PUBLIC ASSESSMENT REPORT
FOR
IMOJEV MD

Common Name: Japanese Encephalitis Vaccine (recombinant)

Application No. 1 A 90001/53(NBC)

Assessment Report as adopted by the TFDA with
all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant **GPO-MBP** submitted on 8 December 2010 an application for Marketing Authorization to the Thailand Food and Drug Administration (TFDA). At the time of submission and validation, IMOJEV MD was designated as medicinal product in the following indication: For prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in adults 18 years of age and over.

The legal basis for this application refers to: Drug Act 2510 B.E.

The application submitted was a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Scientific Advice / Protocol Assistance:

IMOJEV MD comprises a freeze-dried powder and a 0.9 % Sterile Sodium Chloride (NaCl) diluent for reconstitution in 4-dose presentation.

The Drug substance of IMOJEV MD is manufactured at Sanofi Pasteur Biologics Co. (former Acambis Inc) facilities in Canton, United State of America, the Drug Product is manufactured at the Government Pharamceutical Organiztion – Merieux Biological Product Company Limited (GPO-MBP) in Thailand.

IMOJEV MD is also referred to in the application ad ChimeriVa-JE or JE-CV. IMOJEV MD corresponds to the multidose presentation of IMOJEV and same product, same formulation and same diluent as THAIJEV. IMOJEV, THAIJEV and IMOJEV use the same Drug Substance, Non Clinical data and Clinical data. In addition, IMOJEV MD and THAIJEV use the same Drug Product.

The applicant received Scientific Advice in May and October 2010 (External Experts) and Protocol Assistance in October 2010 (Clinical External Experts) from the TFDA. The Scientific Advice in 2010 pertained to Quality, Non-clinical and Clinical Aspects of the dossier and the Protocol Assistance in 2010 pertained to clinical aspects of the Phase IV Clinical Study.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

TFDA Product Team Leader: (PTL)

Quality:	Mrs. Tasanee	Lorchaivej
Non-clinical:	Mr. Pramote	Akarapanon
Clinical:	Ms. Prapassorn	Thanaphollert

The Co Product Team Leader (Co- PTL)

Quality:	Mr. Morakot	Prapatsiripan
Non-clinical:	Mr. Kritsada	Limpananon
Clinical:	Ms. Jaruwan	Toron

1.2 Steps taken for the assessment of the product

- The application was received by the TFDA on 8 December 2010.
- A List of questions, the overall conclusion and review of the scientific data were prepared by the TFDA and sent to the applicant on 5 Jan 2011
- The applicant submitted of the responses on 1 Apr 2011
- TFDA revised the Assessment Report based on responses from the applicant and dispatched the assessment report to external experts for their consideration and comments on May 2011, Jan 2012
- Final draft of English SPC, labeling and package leaflet was sent by applicant to the TFDA PTL on Dec 2011
- TFDA adopted the decision on marketing authorization on 10 Apr 2012

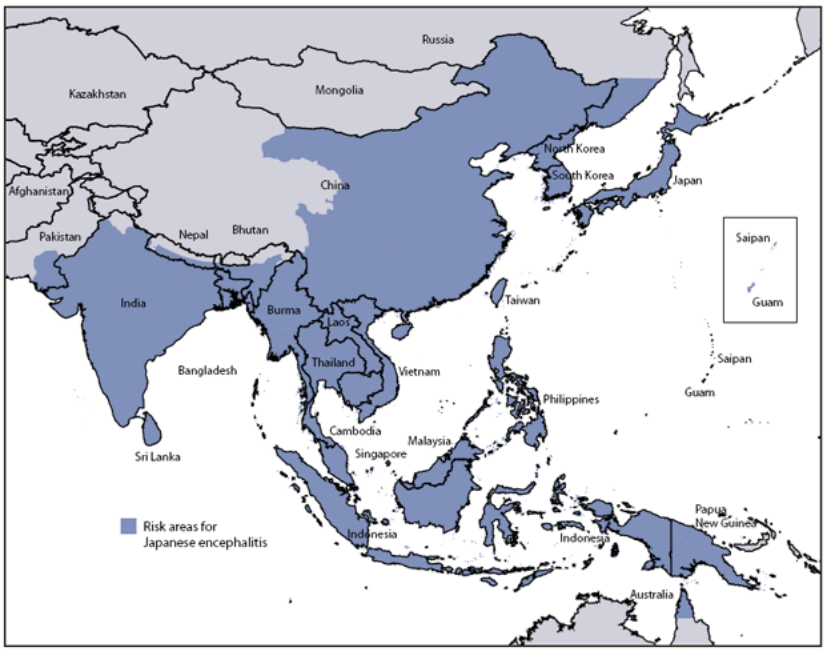
2. SCIENTIFIC DISCUSSION

2.1 Introduction

Japanese encephalitis (JE) is a mosquito-borne arboviral infection and the leading cause of viral encephalitis worldwide with an estimate of at least 50,000 cases of clinical disease per year. Children less than 10 years of age are primarily affected. Japanese encephalitis (JE) is the most common cause of viral encephalitis in the Asia Pacific region. The virus exists in a transmission cycle between mosquitoes and pigs and/or water birds such as herons and egrets, which are the main host reservoir. JE is therefore a mosquito-borne zoonotic viral infection, the reservoirs of which are water birds and in which pigs play the role of amplifying host in rural areas. JEV is transmitted to humans through the bite of infected mosquitoes. Humans usually do not develop a level or duration of viremia sufficient to infect mosquitoes. Therefore, humans are dead-end hosts, and human JE cases imported into nonendemic areas represent a minimal risk for subsequent transmission of the virus. Direct person-to-person spread of JEV does not occur except rarely through intrauterine transmission. On the basis of experience with similar flaviviruses, blood transfusion and organ transplantation also are considered potential modes of JEV transmission.

JE used to be mostly prevalent in countries with a temperate climate, including Japan, but data from tropical countries (Thailand, Cambodia, Indonesia) (See Picture 1) show that these zones also are favorable for JE transmission. Indeed, JE can now be found from the extreme south-eastern part of Russia to the North of Australia and Papua New Guinea, and from Japan to the west of India.

Picture 1 Approximate geographic range of Japanese encephalitis



Clinical Signs and Symptoms

The majority of human infections with JEV are asymptomatic; <1% of people infected with JEV develop clinical disease. Acute encephalitis is the most commonly identified clinical syndrome with JEV infection. Milder forms of disease (e.g., aseptic meningitis or undifferentiated febrile illness) also can occur but have been reported more commonly among adults.

Among patients who develop clinical symptoms, the incubation period is 5-15 days. Illness usually begins with acute onset of fever, headache, and vomiting. Mental status changes, focal neurologic deficits, generalized weakness, and movement disorders might occur over the next few days. Seizures are common, especially among children. The classical description of JE includes a parkinsonian syndrome with mask-like faces, tremor, cogwheel rigidity, and choreoathetoid movements. Out of the approximately annual 50,000 cases of JE more than 10,000 end fatally, and about 15,000 survivors are left with neurological and/or psychiatric sequelae requiring rehabilitation and continued care. Acute flaccid paralysis, with clinical and pathological features similar to poliomyelitis, also has been associated with JEV infection. Status epilepticus, brain hypoxia, increased intracranial pressure, brainstem herniation, and aspiration pneumonia are the most common complications associated with poor outcome and death.

The overall risk of JE for travellers to endemic areas is considered rather low and was calculated to be about 1:5,000 to 1:20,000 per week. However, the risk may significantly increase when travelling in rural destinations and during the season of enhanced transmission (mostly May to September). The CDC reviewed cases of JE among expatriates and travellers that occurred during 1978–1992. From a total of 24 cases outcome information was available for 15 patients, of whom 6 died, 5 were listed as disabled, and 4 recovered. Only 2 of these 24 patients were tourists; the other

patients were doing research or medical relief work or were soldiers. Further cases of JE were reported from tourists visiting Bali, Indonesia or Thailand.

The immune response to JEV infection has not been fully characterized, and both humoral and cellular responses may play a role. However, it is widely accepted that virus neutralizing antibodies provide the best evidence that protective immunity against JEV has been established. A linear titre-protection relationship has been demonstrated and data from efficacy studies in humans and animals corroborate the role of neutralizing antibodies in protection. Monoclonal antibodies to epitopes on the envelopeglycoprotein both neutralize JEV in vitro and protect mice from lethal challenge. Murine studies have also demonstrated that protection can be mediated through either adoptive transfer of T-lymphocytes or passive administration of antisera from mice infected with JEV. Historically, passive transfer of human post-infection sera to at-risk subjects was protective and correlated with detectable neutralizing antibodies in recipients.

JE Vaccines

The control of JE is based essentially on three interventions: mosquito control, avoiding human exposure to mosquitoes and immunization. Mosquito control has been very difficult to achieve in rural settings and avoidance of exposure is difficult as Culex mosquitoes bite during daytime. Immunization is the only effective method for sustainable control. Routine immunization of school-age children is currently in use in Korea, Japan, China, Thailand and Taiwan. There is currently no medication treatment available for JE and thus pre-exposure protection against the disease is essential. The introduction of the JE vaccine into the Expanded Program of Immunization has helped curb the disease in countries like Thailand, Vietnam, Sri Lanka and China

The vaccines for JE are divided to 3 types of vaccines.

1. Inactivated Vaccine, among the currently available vaccines is a formalin-inactivated vaccine derived from mouse brain-grown JEV strain Nakayama, which still is produced by manufacturers in Korea, Thailand and Vietnam. The vaccine is relatively expensive, requires three doses on days 0, 7 and 30, followed by a booster at 1 year and thereafter at intervals of 3 years. The vaccine can often generate neurological adverse reactions. In addition to local and systemic side effects, individual cases of generalized urticaria and angioedema were reported in about 1 case per 1000 vaccinees after vaccination of travelers from western countries.

2. The live attenuated JE vaccine strain, SA14-14-2, which was obtained after 11 passages in weaning mice followed by 100 passages in primary hamster kidney cells, has been developed and used in China since 1988. The vaccine, which is produced by the Chengdu Institute of Biological Products in China, was licensed in recent years in several Asian countries and was extensively used from 2006 to 2008 in mass immunization campaigns in India. Although the product is not WHO prequalified at this time, much investment and efforts have been made to bring the production and quality control to international standards. The vaccine is produced on primary hamster kidney cells, lyophilized, and administered to children at one year of age and again at two years, in annual spring campaigns. Initial observational studies in southern China involving more than 200 000 children had demonstrated the vaccine safety, immunogenicity (99-100% seroconversion rate in nonimmune subjects) and protective efficacy over 5 years. The short-term effectiveness of a single dose of SA14-2-

14 was demonstrated in 2001 in a case control study on Nepalese children where an efficacy of 99.3% was reported. A five year follow-up study found the single-dose efficacy was maintained at 96.2%. Another five-year follow up study showed that neutralizing antibody persistence was close to 90% at 4 years and 64% at 5 years after a single-dose of the vaccine in adult volunteers. Recent studies in the Philippines have demonstrated the safety and efficacy of the vaccine even when co-administered with measles vaccine at 9 months of age. Similar studies in Sri Lanka and Indonesia will help confirm these findings in other Asian settings.

3. Chimeric vaccines, A promising approach for a future JE vaccine has been the construction of a YF-JE chimera based on the attenuated 17D YF virus genome, in which the YFV sequences encoding viral structural proteins prM and E were replaced by the corresponding prM and E sequences from JEV strain SA14-2-14.

IMOJEV MD is indicated for prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in subjects from 12 months of age and over. The vaccination schedule consists of a single 0.5 mL dose of the vaccine administered by the subcutaneous route.

2.2 Quality aspects

Introduction

IMOJEV MD™, the Japanese Encephalitis Chimeric Virus vaccine, (also referred to in this application as Chimeric Vax™ - JE or JE-CV) is a monovalent, live attenuated viral vaccine, which belongs to the pharmacotherapeutic group of encephalitis vaccines (J07BA). It contains between 4.0 and 5.8 log plaque forming units (PFU) of live, attenuated, recombinant JE virus per dose (0.5 mL). This PFU is used to assess the potency of JE-CV.

The virus was obtained via recombinant DNA technology and is based on two well-characterised live attenuated vaccine viruses, the yellow fever (YF) 17D vaccine virus and the JE SA14-14-2 vaccine virus. The YF 17D virus provides the replication engine while the pre-membrane (prM) and envelope (E) proteins are from the SA14-14-2 JE virus. The E protein is the antigen responsible for induction of neutralising antibodies, while the M protein is needed to ensure to the correct conformation of E. The vaccine virus was constructed by inserting RNA encoding the prM and E structural proteins of the JE SA14-14-2 virus into the genome of YF 17D virus.

JE-CV virus is propagated in Vero cells grown in serum-free conditions using a seed lot system. It is purified and then formulated in a stabilizer constituted of lactose, mannitol, histidine, glutamic acid, human serum albumin and salts. The JE-CV formulation is then freeze-dried.

The virus was obtained via recombinant DNA technology and is based on two well-characterized live attenuated vaccine viruses, the yellow fever (YF) 17D vaccine virus and the JE SA14-14-2 vaccine virus.

JE-CV virus is propagated in Vero cells grown in serum-free conditions. It is purified and then formulated in a stabilizer constituted of lactose, mannitol, histidine, glutamic acid, human serum albumin and salts. The JE-CV liquid formulation is then freeze-dried.

The vaccine comprises a freeze-dried powder and 0.9% NaCl diluents for reconstitution in multidose (4-dose) presentation.

Active Substance

After reconstitution, one dose (0.5 mL) contains:

Live, attenuated, recombinant Japanese encephalitis virus: 4.0 - 5.8 log PFU*

* Plaque Forming Unit

Manufacturers

The manufacturing steps and testing of the JE-CV vaccine are performed in the following site under Good Manufacturing Practice (GMP) as shown in table 1.

Table 1: Manufacturing sites and Operations

Manufacturing Facility	Operations
Sanofi Pasteur Biologics Co.*, 38 Sidney St, Cambridge, MA 01581 USA	Manufacture of Pre-Master Seed (PMS)
Sanofi Pasteur Biologics Co., 50-90Shawmut Rd, Canton, MA 02021 USA	Manufacture of Master Seed Lot (MSL), Working Seed Lot (WSL) and Drug Substance (DS)
BioReliance Corporation** 14920 Broschart Rd Rockville, MD 20850 USA	- Quality Control (QC) testing
Government Pharmaceutical Organization-Merieux Biological Product Company Limited (GPO-MBP) 241 Moo 7, Gateway City Industrial Estate, Tambon Huasamrong, Amphoe Plaengyao, Chachoengsao 24190, Thailand.	- Manufacture of the Drug Product, - Manufacturing of 0.4 sodium chloride diluent solution - Quality Control (QC) testing - Batch release
Cogenic (formerly Lark, A Clinical Data Company) 9441West Houston Parkway South Suite 103 Houston, TX 77099 USA	Quality Control (QC) testing
Wuxi AppTec, Inc.	Quality Control (QC) testing

4751 League Island Blvd. Philadelphia, PA 19112 USA	
Sierra Biomedical Charles River Laboratories, Inc. (CRL) Discovery and Development Services (DDC) Sierra Division (Sierra) 587 Dunn Circle, Sparks, NV 89431 USA	Quality Control (QC) testing

*Please note that Acambis Inc., is part of Sanofi Pasteur since September 2008, nevertheless this document may refer to Acambis as development of product and validation lots were manufactured before September 2008.

** Please note that some documentation may refer to Q-One Biotect, which is now part of BioReliance Corporation.

The TFDA recommended on The Quality Dossiers as the followings:

With regard to Manufacturing, Quality control and Viral safety issues the following should be raised with the company and satisfactory responses should be receive before approval is given for the registration of IMOJEV MD vaccine.

Drug product

1. There are no stability data of the commercial batch.
2. In the summary Production Protocol, the quality control data of the concentrate bulk which produced from Sonofi Pasteur is not complete.
3. The Human albumin content in every batch of the final product

The company responded to the above recommendations as the followings:

1. The company committed to provide the stability of the Drug product (commenrcial batch). This is satisfactory

2. In the summary Production Protocol, the quality control data of the concentrate bulk which produced from Sonofi Pasteur is updated. This is satisfactory

3. The Human albumin content in every batch of the final product is indicated in the Summary Production Protocol. This is satisfactory

4. The company showed the stability data (shelf life 24 months at 5+/- 3 C) of Drug product (validated batch) and commercial batch and the stability data (shelf life 24 months at 5+/- 3 C) of the diluents (0.9 % NaCl). This is satisfactory

TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSIONS ON QUALITY ASPECTS

The vaccine is manufactured in accordance with standard GMP, WHO Guidelines, Ph. Eur. Monograph for live attenuated viral vaccine and experience gained during pharmaceutical and clinical development. The reference standards for release specification of the drug product are WHO TRS no. 932, 2006: Guidelines for the production and quality control of candidate tetravelent dengue virus

vaccines (live), WHO TRS no. 910, 2002: Guidelines for the production and control of Japanese encephalitis vaccine (live) for human use and Ph. Eur. monograph 0520 and Ph. Eur. monograph 0153.

The company should perform the test, submit more data and fulfill their commitments according to the recommendation above and monitoring documents regarding Pharmacovigilance plan before approval is given for the registration of IMOJEV MD vaccine.

Proposals for Pre-authorization Testing

Samples for testing the proposed vaccine are not required at time of submission of the application. However the TFDA requests the applicants to submit samples of vaccine and/or its constituents of their vaccines for testing at the Division of Biological, Department of Medical Sciences as early as possible in order to obtain test results in due course.

Overall conclusions

IMOJEV MD is referred to in the application ad ChimeriVa-JE or JE-CV. IMOJEV MD corresponds to the multidose presentation of IMOJEV and same product, same formulation and same diluent as THAIJEV. The TFDA and external experts have reviewed quality, safety, toxicology and clinical studies data and found them evidently supportive; therefore positive opinion was given toward the approval of marketing authorization of IMOJEV MD with one condition requesting the applicant to conduct a clinical phase IV study as under Safety Monitoring Program (SMP) for a period of two years.

The applicant submitted a synopsis of clinical phase IV study on 10,000 subjects and gave commitment to report the progress of the study to TFDA. Final study report should be submitted for further consideration after completion of the study. The applicant also committed to perform the safety monitoring program as part of the pharmacovigilance plan.