

**WHO/IVB/08.09**

**Meeting with International Partners on  
Influenza Vaccine Technology Transfer  
to Developing Country Vaccine  
Manufacturers**

**29 to 30 October 2007**

**Bangkok, Thailand**

**Immunization, Vaccines and Biologicals**

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# Contents

1. Objectives of the meeting .....	4
2. Progress in implementation of the Global Action Plan to increase supply of influenza vaccine .....	4
1.1 Brazil (Instituto Butantan) .....	5
1.2 India (Serum Institute of India Ltd.-SII).....	5
1.3 Indonesia (BioFarma Persero-BF) .....	6
1.4 Mexico (BIRMEX) .....	6
1.5 Thailand (GPO).....	6
1.6 Viet Nam (IVAC) .....	6
3. Perspectives from international funding agencies and partners.....	7
4. Way forward in manufacturing capacity building: .....	7
Annex 1: List of participants.....	8
Annex 2: Agenda .....	11

## **1. Objectives of the meeting**

The purpose of the meeting was (i) to provide an update on the Global Action Plan (GAP); and (ii) to review the progress on the first technology transfer grants, and to allow for networking of the grantees with development partners. The meeting was chaired by Dr Hadjime Inoue, and brought together representatives of the six developing country manufacturers receiving funding from WHO's influenza vaccine technology transfer programme as well as representatives from vaccine manufacturers from Islamic Republic of Iran, Egypt (Vacsera) and South Africa (Biovac), from UNICEF, from development banks (Agence Française de Développement, Asian Development Bank), from donor countries (USA, Japan) and from WHO regional office in South-East Asia and Headquarters.

## **2. Progress in implementation of the Global Action Plan to increase supply of influenza vaccine**

The Global Vaccine Action Plan (GAP) for Pandemic Influenza Vaccines was formulated in May 2006 in response to the need to identify approaches and strategies to increasing supply of influenza pandemic vaccines in order to reduce the anticipated gap between potential vaccine demand and supply during an influenza pandemic. Its implementation requires the participation of international and national partners, including the private sector. An advisory group was formed to oversee the implementation of the GAP. This group met for the first time in Geneva on 19 October 2007 to review activities since May 2006, identify key priorities, and revise and update the GAP. It also examined the business plan prepared by McKinsey Consulting, based on the GAP. McKinsey's business plan identifies three particular options which hold the most promise to bridge the vaccine supply gap in the medium-term: (i) promote seasonal vaccine programs, (ii) increase production capacity beyond seasonal need, and (iii) prepare for the conversion of inactivated influenza vaccine (IIV) to live attenuated influenza vaccine (LAIV) production during a pandemic. The group also underlined the importance of identifying funding sources to conduct priority GAP activities.

Since the creation and publication of the GAP in 2006, a lot of progress has been made. The Initiative for Vaccine Research (IVR) has completed several activities with direct relevance to expansion of production capacity and technology transfer including (i) review of production technologies for influenza vaccines, and their adaptation for use in developing countries, (ii) analysis of cell line availability for manufacturing of influenza vaccines, (iii) mapping of intellectual property related to production of influenza vaccines, (iv) review of the potential advantages of live attenuated influenza vaccine in the control of epidemic and pandemic influenza, (v) review of the state of the art of candidate H5N1 influenza vaccine safety and immunogenicity during the 3<sup>rd</sup> WHO meeting on evaluation of pandemic influenza prototype vaccines in clinical trials, and (vi) preparation of detailed tables (posted on IVR's website) providing results on the clinical trials of pandemic influenza prototype vaccines.

Directly relevant to objective 2 of the GAP (increase manufacturing capacity), WHO issued a call for proposals in October 2006 to developing country vaccine manufacturers willing to initiate domestic production of influenza vaccines and selected six grantees/manufacturers to establish pilot facilities for the production of seasonal and pandemic influenza vaccines. These are located in Brazil (Instituto Butantan), India (Serum Institute of India, SII), Indonesia (BioFarma), Mexico (Birmex), Thailand GPO, and Viet Nam (IVAC). Manufacturers started with their projects in June (Butantan, SII and GPO) and September (BioFarma, Birmex, IVAC) 2007.

The following section details the progress of the six grantees.

### **1.1 Brazil (Instituto Butantan)**

- The grant contract with Instituto Butantan was signed on 21 May 2007 and the first payment was awarded soon after. Production technology being adopted is egg-based inactivated whole virion vaccine with adjuvant.
- Through technology transfer from Sanofi-Aventis, Butantan had previously gained technology production capability for egg-based split seasonal vaccine.
- A plant was built to initially produce 20 million doses of trivalent seasonal vaccine in four months and a smaller plant was built and became operational in 2007 to allow: (i) safe processing of eggs and embryos, (ii) production of H3N2 candidate vaccine as a model (iii) staff training, (iv) testing of vaccine formulations with H3N2 followed by H5N1 with a new MLPA adjuvant formulation developed by Instituto Butantan and (v) production of experimental H5N1 lots (Viet Nam 2005 and Indonesia 2005 strains).
- In 2008-2009, Butantan plans to increase the capacity of its laboratory to conduct analyses of the immune responses induced by their candidate influenza vaccine and to carry out a Phase 1 clinical trial using clinical lots produced for both H5N1 strains. Production of H5N1 vaccine antigens will then be transferred to the large plant, and a stockpile of adjuvant and vaccine will be prepared for use in case of a pandemic.
- Butantan plans to make its future stockpile available to neighboring countries and to some African countries as part of its commitment to help the international community fight the pandemic threat.

### **1.2 India (Serum Institute of India Ltd.-SII)**

- The grant contract was signed on 21 May 2007 and first payment from the \$2 million grant awarded soon after. SII focuses on concrete evaluation and assessment of (i) tissue culture-based inactivated whole virus and split virus preparations with adjuvants and (ii) egg-based live attenuated influenza vaccine for immunization through nasal route.
- SII dedicated a team of scientists for the project. A small manufacturing unit originally used for mumps vaccine production was converted into an influenza vaccine development and analytical laboratory. Test protocols are being established.
- Cell bank preparation and characterization is in progress. Different culture vessels including tissue culture flasks, roller bottles and cell factory were screened for cell growth.
- Toxicological studies and final formulation will take about 12-15 months.
- Future plans include immunogenicity studies with different dosages of whole and split vaccines using adjuvants.
- SII also plans to explore the possibility of Live Attenuated Influenza Vaccine (LAIV) and had preliminary discussions with prospective partners from Russia. Feasibility of this option will be assessed in the next six months.
- SII estimates the number of vaccine doses that they could produce per annum at 23 million for inactivated vaccine or 168 million for LAIV.

### **1.3 Indonesia (BioFarma Persero-BF)**

- The grant contract was signed on 14 August 2007 and first payment from the \$2 million grant awarded soon after. Production technology being transferred is first for fill-finish of egg-based split influenza vaccine antigen produced by a Japanese manufacturer (Biken). Under the terms of the project, BF will subsequently aim at acquiring the capacity for bulk manufacturing of pandemic influenza vaccines. Funds available through the grant will be used for obtaining technology expertise and for procurement of equipment.
- To date, BF has trained staff on production, quality control and clinical trials. Equipment procurement, bulk importation for a future clinical trial are all underway. Capacity for the upstream process will be at 10 million doses of seasonal flu vaccine.

### **1.4 Mexico (BIRMEX)**

- The grant contract was signed on 14 August 2007 and first payment from the \$2 million grant awarded soon after. Birmex intends to acquire technology for blending, filling and packaging of egg-based split influenza vaccine antigen (produced by Sanofi Pasteur). The grant will be utilized for plant design, validation of the design, and equipment for quality control.
- To complement the grant, BIRMEX will invest up to \$31 million to complete the facility including land purchase and construction, equipment, training of staff, and plant and process validation.

### **1.5 Thailand (GPO)**

- Contract signed 21 May 2007, and first payment awarded. GPO plans are to establish domestic production of egg-based inactivated (IIV) and live attenuated vaccine (LAIV).
- For the purpose of developing a process for the production of IIV, selection of seed-strain with appropriate characteristic to be used as a model was the first task to be undertaken. Access to seed strains for LAIV is under negotiation with the owner (BioDiem), in collaboration with WHO.
- Various key parameters (dilution factor, temperature and incubation time) have been studied for the optimum high growth and HA yield of each strain in order to select the most suitable strain for the representative model of process development, then confirming with another strain.
- The development of analytical methods has already been undertaken, in particular the SRID test.
- Commissioning and validation of the GMP pilot facility is already completed. Most of the key equipment has been ordered. Some are already installed and used. In addition, the conceptual design and basic design of a new vaccine manufacturing plant is underway.

### **1.6 Viet Nam (IVAC)**

- The grant contract was signed on 27 August 2007 and first payment from the \$2.7 million grant awarded soon after.
- IVAC is establishing a facility to produce egg-derived whole virion, alum adjuvanted influenza vaccine. It was decided to have an initial capacity of 500,000 doses of seasonal vaccine production with expansion possibilities up to 3 million doses.
- The building site and the location of the supporting chicken farm was established.
- The first phase of the project is ongoing, which involves finalization of conceptual design with international consultants and establishment of a specific in-house technical group aiming to support the project.

- Reference virus strains for seasonal and H5N1 influenza work were obtained from the National Institute of Biological Standards and Control (NIBSC) in the United Kingdom.

### **3. Perspectives from international funding agencies and partners**

- The funding agencies and bilateral donors stated that the results to date were encouraging and that the project had the capacity to increase global production capacity for influenza vaccine, and provide a platform for North - South and regional cooperation.
- The Asian Development Bank proposed that the technology transfer projects are excellent vectors to strengthen technical capacity to produce vaccines for use in developing countries, in addition to providing increased flexibility to respond to emergencies. For the former to be sustainable, WHO and the interested governments may want to consider the following:
  - Establish regional technological *know-how* and experience platforms.
  - Facilitate the development of a commercial portfolio of vaccines based on regional markets and cooperation.
  - Establish and develop policies to support the use of influenza vaccines by collecting evidence to support these policies.
  - Establish financial mechanisms for facilitating access of countries to affordable seasonal influenza vaccine.
- The chair insisted that solid business plans are required to assure that the investments made will lead to sustainable influenza vaccine production. Governments need to ensure that they are really committed to the projects, that will establish influenza vaccine production capacity for their country.

### **4. Way forward in manufacturing capacity building**

- Continuation of seed funding for the six grantees, and extension of the grant programme to new applicants.
- Establishment of a manufacturing hub as an available source of technology transfer.
- Further exploration on the advantages of converting inactivated influenza vaccine production to LAIV for mass-immunization campaigns in case of a pandemic.

## **Annex 1: List of participants**

### **Participants/Observers**

Ms Molly Brady, Avian Influenza Adviser, Office of Public Health, USAID Regional Development Mission/Asia, Bangkok 10330, Thailand

Mr Hervé d'Oriano, Mr Hervé, Ambassade de France à Bangkok, Bangkok 10500, Thailand

Mr Joël Daligault, Agence Française de Développement, Jakarta 12920, Indonesia

Dr Sudarat Damrongwatanapokin, Regional Animal Health Adviser, USAID Regional Development Mission/Asia, Bangkok 10330, Thailand

Dr Rajeev M. Dhere, Director, Vaccine Production, Serum Institute of India Ltd., Pune, 411 028 Maharashtra, India

Mr François-Xavier Duporge, Agence Française de Développement, Bangkok 10500, Thailand

Dr Nagwa Fouad El Kholly, Head, Influenza Reference Laboratory, VACSERA, Egypt

Dr Mohammad Mehdi Goya, Director, Ministry of Health and Medical Education, Republic Islamic of Iran

Dr Jan Hendriks, Account Manager International Support, Netherlands Vaccine Institute (NVI), Netherlands

Dr Le Van Hiep, Vice Director, Institute of Vaccine and Biological Substances, Viet Nam

Dr Douglas Holtzman, Senior Program Officer, Infectious Diseases, Global Health Program, The Bill and Melinda Gates Foundation, Seattle, 98102 WA, USA

Dr Hajime Inoue, Director, International Cooperation Office, Ministry of Health, Labour and Welfare, Tokyo 100-8916, Japan

Dr Jacques Jeugmans, Practice Leader, RSGS/RSDD, Asian Development Bank, Metro Manila 0980, Philippines

Dr Igor Krasilnikov, Head of R&D Department, Microgen State Company, Russian Federation

Dr Dmitry Ledyankin, R&D Department, Microgen State Federal Company, Moscow, 115088 Russian Federation

Dr Dong Han Lee, Senior Scientific Officer, Division of Vaccine Preventable Disease Control and National Immunization Programme, Korea Centre for Disease Control and Prevention, Seoul, Korea, Rep. of

Dr Jong-Koo Lee, Director, Korea Center for Disease Control and Prevention, Seoul, Rep. of Korea

Dr Osman Mansoor, Senior Adviser EPI (New Vaccines), UNICEF, New York, 10017 NY, USA

Dr Isa Mansyur, President Director, PT. Bio Farma (Persero), Bandung, 40161 West Java, Indonesia

Dr Do Minh Si, QC Division, National Institute of Vaccines and Biological Substances, Viet Nam

Dr Francisco Padilla Catalan, General Commercial Director, Laboratorios de Biologicos y Reactivos de Mexico, S.A. de C.V, 06000 Mexico DF, Mexico

Dr Michael L. Perdue, Deputy Director - Pandemic Influenza, Biomedical Advanced Research & Development Authority, Department of Health and Human Services, Washington, DC, 20201 USA

Professor Isaias Raw, Director, Instituto Butantan, São Paulo, 05503-900 Brazil

Dr Rocio Cervantes Rosales, Director, Laboratorios de Biologicos y Reactivos de Mexico, S.A. de C.V, 06000 Mexico DF, Mexico

Dr Mark Simmerman, Emerging Infections Programme, US CDC, Bangkok, Thailand

Dr Mahendra Suhardono, Production Director, 28 Jl Pasteur, PT. Bio Farma (Persero), Bandung, 40161 West Java, Indonesia

Tabora, Ms Liza, Project Administrator, Avian Influenza Secretariat, Bangkok, Thailand

Dr Sit Thirapakpoomanunt, Director of the Viral Division, The Government Pharmaceutical Organization, Bangkok, 10400 Thailand

Dr Patrick Tippoo, R&D Manager, Biovac Institute, Wadeville 1422, South Africa

Ms Kanchala v Utid, Viral Vaccine Division - The Biological Product Department, The Government Pharmaceutical Organization, Bangkok 10400, Thailand

Dr Leo van der Pol, Head Process Development, Netherlands Vaccine Institute, 3720 AL, Bilthoven, Netherlands

Dr Ajchara Vararuk, AHI Regional Coordinator, UNSIC-ADB Regional Office for Asia & Pacific c/o UNOCHA Regional Office for Asia and the Pacific, Bangkok 10200, Thailand

Mr James Waller, Regional Environmental and Health Officer, US Embassy, Bangkok 10330, Thailand

Dr Marie-Odile Waty, Head of the Health Division, Human Development Department, Agence Française de Développement, F-75598 Paris Cedex 12, France

Dr Suwit Wibulpolprasert, Senior Advisor on Health Economics, Ministry of Public Health, Nonthaburi, 11000 Thailand

Dr Leena Ravindra Yeolekar, Scientist and In charge Influenza Project, Serum Institute of India, Pune 411 052, India

## **WHO**

Dr Maureen Birmingham, Acting WHO Representative, World Health Organization, Nonthaburi 11000, Thailand

Mr Peter Carrasco, Expanded Programme on Immunization (EPI), Immunization, Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland

Dr Martin Friede, Product Research and Development (RPD), Initiative for Vaccine Research, World Health Organization, 1211 Geneva 27, Switzerland

Dr Marie-Paule Kieny, Director, Initiative for Vaccine Research, World Health Organization, 1211 Geneva 27, Switzerland

Dr Pem Namgyal, Acting Team Leader, Immunization and Vaccine Development (IVD), Regional Office for South East Asia, India

Dr Laszlo Palkonyay, Product Research and Development (RPD), Initiative for Vaccine Research, World Health Organization, 1211 Geneva 27, Switzerland

Dr Ludy Suryantoro, Epidemic and Pandemic Alert and Response (EPR), World Health Organization, Geneva 27, 1211 Switzerland

## Annex 2: Agenda

Chair: Dr Hajime Inoue, Japan

### Monday 29 October

<b>13:00</b>	Registration	
14:00	Welcome address and opening remarks	Pem Namgyal
14:30	Presentation of the Global Action Plan as updated in October 2007	Marie-Paule Kieny
15:00	Discussion	
15:30	The WHO influenza vaccine technology transfer project	Laszlo Palkonyay
<b>16:00</b>	<b>Coffee break</b>	
16:30	Discussion	
	Presentation by the WHO grantees	
17:00	<ul style="list-style-type: none"><li>• The Government Pharmaceutical Organization, Thailand</li></ul>	Sit Thirapakpoomanunt
	<ul style="list-style-type: none"><li>• Serum Institute of India Ltd., India</li></ul>	Rajeev M. Dhere
<b>18:00</b>	<b>Closure for day</b>	

### Tuesday 30 October

9:30	Presentation by the WHO grantees (Contd.)	
	<ul style="list-style-type: none"><li>• Fundaçao Butantan, Brazil</li></ul>	Isaias Raw
10:00	<ul style="list-style-type: none"><li>• Birmex, Mexico</li></ul>	Francisco Padilla Catalan
<b>10:30</b>	<b>Coffee break</b>	
11:00	<ul style="list-style-type: none"><li>• Institute of Vaccine and Biological Substances, Hanoi</li></ul>	Le Van Hiep
11:30	<ul style="list-style-type: none"><li>• PT. Bio Farma (Persero)</li></ul>	Mahendra Suhardono
12:00	Discussion	
<b>12:30</b>	<b>Lunch break</b>	
13:30	International initiatives to increase potential supply of pandemic influenza vaccines	
	<ul style="list-style-type: none"><li>• Department of Health and Human Services</li></ul>	Michael L. Perdue

	<ul style="list-style-type: none"> <li>• Government of Japan</li> </ul>	Hajime Inoue
	<ul style="list-style-type: none"> <li>• (on behalf of) The Bill and Melinda Gates Foundation</li> </ul>	Marie-Paule Kieny
	<ul style="list-style-type: none"> <li>• Asian Development Bank</li> </ul>	Jacques Jeugmans
<b>15:00</b>	<b>Coffee break</b>	
15:20	<ul style="list-style-type: none"> <li>• Agence française du Développement</li> <li>• Netherlands Vaccine Institute</li> <li>• Others</li> </ul>	Marie-Odile Waty Jan Hendriks
16:00	Next steps and prospects for additional funding for capacity building for pandemic influenza vaccines production	
17:00	Close of meeting	