data from the booster study showed a favorable adverse event profile, Valneva did not find it neccesary to revise the PVP. CBER concurred with this justification.

Cross-referenced applications:

- IND 8589: Japanese Encephalitis Virus (SA14-14-2; Vero cells), Formalin Inactivated, Purified Vaccine with Alum

- BLA 125280/0: License to manufacture Japanese Encephalitis Virus, Vaccine, Inactivated, Adsorbed, for the prevention of disease caused by Japanese encephalitis Virus in persons 17 years of age and older.

- MF (b) (4) MASTER FILE TYPE III - (b) (4)

- MF (b) (4): MASTER FILE TYPE II - (b) (4)