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Vaccines, Blood & Biologics

Ixiaro - Summary Basis for Regulatory Action

Summary Basis for Regulatory Action

Date	March 30, 2009
From	Lewis Markoff, M.D.
Subject	Summary Basis for Regulatory Action
BLA #	125280/0
Supplement#	
Applicant	Intercell
Date of Submission	December, 2007
PDUFA Goal Date	October 17, 2008; revised to April 3, 2009, after CR letter issued on September 24, 2008.
Proprietary Name / Established (USAN) names	IXIARO ®/Japanese encephalitis vaccine, inactivated
Dosage forms	0.5 ml in syringe
Proposed Indication(s)	Prevention of disease caused by Japanese encephalitis virus
Recommended Action:	<i>Approval</i>
Signatory Authority(ies) Action	<i>Offices Signatory Authority:</i> <i>I concur with the summary review</i> ☐ <i>I concur with the summary review and include a separate review or addendum to add further analysis</i> ☐ <i>I do not concur with the summary review and include a separate review or addendum</i>

Material Reviewed/ Consulted List of specific documentation used in compiling SBRA

Clinical Review	Jeff Roberts, M.D., review dated March 27, 2009; Rose Tiernan, M.D.
Statistical Review	Mridul Chowdhury, Ph.D., dated August 25, 2008
Reproductive Toxicology Review	Marion Gruber, Ph.D., dated July 24, 2008, etc.
CMC Review	Li Yu, M.D., Ph.D., dated October 10, 2008; updated February 10, 2009; March 26, 2009
Cell Substrate	

Barry Falgout, Ph.D., dated February 11, 2009

EIR/Facilities/Inspection

Destry Sillivan, Li Yu: (483 submitted May 15, 2008; facilities review dated February 13, 2009; 483 response review memo dated March 26, 2009; EIR finalized March 26, 2009)

Joyce Rockwell: 483 response review memo dated October 20, 2008

Bioresearch Monitoring Review Anthony Hawkins, dated August 27, 2008

Bioassay Reviews Bill McCormick; March 17, 2009

PI/PPI J Roberts, R Tiernan, L Markoff: January 27, 2009

Container/Carton Jean Makie; dated January 8, 2009; March 4, 2009.

Daphne Stewart: January 18, 2008; February 26, 2009

Proprietary Name Review Jean Makie, dated January 5, 2009

Manette Niu, dated March 15, 2009

Pharmacovigilance Plan/PMC Bill McCormick, Joseph Quander III: Finalized, December 12, 2008; Approved, February 26, 2009; Submitted to BLA, March 27, 2009

Post-Licensure Lot Release

Introduction

IXIARO ®, Japanese encephalitis vaccine, inactivated, *adsorbed*, is indicated for the prevention of disease caused by Japanese encephalitis virus in persons 17 years of age and older. The vaccine is administered as a two-dose series, with 28 days between doses. The vaccine consists of purified and formalin-inactivated Japanese encephalitis (JE) virus strain SA14-14-2 that was grown in cultured monkey kidney cells (Vero cells). After protamine sulfate extraction, sucrose gradient purification, and formalin-inactivation, one dose of the final product consists of 6 mcg of JE proteins adjuvanted with -(b)(4)- aluminum hydroxide (-----(b)(4)----). The vaccine is presented in pre-filled syringes containing a single dose of 0.5 ml liquid volume. It is administered by the intramuscular route, in the deltoid. SA14-14-2 is an attenuated JE virus strain that is used as a live vaccine in many Asian countries.

Background

Provided by Dr. Lewis Markoff

The Biologics License Application (BLA) for inactivated Japanese encephalitis virus vaccine (IXIARO ®) was received by CBER in December, 2007, from the sponsor, Intercell.

Data in the BLA are based on clinical studies done under IND -(b)(4)-, which was first submitted in September, 1999. Development of IXIARO (internally known as "IC51") was initiated based on a perceived need for an inactivated JE vaccine to replace a then existing licensed product, JE-VAX. JE-VAX was a formalin-inactivated JE vaccine marketed by Biken in Japan and manufactured by formalin inactivation of JE virus strain Nakayama grown in mouse brains. The efficacy of JE-VAX had been formally demonstrated in a large-scale study conducted by the US Army in Kamphet Phong province in Thailand, in 1988 (CH Hoke et al. 1988. Protection against Japanese encephalitis by inactivated vaccines. NEJM **319**:608-614). A similar inactivated JE vaccine had been developed in Japan in 1954 and was extensively used to reduce dramatically the incidence of JE in Japan and Taiwan and elsewhere. JE-VAX was licensed in the US in 1992 by Biken. Its use was associated with a fairly high incidence of allergic and hypersensitivity reactions, presumably owing to its residual content of mouse serum and mouse brain proteins and/or to gelatin added to stabilize the product. Its withdrawal from the market had been announced by Biken a year or more before the BLA for IXIARO was submitted. In safety and efficacy trials, IXIARO was shown to be non-inferior to JE-VAX in all aspects.

In addition to the inactivated JE vaccines that have long been in use in JE endemic areas (e.g., Japan, China, Taiwan, Thailand), a live JE vaccine also exists. This vaccine was derived about two decades ago in China by serial passage of a virulent strain of JE virus (strain SA14) in hamsters and then in primary hamster kidney cells (published data from China, 1973). This process ultimately resulted in the live, attenuated JE vaccine strain SA14-14-2. Many millions of doses of strain SA14-14-2 have been administered to children and adults primarily in China since the early 1990s. Large scale studies were done in China demonstrating over 90% efficacy after a single dose of vaccine. A formal short-term safety study involving more than 26,000 children who were randomized to receive either placebo or vaccine was published in 1997 in the Journal of Infectious Diseases. Results confirmed the safety of the vaccine as regards its ability to cause meningitis or encephalitis during a 30-day period post-vaccination. No cases were reported. Since 2007, the SA14-14-2 vaccine is also in widespread use in India; over 10 million doses were administered during the initial phase of a campaign to immunize at-risk children. The SA14-14-2 vaccine virus was acquired from China by scientists at Walter Reed Army Institute for Research (WRAIR) in 1986. It was passaged eight times in Primary Dog Kidney cells (PDK) (Eckels et al. Vaccine. 1988;**6**:513-588) -----

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------(b)(4)-----

----- In the course of the review of IND -(b)(4)-, which is the precursor to this BLA, it became apparent to the review panel that the country of origin of the serum supplied by -(b)(4)- could not be documented, although all available information suggested that this product had been sourced from the US. It was the final opinion of the review team that this discrepancy posed an infinitesimally small theoretical risk, because of the subsequent passage history of the seed virus in certified sera and cell lines, and because it did not in any way pertain to the -(b)(4)--

-(b)(4)-. The issue was thus successfully resolved. (See also the Cell Substrate summary herein and the complete Cell Substrate review by Dr. Barry Falgout.)

Two major issues regarding JE vaccine development were dealt with by the international community of vaccine developers and regulators during the last approximately ten years, starting with a WHO-sponsored meeting held in Thailand in 1998. The first issue was the question of antigenic variation among JE virus strains or isolates. Studies in mice and in vitro cross-neutralization assays both suggest that antigenic variation could be an issue for JE vaccine development; mice immunized with one strain of JE virus are not necessarily fully protected from challenge by a distantly related strain, and cross-neutralization assays reveal that the titer of neutralizing antibodies against a homologous JE virus may be much higher than titers against distantly related strains. Further, nucleotide sequencing of JE virus genomes has revealed that there are at least 3 distinct genotypes of the virus. However, there are several reasons for rejecting the hypothesis that there is more than one serotype of JEV. For example, there are no data to show neutralization escape among naturally occurring isolates. In addition, epidemiologic data from countries that have conducted routine childhood immunization against JE for several decades, using inactivated vaccines derived from JE strain Nakayama virus (which was first isolated in 1933) show no drop off in vaccine efficacy against modern strains that are genotypically different from strain Nakayama. Thus the international consensus of opinion is that there is only one serotype of JE. Nevertheless, this issue was said to merit "further investigation". Relevant data were summarized in a special issue of the journal *Vaccine* (Vol 18; supp 2; 26 May 2000).

The second issue considered by the WHO committee was the question of a surrogate of efficacy for JE vaccines. A surrogate of efficacy was essential for the development of novel modern JE vaccines, such as IXIARO, because (i) it would be unethical to conduct a classical pivotal efficacy trial in endemic areas, given the availability of existing effective vaccines, and (ii) given the effectiveness of current immunization programs in JEV endemic areas, FDA estimated that a field trial to prove 80% efficacy of a novel JE vaccine with 95% CI would require >250,000 subjects (P. Lachenbruch, *unpublished data*). There is an overwhelming plethora of data from human and animal studies done over the last 50 years to suggest that in vitro neutralizing antibody titers correlate with protection against JE (see L Markoff. 2000.*Vaccine***18**:26-32). During that time frame, methods for assessing the presence of neutralizing antibodies in sera have changed. Early studies were done in mice challenged by the intracranial route, so that protection depended upon the neutralization of all infectious particles in a challenge inoculum. Modern techniques measure the ability of serially diluted serum samples to reduce the number of plaques of JE virus formed in a tissue culture cell monolayer, as compared to controls. In this assay, a constant pre-determined number of plaque forming units of virus is pre-incubated with serum that has been heat-inactivated, prior to infecting cells in tissue culture. (This is known as a plaque-reduction neutralization assay [PRNT].) The issues debated by participants in the WHO meetings on JE vaccine efficacy were (i) what titer of antibodies is protective in humans and (ii) exactly how the PRNT should be performed. The WHO committee ultimately decided that a 50% reduction in plaque count induced by a 1:10 or greater dilution of the test serum was indicative of protection. In addition, the WHO laid down methodologies for the conduct of the assay. These methods and the definition of seroconversion have been adopted by the sponsor in evaluating the efficacy of IXIARO. FDA informally accepted the principles laid down by WHO during review of IND

-(b)(4)- and this BLA. Thus, no field trial to prove vaccine efficacy was done. Instead, efficacy was established by a head-to-head immunogenicity study comparing IXIARO to JE-VAX.

3. Chemistry Manufacturing and Controls (CMC)

CMC Summary provided by Dr. Li Yu

In the manufacture of IXIARO, Japanese Encephalitis virus (JEV) strain SA14-14-2 is produced on Vero cells in the presence of -----(b)(4)-----, purified by ultrafiltration and sucrose gradient centrifugation, inactivated with -(b)(4)- formalin, and formulated with aluminum hydroxide -(b)(4)- in Phosphate Buffered Saline (PBS). IXIARO is provided in pre-filled syringes containing ~ 6 µg of JEV protein in 0.5 ml of PBS solution as a single dose.

The sponsor presented data ensuring that virus master seeds and virus working seeds used in the production of the vaccine are sterile. The sponsor also presented results showing that the -----(b)(4)----- throughout the process is consistently higher than -----(b)(4)----- content in commercial bulks is -----(b)(4)----- . These values are all well within the range of acceptable limits. The vaccine manufacturing process is robust, and the titers of virus prior to inactivation are highly consistent. The sponsor has agreed to perform in-process testing at different stages of production to ensure that the product meets specifications and is consistent. Testing for Lot Release of final containers (inactivated JE virus) includes: -----(b)(4)-----, identity, sterility, potency, -----(b)(4)----- pyrogenicity. The sponsor completed studies prior to licensure demonstrating the stability of the inactivated vaccine for 18 months at the recommended storage condition of 5°C ± 3°C.

During the BLA review process, a Complete Response (CR) letter was issued on September 26, 2008, due to the failure of the sponsor to reply adequately to several deficiencies cited during inspection of the manufacturing facility (see also the section on Inspection), a deficiency of the pharmacovigilance plan (see Pharmacovigilance section), and a deficiency of the proposed lot release protocol. Specifically, the lot release protocol lacked an Identity Test, which is required under 21CFR 610.14. The sponsor responded to the latter element of the CR letter in the form of amendments to the IND submitted on October 1, 2008, and subsequently, in which they proposed to introduce an -----(b)(4)----- Identity Test. Data were submitted in support of validation of the -(b)(4)- and to demonstrate the -----(b)(4)----- in the final product. These data were reviewed by CBER and found to be acceptable. Further, the sponsor is now using the -----(b)(4)----- . Lot release specifications for the Identity Test have been defined. Other issues addressed toward the end of the review period, via direct interaction between the CBER review team and the sponsors, included

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Based on the above statements, I recommend approval of the product.

4. CELL SUBSTRATE/ADVENTITIOUS AGENT TESTING

The parental JE virus was a human virulent virus, strain SA14, isolated in China in the early 1970s. It was amplified in mosquitoes and then repeatedly passaged in mouse brain. After one passage in *Culex pipiens* larvae, it was passaged 100 times in primary hamster kidney cells (PHK) and plaque-purified a total of five times in primary chick embryo (PCE) cells. It was then passaged intraperitoneally in mice, after which virus in spleen was used to infect PCE cells, and three more plaque purifications were done. This was followed by another mouse passage and further cultivation in PCE. The virus was then passaged six times in hamsters, and virus in hamster spleen was used to infect PHK cells, then suckling mice, then PHK cells again. (At several of these junctures between animal and tissue culture passage, the virus was re-assessed for its neurovirulence.) The final non-neurovirulent isolate is referred to as strain SA14-14-2. The entire process occurred during the 1970s in China, using locally sourced materials. Therefore, there is deemed to be no possibility of contamination with TSE agents related to the subsequent outbreak in the UK.

- (b)(4)- could not provide documentation of the source of the serum that was supplied to
- (b)(4)- for cultivation of the vaccine seed virus, although it had been their policy to
source such materials from within the US. Because the chance for TSE contamination of
the MVS is infinitesimal, occurred at an early stage of development prior to the serial
passages in Vero cells, and did not in any way involve derivation and use of the MCB or
the subsequent WCB, CBER decided that no further action was necessary.

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5. FACILITIES REVIEW/INSPECTION

IXIARO bulk drug substance is manufactured at Intercell's Livingston, Scotland UK facility and filled under contract at -----(b)(4)----- at their -----(b)(4)----- facility. Overall manufacturing facilities and their respective roles are listed below:

- Role: manufacture of bulk drug substance.

- -----(b)(4)-----

----- (b)(4) -----

3. -----(b)(4)-----

----- (b)(4) -----

CBER conducted pre-approval inspections of the Livingston, Scotland facility from May 8, 2008 through May 15, 2008. This was the first FDA inspection of this facility. During this inspection, Intercell was cited for nineteen FDA 483 items related to facility, manufacturing, product, and quality issues. Briefly, 483 observations covered the following:

- failure to properly validate in-process testing assays
- failure to establish manufacturing step time limits
- failure to incubate all media used in a media fill,
- failure to execute three successful cleaning validation runs for product contact equipment
- failure to document equipment cleaning
- implementation of a manufacturing process and/or testing without supportive data
- failure to follow Quality Unit and manufacturing SOPs
- utilization of improper environmental monitoring practices
- deficient stability sampling procedures
- failure to conduct container closure studies for the bulk drug substance containers under extremes of pressure
- failure to evaluate potential leachables and extractables from a product contact material
- failure to store temperature sensitive materials in a manner that would assure correct temperature maintenance
- failure to assure that Quality Unit released materials remain segregated from materials not yet so released
- failure to properly qualify a facility utility
- Allowance of a potential breach in integrity of the bulk drug product fill line downstream of the sterile filter

The responses to the FDA 483 items were received, reviewed, and found to be acceptable.

There are no ongoing or pending investigations or compliance actions with respect to the above facilities or their products. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this submission.

The facilities reviewer (Destry Sullivan) considers this submission approvable on the basis of the facilities information provided.

6. CBER LOT RELEASE

Due to the lack of a production and testing track record in the U.S., CBER will require Lot Release of this vaccine. Review of results from tests performed by the manufacturer at various stages of manufacture of the product (submitted in the protocols) and confirmatory testing of Final Container vaccine is the mode of CBER regulation of this vaccine.

7. ENVIRONMENTAL ASSESSMENT

Submitted by Dr. Destry Sillivan.

The sponsor has requested categorical exclusion from performance of an environmental assessment under both 21 CFR 25.31 (a) and 21 CFR 25.31 (c). Intercell claims that 21 CFR 25.31 (a) is relevant because the only JEV vaccine currently licensed by FDA in the U.S., JE-VAX®, also containing formalin-inactivated JEV, is no longer being manufactured and supplies are anticipated to be depleted in the private market by mid 2009. Thus, the introduction of the sponsor's JEV vaccine to the U.S. commercial market will replace, but not increase, the use of the active moiety. The sponsor will not be granted categorical exclusion under 21 CFR 25.31 (a) because certain safety issues associated with use of JE-VAX® are not considered; JEV vaccine does not have the same safety issues associated with its use. Increased safety may lead to significantly increased sales of the sponsor's JEV vaccine, thereby likely increasing its use.

The sponsor also claims categorical exclusion under 21 CFR 25.31 (c) because it is formalin inactivated and therefore carries minimal risk of introducing or significantly altering the concentration of infectious JEV in the environment. Furthermore, the quantity of formalin-inactivated virus per vaccine dose (6 µg) is low and generally will be administered within the U.S. to laboratory workers, military personnel and civilian travelers to endemic areas and therefore will not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment

8. Pharmacology/Toxicology

Submitted by Dr. Marion Gruber.

Intercell has performed one developmental toxicity study to evaluate the reproductive and developmental toxicity potential of IC51 (Japanese Encephalitis vaccine, JE-PIV). Two groups of female rats -----(b)(4)-----, 48 animals/group, were dosed either 3 and 1 weeks prior to mating and again on day 6 of gestation (vaccine I) or were dosed one week prior to mating and again on day 6 of gestation (vaccine II). Doses (4.9 µg test article in 0.5 ml) were administered by IM injection into the lateral compartment of the thigh muscle, control animals received vehicle accordingly. Animals were subdivided into subgroups of 24 rats per group, and either underwent Caesarean sectioning on gestation day 20 or were allowed to rear their offspring.

There were no overt signs of treatment related maternal toxicity. Treatment did not affect body weights and body weight gains of the F0 generation neither did it affect body weight gain of the F1 generation born to treated dams. The Japanese encephalitis vaccine, IC-51, did not affect F0 female fertility, mating performance, embryo-fetal development and postnatal development. There were no observed treatment related effect on the incidence of major and minor abnormalities and skeletal variants in the offspring of dams treated with the test article. Of note, in the group of dams that received two (2) injections of IC-51 1 week prior to mating and then again on GD6 (vaccine II), there were delays in *in utero* ossification in some regions (in particular in pelvis and skull) in some of the fetuses when compared to concurrent control group values. Notably, this delay in *in utero* ossification in the pelvis and skull region was not observed in the group treated with three (3) injections of vaccines (vaccine I). There were no other parameters that would have suggested a potential *in utero* growth delay. Pup weights at birth were comparable between groups. There appeared to be no vaccine related effect on *in utero* survival of fetuses and there was no incidence of teratogenicity. Also, postnatal growth and development did not appear to be affected by vaccine

administration. Together, the observed higher incidences of incomplete ossification of fetuses in vaccine II does not appear to be a vaccine related event.

9. Clinical

Submitted by Drs. Jeff Roberts and Rose Tiernan.

Executive Summary

This Biologics License Application (BLA) contains immunogenicity and safety data provided by Intercell AG to support approval of IXIARO for the proposed indication of active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV) in persons 17 years of age and older. IXIARO is produced in Vero cell culture using the attenuated JEV strain, SA14-14-2. It is formalin-inactivated, aluminum-adsorbed, and packaged in a pre-filled syringe containing 6µg of the inactivated vaccine in a volume of 0.5ml. The recommended vaccination regimen is one dose intramuscularly on Day 0 and Day 28.

JEV is the most common cause of viral encephalitis in Asia, with ~50,000 cases reported annually. Infection is frequently subclinical; only 1 in 250-500 infected individuals manifest clinical disease. However, symptomatic disease results in ~ 25% death rate, and 30%-40% of survivors are left with serious neurological sequelae. No effective treatment exists; intervention consists of supportive measures. ACIP recommends vaccination against JEV for certain travelers at risk for infection during visits to endemic regions. Production of the only currently available U.S.-licensed JE vaccine, JE-VAX, has been discontinued. IXIARO is therefore expected to fill an anticipated need for immunization against JEV among U.S. military personnel and civilians traveling to JE-endemic areas.

The Biologics Licensing Application (BLA) contains one Phase I, one Phase II, and six Phase III trials. The basis for licensure rests primarily on the data from the pivotal Phase III efficacy trial (IC51-301) and from the pivotal Phase III safety trial (IC51-302). Supportive studies include a vaccine co-administration study (IC51-308), a rapid immunogenicity study (IC51-304), and two lot consistency studies (IC51-309 and IC51-310). In-depth reviews of the pivotal trials and summaries of the supportive studies can be found in the complete clinical review.

Immunogenicity

Two randomized, double blinded, placebo-controlled field trials established efficacy of formalin-inactivated, parenterally administered JEV vaccine preparations in the prevention of invasive disease caused by JEV (Hoke et al), (Hsu et al). Because safe and effective vaccines against JE are now widely available, a placebo-controlled field trial of true efficacy of a JE vaccine in development would be considered unethical. Data from the original efficacy trials and subsequent preclinical studies have established that serum neutralizing antibody against JEV is a reliable surrogate for efficacy. Broad consensus has developed around the use of Plaque Reduction Neutralization Tests (PRNT) to evaluate the efficacy of JE vaccines in development. WHO recognizes a PRNT titer of $\geq 1:10$ as being a reasonable correlate threshold for protection (Hombach et al).

The pivotal Phase III efficacy trial, IC51-301, was designed to demonstrate efficacy by meeting a predefined statistical standard for non-inferiority compared to JE-VAX. In this trial, 858 subjects were randomized in equal proportions to receive either: two injections

of IXIARO (6 mcg in 0.5 mL) intramuscularly (i.m.) on days 0 and 28 and one 0.5 mL injection with phosphate-buffered saline containing 0.1% aluminum hydroxide (PBS + Al(OH) 3) on day 7, or three injections of JE-VAX (1.0 mL dose) subcutaneously (s.c.) on days 0, 7 and 28. A final evaluation took place four weeks after last vaccination on day 56 or in the event of early termination. The primary endpoints were seroconversion rate (SCR), defined as PRNT titer of $\geq 1:10$, and geometric mean titers (GMT).

A CBER statistical analysis found that the results supported the non-inferiority of IXIARO vaccine to JE-VAX with regard to both co-primary endpoints. The SCRs ($\pm$ SE) in IXIARO and JE-VAX were respectively 96.4% ($\pm 1.0\%$) and 93.8% ($\pm 1.3\%$), with measures of $\log_{10}\text{GMTs} \pm \text{SD}$ in respective arms being found as 2.39 ± 0.50 and 2.01 ± 0.51 .

Long term immunogenicity and booster immunization studies were incomplete at the time the BLA was filed.

Safety

IC51-302 – Pivotal Phase III Safety Trial

The safety of IXIARO was evaluated primarily in study IC51-302, a randomized, controlled, double blind clinical trial in healthy male and female subjects. The primary objective was to investigate the safety and tolerability of IXIARO during a vaccination period of 28 days until 4 weeks after the last vaccination compared with a control (PBS + Al(OH) 3). A total of 2,675 subjects were randomized in a 3:1 ratio to receive either an intramuscular injection of IXIARO (0.5 ml) each on Day 0 and Day 28, or an intramuscular injection of PBS + Al(OH) 3 (0.5 mL) each on Day 0 and Day 28.

Analysis of safety was carried out using the safety population including 1,992 subjects receiving IXIARO and 657 subjects receiving PBS + Al(OH) 3. The IXIARO and control groups were similar with regard to demographics. Adverse events were recorded on a diary card by the subject for the first seven days after each vaccination. Adverse events were also solicited by study investigators, who took a medical history and performed a physical exam on the day of each vaccination and at a visit 4 weeks after the second vaccination.

Treatment Emergent Adverse Events (TEAE)

In the safety population over the total study period, the percentage of subjects who experienced a TEAE was 58.9% and 56.6% in the IXIARO and control groups, respectively. TEAEs that required medical attention occurred in 12.7% of subjects in the IXIARO group and 12.2% of subjects in the control group. A comparison of the temporal relationship between treatment and occurrence of TEAE's revealed virtually no difference between the IXIARO and control groups. In both groups, the probability of remaining TEAE-free went from about 90% at 1 hour post vaccination to 75% at 1 day to 50% at 1 month.

Serious Adverse Events (SAE)

Sixteen SAE s were reported during the study period. Ten subjects receiving IXIARO (0.5%) and 6 subjects receiving PBS + Al(OH) 3 (0.9%) experienced an SAE. No deaths were reported during this study. The serious adverse reactions occurring in the IXIARO group are as follows: dermatomyositis, appendicitis, rectal hemorrhage, limb abscess

(contralateral to the injected arm), chest pain, ovarian torsion, ruptured corpus luteal cyst, and three orthopedic injuries.

Injection Site Reactions

Injection site reactions, including pain, tenderness, redness, hardening, swelling and itching, were recorded into a subject diary for the first seven days after each injection, and the injection site was assessed by the investigator at each visit. Overall, X% of subjects in the IXIARO group and X% in the PBS + Al(OH) 3 group experienced at least one injection site symptom. In the subset of reactions reported as "severe", the percentage of subjects in the IXIARO group and the PBS + Al(OH) 3 group is as follows: post vaccination 1: 0.4% in IXIARO group versus 0.4% in PBS + Al(OH) 3 group; post vaccination 2: 0.6% in IXIARO group versus 0.8% in PBS + Al(OH) 3 group.

Safety Across Trials – Pooled Safety Data

In five clinical studies, a total of 3,558 adults aged 18 to 86 years received at least one dose of IXIARO (92% completed the 2 dose series) and were followed-up for safety for at least 6 months after the first dose. Approximately 1% of subjects experienced a serious adverse event, and approximately 1% discontinued due to adverse reactions. One death occurred in a 70 year old female who was diagnosed with metastatic lung adenocarcinoma 6 weeks after receiving the second dose of vaccine.

Clinical Data to Support Manufacturing Consistency

Studies IC51-309 and IC51-310 were conducted to examine immunogenicity in 3 different study and commercial batches, respectively. In study IC51-309, the three study lots failed to meet criteria for equivalence, whereas in study IC51-310, the commercial lots met those criteria. CBER statisticians reviewed both studies in detail and concurred with the immunogenicity conclusions. Because the manufacturing process underwent several technical changes between the production of the study lots and the commercial lots, CBER places primary emphasis on the clinical data from the commercial lots, which were studied in IC51-310 and met criteria for equivalence.

Co-Administration with HAVRIX

IXIARO is expected to be given to patients who will be receiving other vaccines concomitantly before traveling. The sponsor conducted a study to investigate co-administration of IXIARO with a Hepatitis A vaccine, HAVRIX (Study IC51-308). By predefined statistical standards, co-administration met non-inferiority criteria versus individual administration of each vaccine. In addition, there was no evidence of compromised safety with co-administration.

Pediatrics

Intercell was granted a deferral of pediatric studies because studies in adults are sufficient to consider the license application for adults. Therefore, no data in subjects <18 years of age were submitted in support of licensure. CBER defines a pediatric population as age 0-16, and the data from subjects ≥18 years of age is considered applicable to 17 year olds. Therefore, the studies in the license application support the indication for use in adults ≥17 years of age. To meet the requirements of the Pediatric Research Equity Act of 2003, Intercell has agreed to a post-marketing plan that includes

studies in ~1500 subjects from 12 months through 16 years of age. InterCell was granted a waiver as regards studies in children less than 12 months old.

Conclusion

InterCell has submitted data in support of licensure of IXIARO that were adequate to assess efficacy and safety. IXIARO met a predefined standard correlate for efficacy compared to the U.S.-licensed JEV vaccine, JE-VAX. IXIARO appears to be safe and well-tolerated, both systemically and locally at the injection site. InterCell has committed to a post-marketing pharmacovigilance plan that includes a study in military personnel powered to detect a doubling or tripling of rare, serious events.

Recommendation

IXIARO should be approved active immunization for the prevention of disease caused by JEV in persons 17 years of age and older.

References

Hoke CH, Nisalak A, Sangawhipa N, Jatanasen S, Laorakapongse T, Innis BL, Kotchasene S, Gingrich JB, Latendresse J, Fukai K, et al. Protection against Japanese encephalitis by inactivated vaccines. N Engl J Med. 1988 Sep 8;319(10):608-14.

Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004.

Hsu TC, Chow LP, Wei HY, Chen CL, Hsu ST. A controlled field trial for an evaluation of effectiveness of mouse-brain Japanese encephalitis vaccine. Taiwan Yi Xue Hui Za Zhi. 1971 Feb 28;70(2):55-62.

10. BIOASSAY REVIEW

Submitted by Dr. Alfred Del Grosso through Dr. William McCormick.

The following analytical procedures and validation studies were reviewed:

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In general, procedural descriptions and validation information were found to be adequate with no critical errors or omissions. Regarding the above item 2), the determination of -- (b)(4) ----- in drug substance by the ----- (b)(4) ----- procedure, we suggested that the this test should be replaced by the ----- (b)(4) ----- Assay (a more sensitive assay) as a post-marketing commitment, to be included as part of the action letter for this submission. The limit of quantification of the ----- (b)(4) ----- procedure is close to the expected concentration in the drug substance, making it

suboptimal for this application. The sponsor had already acknowledged this fact and their plans to introduce the ---(b)(4)---- assay. We recommended that the -(b)(4)- assay should be submitted as a post-license BLA supplement within three months of the product licensure. The sponsor agreed to take this action.

11. BIOSTATISTICAL REVIEW

Submitted by Dr. Mridul Chowdhury.

This was a multi-center (with 11 centers in the US and Europe), phase-3, observer blinded, controlled study to compare the safety and immunogenicity of IC51 vaccine with JE-VAX vaccine" for Japanese Encephalitis in healthy subjects. The seroconversion rate (SCR) and geometric mean titer (GMT) at Day 56 were the two co-primary endpoints for pivotal efficacy evaluation. The evaluation initially planned 858 subjects with a random allocation of 1:1 to both arms, and was conducted using non-inferiority tests (Study Protocol IC51-301). The results supported the non-inferiority of IC51 vaccine to JE-VAX with regard to both co-primary endpoints. The SCRs (95% confidence interval) in IC51 and JE-VAX were respectively 96.4% (94.0%, 98.1%) and 93.8% (90.8%, 96.0%), with measures of log 10GMTs±SD in respective arms being found as 2.39±0.50 and 2.01±0.51.

Three manufacturing batches of IC51 were evaluated for clinical consistency in terms of GMTs. With the observed GMTs of 160.7, 272.2, and 127.6 in the three individual batches, the GMT ratio in only one pair of batches excluded both a ½-fold decrease and a 2-fold increase, the bounds that were pre-specified for batch consistency evaluation. This condition was not satisfied for the other two pairs of batches, and the three batches could not be considered to be clinically consistent although each batch's seroconversion rate was as high as 96.5% or more (IC51-309). In a set of three new batches, however, the consistency criterion was satisfied (IC51-310).

In terms of safety, the IC51 had a comparable general safety profile with JE-VAX (IC51-301) and with placebo as well (IC51-302).

12. BIORESEARCH MONITORING REVIEW

Submitted by Anthony Hawkins.

Eight clinical investigator inspections were performed in support of this Biologics LicenseApplication (BLA). Study subject population, geographic distribution, and field resource considerations were among the factors used to select the inspected sites. Information from the BLA was compared to source documents, during the inspections.

CLINICAL INVESTIGATORS

Inspection

	Site #	#Subjects	483?	Classification
Radiant Research Austin , Texas	1402	187	Yes	VAI
Radiant Research Cincinnati , Ohio	1408	173	No	NAI

Radiant 1418 180 No NAI
 Research
 Scottsdale ,
 Arizona

STUDY TITLE:

Observer Blinded, Randomized Phase 3 Study to Investigate the Non-Inferiority of IC51 (JE-PIV) vs. JE-VAX® as Vaccines for Japanese Encephalitis in Healthy Subjects

(Study code IC51-301)

Inspection

	Site #	#Subjects	483?	Classification
Radiant Research West Palm Beach , Florida	2405	80	Yes	VAI
Radiant Research St. Louis , Missouri	2407	138	Yes	VAI
Radiant Research Greer , South Carolina	2412	102	No	EIR pending
Radiant Research Santa Rosa , California	2413	58	Yes	VAI
Radiant Research Lakewood , Washington	2414	62	Yes	VAI

STUDY TITLE:

Safety and Tolerability of the Japanese Encephalitis Vaccine IC51 (JE-PIV). Double Blind, Randomized, Placebo Controlled Phase 3 Study

(Study code IC51-302)

SPONSOR ISSUES

No sponsor or monitoring issues were noted.

NOTEWORTHY INSPECTIONAL FINDINGS

There were only a few minor problems noted. Post vaccination discharge time was not adequately documented (30 subjects - Site 1408). Six subjects left the study site before the minimum 60 minutes post vaccination timeframe, or the subjects' time of departure could not be determined (Site 2414). A phlebotomist administered injections of the study drug or placebo to 11 subjects and she performed study visit procedures and completed case report form entries for 10 subjects; another staff member administered injections of study drug or placebo to eight subjects and she also determined inclusion/ exclusion

criteria and entered case report form entries for two subjects. The clinical investigator did not authorize either of the individuals to perform those responsibilities (Site 2407). Six subjects' electronic case report form entries did not match the information contained within the corresponding source documents including SAE causality and severity criteria, urinalysis test results, concomitant vaccination date, and vital signs (Site 2413).

BIMO ADMINISTRATIVE FOLLOW-UP

We issued inspection closeout letters to sites 1402, 1408, 1418, 2405, 2407, 2413 and 2414. Correspondence was issued to site 2412 after review of the establishment inspection report and final inspection classification were completed.

13. Labeling

Submitted by Dr. Jean Makie .

- The sponsor's proprietary name, IXIARO, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective and was found to be initially acceptable on September 26, 2007, and subsequently on re-evaluations completed on September 4, 2008 and January 5, 2009. OVRP concurred.
- Full Prescribing Information (FPI), Patient Package Information (PPI), and Carton and immediate container labels: APLB reviewed the proposed FPI, PPI, and carton and immediate container labels submitted by the sponsor. Comments from a promotional and comprehension perspective were provided to OVRP in Review Memorandums dated February 13 and May 30, 2008, and January 8, 2009. OVRP held multiple internal meetings to discuss labeling issues raised by committee members. Subsequent labeling discussions were held with the sponsor. All labeling issues have been adequately resolved to proceed with final approved labeling.

14. Pharmacovigilance plan

Submitted by Dr. Manette Niu .

Intercell have committed to:

1. A large-scale enhanced surveillance post-licensure safety study to be conducted within the U.S. military 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 . A time window(s) following vaccination with IXIARO ® will be considered the "risk period." All 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 ®. This study will be conducted in the Defense Medical Surveillance System (DMSS) database. Details of the study protocol will be determined in consultation with CBER.

- Surveillance of spontaneously reported pregnancy cases will be followed up via a pregnancy questionnaire and follow-up of the newborn will be completed through

the third month of life. 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. This study in will be conducted in the DMSS database.

3. A n open-label, Phase 3B study of IXIARO in the elderly addressed in 200 subjects at least 65 years of age in an observational post-licensure safety study. Subjects will be followed for up to 6 months post vaccination. Blood samples for immunologic assessment will also be collected. The draft protocol concept sheet was submitted to CBER to the IXIARO BLA on January 13, 2009. The final study protocol will be determined in consultation with CBER.

4. 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.

RECOMMENDATION: Approval