

**BASIC DESIGN STUDY REPORT
ON
THE PROJECT FOR CONSTRUCTION OF
THE MEASLES VACCINE PRODUCTION FACILITIES
IN
THE SOCIALIST REPUBLIC OF VIET NAM**

JANUARY 2003

JAPAN INTERNATIONAL COOPERATION AGENCY

**THE CONSORTIUM OF
NIHON SEKKEI, INC. AND JGC CORPORATION**

PREFACE

In response to a request from the Government of the Socialist Republic of Viet Nam, the Government of Japan decided to conduct a basic design study on the Project for Construction of the Measles Vaccine Production Facilities and entrusted the study to the Japan International Cooperation Agency (JICA).

JICA sent to Viet Nam a study team from March 12th to April 5th, 2002 and from May 22nd to June 2nd, 2002.

The team held discussions with the officials concerned of the Government of Viet Nam, and conducted a field study at the study area. After the team returned to Japan, further studies were made. Then, a mission was sent to Viet Nam in order to discuss a draft basic design, and as this result, the present report was finalized.

I hope that this report will contribute to the promotion of the project and to the enhancement of friendly relations between our two countries.

I wish to express my sincere appreciation to the officials concerned of the Government of the Socialist Republic of Viet Nam for their close cooperation extended to the teams.

January 2003

Takao Kawakami
President
Japan International Cooperation Agency

January 2003

Letter of Transmittal

We are pleased to submit to you the basic design study report on the Project for Construction of the Measles Vaccine Production Facilities in the Socialist Republic of Viet Nam.

This study was conducted by the Consortium of Nihon Sekkei, Inc. and JGC Corporation, under a contract to JICA, during the period from March, 2002 to January, 2003. In conducting the study, we have examined the feasibility and rationale of the project with due consideration to the present situation of Viet Nam and formulated the most appropriate basic design for the project under Japan's grant aid scheme.

Finally, we hope that this report will contribute to further promotion of the project.

Very truly yours,

Tomonao Hamada
Project Manager

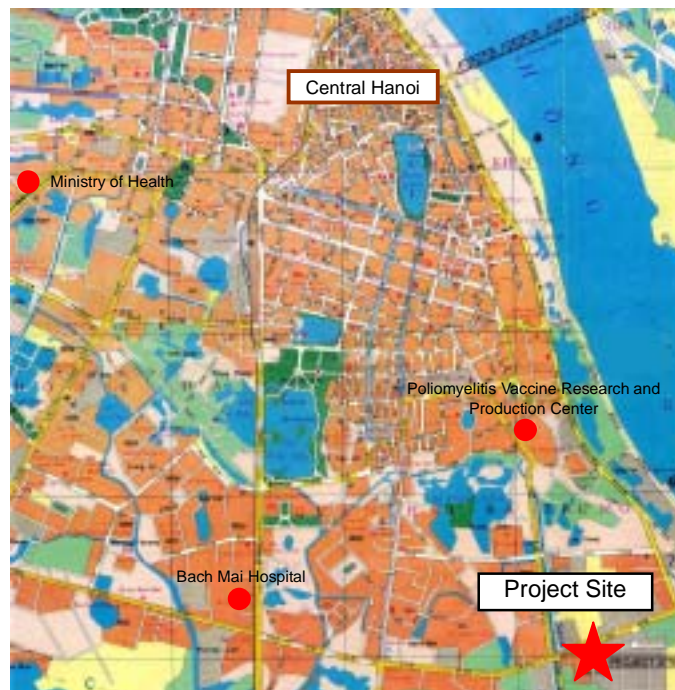
Basic design study team on
the Project for Construction of the Measles Vaccine Production Facilities

The Consortium of Nihon Sekkei, Inc. and JGC Corporation

Location of Project



Map of the Socialist Republic of Viet Nam



Map of Hanoi and Location of Site



Perspective

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ABBREVIATIONS

AVR	Automatic Voltage Regulator
BS	British Standard
CENCOBI	National Center for Control of Medico-Biological Products
EPI	Expanded Program on Immunization
GMP	Good Manufacturing Practices
HEC	Hanoi Environment Company
HEPA	High Efficiency Particulate Air filter
HPC	Hanoi Power Company
HPO	Hanoi Post Office
HWBC	Hanoi Water Business Company
IVAC	National Institute of Vaccines and Biological Substances
JASS	Japanese Architectural Standard Specification
MDF	Main Distribution Frame
MOH	Ministry of Health
NIHE	National Institute of Hygiene and Epidemyology
NRA	National Regulatory Authority
POLIOVAC	Poliomyelitis Vaccine Research and Production Center
WHO/WPRO	World Health Organization / Western Pacific Regional Office

Summary

The Socialist Republic of Viet Nam (hereinafter called Viet Nam) lies along the eastern seaboard of the Indochina Peninsula, from 9 degrees north to 23 degrees north in latitude and from 102 degrees east to 110 degrees east in longitude. The population is approximately 78,770,000 (2000) and the land area is 331,689 km², about 90% the size of Japan. The capital Hanoi, where the Project site is located, has a population of 2.1 million and lies in the Hong River Basin in Northern Viet Nam. Hanoi belongs to the temperate monsoon climate zone. The average temperature is 28 to 30 in summer (from June to September) and is 15 to 20 in winter (December to March). The highest temperature in summer climbs above 35, but the lowest temperature in winter drops below 10. The average annual humidity is above 70% and is particularly oppressive during the summer. Annual precipitation is only 600 mm, which is not very high, but is concentrated in June and July.

The Gross National Product (GNP) of Viet Nam is US\$28,156 million (1999) and the per capita GNP is US\$370. The country was divided into north and south for a long period, but was re-united in April 1975. During the 6th Party Congress held in December 1986, the “Doi Moi” or “renovation” policy was adopted with the intention of moving from a war based economy to an open socialist market economy. The “Doi Moi” policy gradually overcame its initial inconsistencies and the benefits of a market economy began to take effect from 1992 with economic growth achieving 8.0% in 1994. Good rice harvests and active introduction of foreign investment had a positive impact on economic recovery. However, a slowdown in economic growth became apparent in 1997 and combined with the effects of the Asian economic crisis, foreign direct investments declined sharply and exports were forced to face increased competition with neighboring countries, causing economic growth to drop to 4.8% in 1999. Subsequently, economic growth has shown signs that it has entered a period of recovery, with growth of 6.7% in 2000 and 6.8% in 2001, due to growth of exports. However, a drop in international prices for main agricultural produce and an underdeveloped investment environment are continuing factors of concern.

The Government of Viet Nam, in its summary of the accomplishments in the field of health and medical care over the past 10 years, emphasizes the importance of public health care policies and preventive medicine. In the “Strategy for Public Health Care and Protection in the Period 2001-2010”, high priority is placed on the reduction of the infant mortality rate (under 1), the under-5 mortality rate and the suppression of outbreaks of infectious diseases. Under this policy, the Government of Viet Nam has developed an Expanded Program on Immunization (EPI) as one of its measures in the health care and medical field. The EPI plans to maintain the high immunization coverage and also to proceed with domestic procurement of EPI vaccines (poliomyelitis, measles, diphtheria, pertussis, tetanus and tuberculosis). At present, all EPI vaccines except measles vaccine are produced domestically. Especially, polio vaccine has been developed since the 1960’s by Poliomyelitis Vaccine Research and Production Center

(POLIOVAC), with mass production becoming possible during the 1990's and all domestic needs for polio vaccine are now procured locally. According to the Western Pacific Regional Office of the World Health Organization (WHO/WPRO), the eradication of polio has been largely achieved in the Western Pacific Region which includes Viet Nam. The present required production of polio vaccine in Viet Nam has declined to a third of its peak of 30 million doses. Based on these achievements in the past, POLIOVAC has been designated as the executing agency for the Project.

Young children are particularly susceptible to measles and it ranks as one of the leading causes of childhood mortality. Measles can trigger malnutrition and lowered resistance to infection for several months after infection. Measles has a comparatively higher communicability than other child diseases preventable by immunization (diphtheria, pertussis, poliomyelitis, neonatal tetanus, pulmonary tuberculosis, et cetera). Viet Nam began preventive policies against measles with the introduction of immunization with measles vaccine in 1981 (The measles suppression program), which was expanded to cover the whole nation in 1985. Due to the immunization program, the reported cases of measles declined from approximately 82,000 in 1985 to approximately 6,000 cases ten years later in 1995. However, in spite of the high immunization coverage maintained since 1990, morbidity began to rise after 1997, with approximately 19,000 cases reported in 2000. This is believed to be due to the fact that the measles suppression program in Viet Nam has relied on one-dose routine schedule for infants.

Measles vaccine has relatively low heat stability and deficiencies in the cold chain system can be the cause of reduction in the potency of the vaccine. This can be result in non-seroconversion after vaccination (Primary Vaccine Failure, PVF). Furthermore, immunity to measles can weaken over a period of time and infection with measles can occur several years after immunization, even when seroconversion originally occurred (Secondary Vaccine Failure, SVF). In recent years, the rise of PVF and SVF has become problematical. The Government of Viet Nam has striven to reduce the incidence of measles cases by conducting nation-wide mass measles immunization campaigns targeting children (9 month olds to under 10 year-olds) along with the phased introduction of two-dose routine immunization schedule for measles vaccine recommended by WHO/WPRO. Due to this development, the need for measles vaccine will double, but vaccines producers in developed countries are turning to production of vaccines with higher added value. There is rising concern about the stable supply of measles vaccine among countries like Viet Nam that depend on imported measles vaccine.

WHO/WPRO from a strategical viewpoint, considers that Viet Nam has high potential capability of producing international standard vaccines and bio-medical products. Therefore, WHO/ WPRO considers that by establishing internationally certifiable production management and quality standards, Viet Nam can domestically produce measles vaccine.

In response, the Government of Viet Nam, in an effort to achieve the targets of the "Strategy for Public Health Care and Protection in the Period 2001-2010", increase the sustainability of the EPI Program and Measles Control Program, establish a domestic production system for measles

vaccine and provide for stable supply of measles vaccine, has formulated the “Project for Construction of Measles Vaccine Production Facilities in Viet Nam”. However, due to financial difficulties, the Government of Viet Nam cannot carry out the Project on its own and therefore requested the Government of Japan for Japanese Grant Aid cooperation for the Project.

In the implementation of the Project, the governing principle is that the production facilities and production process comply with the requirements of WHO standards for production management and quality control (WHO-GMP). Therefore, it is held necessary that the National Regulatory Authority (NRA), which oversees bio-medical products, their nation-wide distribution and holds the authority to issue licenses to manufacturers of bio-medical products, should be reinforced to the level required by WHO standards. An institutional development plan for The National Center for Control of Medico-Biological Products (CENCOBI) is under implementation, mainly with assistance from WHO. CENCOBI which is an independent organization under the jurisdiction of the Ministry of Health, is duly considered to be the NRA of Viet Nam. The CENCOBI development plan aims to establish a Vietnamese GMP based on WHO-GMP by 2005 with the development of the necessary legal systems and human resources.

In response to the request, the Government of Japan decided to carry out a Basic Design Study. Based on this decision, JICA sent the 1st Basic Design Study Team to Viet Nam in March 2002 and the 2nd Basic Design Study Team in May 2002. The Study Teams held meetings with concerned parties in Viet Nam, conducted inspections of related facilities, accumulated required information and conducted on-site studies of the proposed construction site for the facilities. Following analysis of the collected data in Japan and explanation of the Draft Basic Design to the Vietnamese side in August 2002, this Basic Design Report was finalized.

Based on the Study, the necessity for the measles vaccine production facilities was confirmed. It was concluded that it was necessary to construct the vaccine Production Building, including Animal Laboratory and Machinery Building and to procure and install the related production equipment on a site in Than Tri District in the suburbs of Hanoi.

The Project is based on the following requirements.

- Design Standards

The Project facilities are to be designed on the premises that they will be required to comply with WHO-GMP standards.

- Production Capacity

Under the EPI schedule for two-dose routine immunization schedule for measles, the target

population for the 1st dose is 2.4 million per annum (the total for infants and children in high risk areas such as mountainous districts) and the 2nd dose target population is 2.4 million per annum (the total of 5 year olds and children in high risk areas such as mountainous districts), making a combined target population of 4.8 million per annum. The required base production volume is 7.2 million dosages per annum, taking into consideration 50% wastage due to underdeveloped cold chain (National Institute for Health and Epidemiology (NIHE) has set the wastage at 50% based on past results). To this volume, additional requirements for mass immunization campaigns for measles elimination held every 3 to 4 years raises the total annual requirement to 7.5 million dosages per annum as the required production capacity for the Project facilities.

- Measles Vaccine Production Technology

The facility planning and production process planning for the Project facilities will be based on the measles vaccine production technology of Kitasato Institute. In order to establish the contractual basis, a technology transfer agreement between POLIOVAC and Kitasato Institute for transferring measles vaccine production technology and the seed virus (AIK-C strain) has been concluded.

- Validation Requirements

As stipulated in the WHO-GMP, validation is the activity under which all procedures, processes, equipment, raw materials and building services systems must be proven to attain the desired results. POLIOVAC, the main operator of the facilities, will be involved as the responsible agent for production from preparation of the Basic Validation Plan, to Installation Qualification (IQ) and Performance Qualification (PQ).

In order to ensure the smoother implementation of validation, the Soft Component will be implemented as part of Grant Aid cooperation.

The components of the Project for the Construction of Measles Vaccine Production Facilities are summarized below:

Responsible Organization: Ministry of Health, Socialist Republic of Viet Nam
(MOH)

Implementing Agency: Poliomyelitis Vaccine Research and Production Center
(POLIOVAC)

Total Project Schedule: The total schedule for this Project will be 35 months from detail design stage to end of construction. Of this period, 8 months is required for Detailed Design, 4 months for tendering procedures and

17 months for construction of facilities and procurement and installation of equipment and 6 months for Validation.

Construction Site: Than Tri District, Hanoi

Structure of Facilities: Production Building reinforced concrete, 2 stories
 Animal Laboratory reinforced concrete, 2 stories
 Mechanical Building reinforced concrete, single story
 (the structure and architectural components of Machinery Building will be implemented under Vietnamese budget)

Floor Area of Facilities: Production Building 3,116 m²
 Animal Laboratory 358 m²
 Mechanical Building 484 m²
 Total Floor Area 3,958 m²

Summary of items to be borne by the Government of Viet Nam:

Landfill and grading of site, construction of Administration Buildings, Parking Garage, Canteen, Security Guard House and the architectural and structural works for the Mechanical Building, site works, procurement and installation of some production equipment, lead-in works, wells, incinerators and others.

The project facilities to be borne by Japanese Grant Aid Portion is summarized below:

Construction of Facilities	Production Building 1 st floor: (Final product Production Zone) Final bulk formation, vial filling, and freeze-drying, capping and inspection, labeling, packing and loading 2 nd floor: (Bulk Production Zone) SPF eggs receiving and incubation, cell culture, virus culture, medium preparation (Quality Control Zone) Sterility Tests, biological tests, chemical tests Animal Laboratory (Animal Test Laboratories) Animal testing, washing Mechanical Building Mechanical and electrical systems for mechanical room (boilers, pumps, others), transformer room and generator room
Procurement of Equipment	The minimum required equipment for the production activities of the above facilities (vial filling machine, freeze-drying machine, et cetera)
Soft Component	Assistance in Validation Assistance in operation and maintenance of facilities

The initial 2 years after completion of the Project facilities will be the technology transfer period, during which measles vaccine will be produced from imported bulk. From the 3rd year, full production is planned to be commenced using specific pathogen free eggs (SPF eggs). The maintenance cost after the 3rd year is estimated to be US\$560,000 annually, of which US\$510,000 will be facility maintenance costs and US\$50,000 will be equipment maintenance cost.

The staffing of the facilities after completion is estimated to be 63 persons in total. The personnel budget cost is estimated to be US\$210,000 annually. These costs will be included in the production cost of the vaccine and will be reflected in the Government buying price for the vaccine.

Based on the above premises, it has been confirmed in the Minutes of Discussion for Explanation of Draft Basic Design that the Vietnamese side will undertake the following budgetary measures.

1. Initial Construction Investment for Vietnamese Portion (from 2003 to 2005): US\$901,600
2. Technology transfer and staff training (from 2003 to 2007): US\$1,000,000

The following direct and indirect benefits will be realized when the Project (both Japanese and Vietnamese portions) is implemented.

Stable supply of measles vaccine will become possible

Through the implementation of the Project, production facilities in compliance with WHO-GMP will be constructed. This will enable domestic production of measles vaccine and ensure the stable supply of measles vaccine throughout Viet Nam.

Reduction of measles morbidity and mortality

The implementation of the Project will promote the two-dose routine schedule for measles vaccine, leading to reduction in morbidity and mortality of measles. Consequently, through the suppression of measles, it will become possible to reduce the socio-economic costs of the disease throughout Viet Nam.

Supply of measles vaccine to neighboring countries

The production facilities in the Project have been designed to allow further increase in production capacity when the necessary equipment have been procured and installed. This will enable export of measles vaccine to neighboring countries and contribute to the reduction of measles morbidity and mortality in the region.

As seen above, the implementation of the Project facilities will not only lower the morbidity of measles in Viet Nam (population approximately 78,770,000), but also enable supply of measles vaccine to the 3 countries of Indochina (combined population approximately 95,000,000).

Therefore, implementation of the Project under Japanese Grant Aid cooperation is deemed to be highly beneficial and the feasibility and necessity of the Project is extremely high.

Finally, the commencement of the Project depends on the timely completion of Viet Nam side obligations, especially provision on schedule of infrastructure such as water supply and power supply which are indispensable for vaccine production. It is desirable that the following programs and institutions are strengthened and developed for the smooth and effective operation of the Project.

Smooth Transfer of Technology and Education / Training

POLIOVAC already has experience in poliomyelitis vaccine production, but does not have any experience in production of measles vaccine and will require further training and education of its staff for the higher requirements in process control and quality control required for measles vaccine production. Presently, there are plans for further improvement of technical assistance with cooperation among Japan, Viet Nam and WHO. Under the agreement for technology transfer of measles vaccine production process signed between Kitasato Institute, a measles vaccine producer in Japan, and POLIOVAC, the transfer of production process technology and the supply of seed virus (AIK-C strain) for the Project has been assured. Measles vaccine production technology transfer agreement has been signed between POLIOVAC and Kitasato Institute, insuring the smooth transfer of the necessary technology for the Project and supply of the seed vaccine (AIK-C strain).

The Strengthening of the National Regulatory Agency (NRA) and Quality Control

The Project is based on the premise of compliance with WHO-GMP standards. This can be achieved through establishing an effective Quality Assurance System in Viet Nam including not only the production facilities and production process, but also the distribution process, and surveillance of immunization and adverse effects. Therefore, it is imperative that a Vietnamese GMP in compliance with WHO-GMP is introduced and the capabilities of CENCOBI, the NRA of Viet Nam, are reinforced before the commencement of validation procedures for the Project begins in mid 2005.

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