



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852-1448

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MARCH 16, 2009

MEMORANDUM

TO: Lewis Markoff, MD, Division of Vaccines and Related Products Applications (DVRPA), Office of Vaccines Research and Review (OVR), Chair, BLA 125280 Committee

FROM: Manette Niu, MD, Vaccine Safety Branch (VSB), Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE)

APPROVED
By Manette Niu at 10:26 am, Mar 18, 2009

THROUGH: Andrea Sutherland, MD, MPH, Acting Chief VSB, DE, OBE
Robert Wise, MD, MPH, Acting Director, DE, OBE

APPROVED
By Andrea Sutherland, MD, MSc, MPH at 10:29 am, Mar 18, 2009

DATE: March 16, 2009

APPROVED
By Robert P. Wise at 10:28 am, Mar 19, 2009

SUBJECT: Pharmacovigilance review,
BLA Submission, 125280 Intercell

Reference: STN: BL 125280

Sponsor: Intercell

This memorandum is to provide you with a summary of my reviews regarding postmarketing commitments for Intercell's Biologics License Application (BLA) for the Japanese encephalitis vaccine (IXIARO®).

(A) The Sponsor's proposal regarding the postmarketing safety evaluation of IXIARO® was outlined in Intercell's submission of a Pharmacovigilance Plan (PVP) to the BLA as of June 6, 2008 (Amendment #5). The pharmacovigilance plan (PVP) includes three studies: 1) Phase IV, prospective, descriptive cohort study to assess the safety of IXIARO® with enhanced surveillance of the first 10,000 subjects being vaccinated within the military. Military personnel vaccinated with IXIARO® will be surveyed by checking the presence/absence of ICD-9 codes for predefined Adverse Events Following Immunization (AEFI) in the electronic health records starting at the day of vaccination and lasting until 30 days after the second IXIARO® vaccination (administered at Day 28). The frequency of these reports will be calculated (rate per number of administered doses). AEFI will be considered severe, if at least 2 outpatient visits or

a hospitalization occur within seven days after the primary AE report date; case report for severe AEFI will be generated as for the cases in Tier 1. Temporal association will be calculated and grouped into onset of AEFI within seven days or after seven days after the first or second vaccination. Monthly summary reports will be generated for these events; 2) Intercell will maintain a pregnancy registry and will follow-up each spontaneously reported pregnancy case via a pregnancy questionnaire (data on pregnancy courses and delivered child's health). Newborns will be followed-up through the third month of life; 3) A retrospective cohort study based on data in the Defense Medical Surveillance System (DMSS) database, in order to compare AEFI rates with two control groups: subjects who have received JE-VAX®, and subjects will serve as their own control (prior to vaccination and after vaccination).

On August 14, 2008, CBER responded to the Sponsor's Amendment #5 requesting the Sponsor to provide a detailed statistical analysis plan, and justification for the sample size of 10,000 subjects, since in general, we would like to see at least a 20,000 subject postmarketing general safety study. The study will need sufficient power to detect a doubling or tripling of serious, rare events. Additionally we requested the Sponsor to specify the predefined AEFI and explain why those endpoints were chosen, and to include an exploratory component to the cohort analyses which would identify all AE FI (i.e., not only predetermined AEFI) more common after IXIARO®. Additional comments included a request for safety data in elderly individuals, consideration of extending the risk window for follow up of AEFI of 42 days, the rationale for classifying hypotension and circulatory collapse as not expected to be serious AEFI, and a copy of the neurologic and pregnancy questionnaires. CBER also requested the Sponsor to provide a plan in which the DMSS database is monitored for pregnancies in female service members who receive JEV vaccine. In the event that the female service member receives JEV vaccine during pregnancy or the pregnancy begins ≤ 3 months after last dose of JEV, please have these individuals followed-up with the pregnancy questionnaire, and their newborns followed up through the third month of the life. The Sponsor was asked to comment if subjects who will serve as their own control in the retrospective cohort study will be adjusted by age and gender.

(B) Responses to comments regarding the post-marketing safety evaluation and PVP were submitted to the BLA as of September 8, 2008 (Amendment #9). The Complete Response Letter, issued by CBER on September 26, 2008, acknowledged that the Sponsor included a PVP in the BLA. However, the September 8, 2008 response to CBER's August 14, 2008 information request (for a detailed statistical analysis plan including a justification for the Sponsor's proposed post-marketing sample size of 10,000 subjects) is inadequate, and as currently designed, will not be sufficient to address the goal of gaining additional knowledge regarding the general safety of this vaccine in the U.S. population. The Sponsor was asked to re-submit a revised observational postmarketing study plan to include 20,000 vaccinated U.S. subjects.

(C) On October 1, 2008 the Sponsor submitted response to the Complete Response Letter and updated version of the postmarketing safety evaluation plan (Amendment #12). Based on the positive response from the Sponsor to the comments outlined above, CBER accepted the revised post-marketing commitments on January 29, 2009: 1) a large-scale enhanced surveillance post-licensure safety study conducted within the U.S. military, conducted in the Defense Medical Surveillance System (DMSS) database in 20,000 vaccinated subjects to gain further knowledge of the safety of the vaccine. The primary objective of this study is to assess the safety of IXIARO® in the military population (a population with rapid vaccine uptake). This post-licensure study is

designed to detect rates of adverse events after IXIARO®. ICD-9 codes from the health records of vaccinated subjects in the risk window of 42 days after vaccination will be retrieved. The total adverse event rate in subjects who received IXIARO® will be compared with that of a comparable cohort of subjects (in terms of other vaccinations and age) not having received IXIARO®. Details of the study protocol will be determined in consultation with CBER; 2) Surveillance study of spontaneously reported pregnancy cases with follow-up of the newborn through the third month of life in the DMSS database will be completed. Additionally, active surveillance for pregnancy cases will be done through checking electronic health records of women who receive IXIARO® during the active surveillance of the 20,000 service members. Medical events which occur during pregnancy and birth as well as health data reported for the newborn up to the completed third month of age will be reviewed; 3) A retrospective cohort study in the DMSS database. Adverse event rates in subjects that have been vaccinated with IXIARO® will be compared with two control groups, one consisting of subjects who have received JE-VAX® instead of IXIARO® along with otherwise unchanged vaccination schedules; in the other study, subjects will serve as their own control by comparing adverse event rates during a defined baseline observational period before and after vaccination. Details of the study protocol will be determined in consultation with CBER; 4) a multi-center, single arm, open-label exploratory phase 3 study including 200 elderly subjects aged 65 years and above.

(D) On October 24, 2008, the Sponsor submitted a waiver to submit postmarketing safety updates in ICH format and in 6-month intervals (Amendment #16), to which OBE responded: 1) It is acceptable for Intercell to submit Periodic Safety Update Reports (PSUR) for IXIARO according to the ICH E2C (R1) guideline format as long as the contents of the report is the same as Periodic Adverse Experience Reports (PAER) specified by regulation [21 CFR 600.80(c)(2)(ii)]; 2) Intercell may submit the PSUR to the FDA based on the international birthdates of IXIARO, as long as the first PSUR is submitted within 3 months of U.S. licensure (approval). Intercell should submit the PSUR, in accordance with the regulations specified in 21 CFR 600.80(c)(2), at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals.

(E) On January 12, 2009, the Sponsor submitted a synopsis of the proposed postmarketing study in elderly population (Amendment #22) as a multi-center, single arm, open-label exploratory phase 3 study including 200 elderly subjects aged 65 years and above. On January 29, 2009, CBER/OBE requested that the Sponsor provide rationale for limiting time to serious adverse events and medically attended adverse events during the vaccination period until Day 56 after the first vaccination, and to consider using a risk window of 42 days after the last dose of vaccine, consider calculating the rate of subjects with unsolicited adverse events up to Month 6 after the last vaccination, consider following subjects with abnormal safety laboratory parameters (hematology, serum chemistry, urinalysis) up to Day 42 after the last vaccination, submit a clinical study report including safety data at Month 6 after the last vaccination, and consider a scripted phone call soliciting any adverse events occurring 42 days after the last vaccination.

The revised post-marketing studies include their agreement of an action plan to implement safety surveillance activities, including a large U.S. postmarketing study to address general safety concerns in 20,000 military subjects, a pregnancy and newborn outcome follow-up study, a retrospective cohort study in the DMSS database comparing subjects vaccinated with IXIARO® with two control groups (one consisting of subjects who have received JE-VAX® instead of IXIARO® along with otherwise unchanged vaccination schedules), a self-control study, in which subjects will

serve as their own control by comparing adverse event rates during a defined baseline observational period before and after vaccination, and a multi-center, single arm, open-label exploratory phase 3 study including 200 elderly subjects aged 65 years. CBER has negotiated specific timelines for finalization of study protocols, date first subject enrolled, date clinical study report, and completion and submission of final reports with the manufacturer.