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Establishment of pandemic influenza vaccine production capacity at Bio Farma, Indonesia

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ABSTRACT

In Indonesia, avian influenza A(H5N1) virus started to spread in humans in June 2005, with an alarming case-fatality rate of more than 80%. Considering that global influenza vaccine production capacity would barely have covered 10% of the world's pandemic vaccine needs, and that countries with no production facilities or prearranged contracts would be without access to a vaccine, the Government of Indonesia embarked on a programme to increase its readiness for a future influenza pandemic. This included the domestic production of influenza vaccine, which was entrusted to Bio Farma.

This health security strategy consists of developing trivalent influenza vaccine production capacity in order to be able to convert immediately to monovalent production of up to 20 million pandemic doses for the Indonesian market upon receipt of the seed strain from the World Health Organization (WHO). For this purpose, a dedicated production facility is being constructed within the Bio Farma premises in Bandung.

As an initial stage of influenza vaccine development, imported seasonal influenza bulk has been formulated and filled in the Bio Farma facility. Following three consecutive batches and successful clinical trials, the product was licensed by the Indonesian National Regulatory Authority and distributed commercially for the Hajj programme in 2009. With continued support from its technology transfer partners, Bio Farma is now advancing with the development of upstream processes to produce its own bulk for seasonal and pandemic use.

1. Introduction

The highly pathogenic avian influenza outbreak in Asia started spreading in Indonesia in June 2005, with a case-fatality rate of more than 80%. Although antiviral drugs and personal protective measures can contain such a spread to some extent, only an effective pandemic vaccine can protect the millions of vulnerable human lives from an influenza virus of this severity. At that time, the maximum global capacity for monovalent influenza vaccine production was a fraction of the doses needed to vaccinate the entire population, and countries in South-East Asia with no production facilities or prearranged contracts would be without access to vaccine for anything up to a year or more [1].

The Government of Indonesia therefore embarked on a programme to increase its readiness for a future influenza pandemic, including the domestic production of influenza vaccine which was entrusted to its long-established manufacturer of human vaccines, Bio Farma. This health security strategy consisted of the development of capacity for trivalent seasonal influenza vaccine production in order to be able to convert immediately to monovalent pandemic production of up to 20 million doses for the Indonesian market upon receipt of the seed strain from the World Health Organization (WHO).

Founded over 120 years ago, Bio Farma is the sole supplier of traditional EPI (Expanded Programme on Immunization) vaccines for the national immunization programme. The company facilities meet the highest standards of Good Manufacturing Practices (GMP) and quality assurance as witnessed by many of its vaccines prequalified by WHO. Bio Farma is one of the largest producers of human vaccines in Asia, and is also well versed in international vaccine technology transfer partnerships such as from Japan, the Netherlands and the USA.

From 2007, to complement significant multi-year Government support, Bio Farma was successful in identifying technical and financial assistance to achieve this ambitious goal. An agreement was signed with Biken Institute, Japan covering the transfer of technology to formulate and fill imported egg-based inactivated split trivalent influenza bulk vaccine and progressively the upstream process technology and quality control for antigen production at Bio Farma. For this purpose, a dedicated production facility is being constructed within the Bio Farma premises in Bandung.

In parallel, Bio Farma was selected as a grantee of the WHO influenza vaccine technology transfer initiative, which sought to increase access of developing countries to a pandemic influenza

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Table 1
Experimental batches of H1N1 monovalent bulk in developing the upstream process.

No. of batches	Seed strain	Egg scale	Date	
2	A/California/7/2009 (H1N1)v-like IVR-153	1 000	Q3 2009	From NISBC, propagated and distributed in aliquot at Airlangga University BSL3+ facility
3	A/California/7/2009 (H1N1)v-like NYMC X-179A	1 000	Q4 2009	From NISBC, propagated and distributed in Bio
6	A/California/7/2009 (H1N1)v-like NYMC X-179A	5 000	Q2 2010	Farma BSL2+ facility using BSL3+ practices
9	A/California/7/2009 (H1N1)v-like NYMC X-179A	10 000	Q4 2010	Experimental batches leading to consistency lots

vaccine through domestic production capacity. The WHO seed funding for transfer of the technology, procurement of equipment for quality control and production, and formulation and filling training for seasonal vaccine imported from Biken, complemented the financial contributions of Bio Farma and the Indonesian Government.

This article describes the progress made towards the following four objectives of the project: (i) technology transfer for the production of influenza vaccine; (ii) installation and operationalization of a formulation and filling unit; (iii) registration in Indonesia of seasonal vaccine developed from imported bulk antigen; (iv) production of bulk inactivated influenza antigen for seasonal and pandemic use.

2. Downstream formulation and filling capacity

Since the existing formulation and filling lines at Bio Farma were fully occupied for routine vaccine production, a new unit was established and fully equipped.

Following the transfer from Biken, Japan of the technology to formulate, fill and quality control trivalent seasonal influenza vaccine, three monovalent bulks each of the following strains were received from Biken in December 2007: A/Hiroshima/52/205 (H3N2); A/Solomon Islands/3/2006 (H1N1); B/Malaysia/2506/2004.

In 2008, three consecutive batches were successfully produced from the imported bulk antigen in two presentations: single-dose ampoules for use in clinical trials, and multi-dose vials for stability studies. Within 1 year of the start of the project, candidate seasonal influenza vaccine lots prepared for clinical trial were approved by the National Agency of Drug and Food Control (NADFC) in Indonesia. The results of analyses performed in Indonesia on clinical trial lots were confirmed in samples sent to Biken.

In response to a request from NADFC, Bio Farma also carried out a prelicensure bridging study to assess the safety and immunogenicity of the vaccine in 405 adolescents and adults (12–64 years old), randomly assigned to above three bulk batches. A single 0.5 mL dose was administered intramuscularly and blood samples taken before and 28 days after immunization. Results showed that the vaccine induced high antibody titres against influenza antigens in all subjects ($\geq$1:40 haemagglutination inhibition to A/Hiroshima, A/Solomon Island and B/Malaysia strains 97.8%, 98.2% and 95.5%, respectively; $p = 0.025$). The geometric mean titres after immunization increased (A/Hiroshima: 66.16–323.37; A/Solomon Islands: 41.89–554.26; B/Malaysia: 24.02–231.83), and subjects with a fourfold increase in antibody titre were 61.2%; 85.5%; 81.5%, respectively. All vaccines were well tolerated and no serious adverse events were noted after 28 consecutive days of observation after immunization.

Results of these studies showed that the vaccine to be immunogenic and safe. The NADFC therefore issued marketing authorization and Bio Farma's seasonal influenza vaccine Flubio® became the first licensed product of the WHO technology transfer initiative in June 2009. Some 165,000 doses were produced for commercial distribution focusing principally on mass immunization of Hajj pilgrims. Until such time as Bio Farma is able to produce its own seasonal (and ultimately pandemic) antigen, bulk seasonal vaccine supplies will continue to be imported from Biken Institute in Japan, for which a commercial agreement has been signed.

3. Upstream development and production of inactivated influenza vaccine

The majority of the critical equipment for the preparation of seed lots, upstream process and quality control in pilot scale has been received.

In 2008, Bio Farma started the preliminary development of the upstream process for seasonal influenza vaccine, and by April 2009 had produced three batches of seasonal bulk antigen derived from A/Solomon Islands/3/2006 IVR-145 seed strain at 1 000 egg scale.

A Technical Collaboration and License Agreement was signed between Bio Farma and Biken Institute of Japan in December 2009 for the transfer of influenza vaccine upstream production process. This was implemented through the training of Bio Farma staff at the Biken campus and follow-up training in Indonesia (see Section 4 below). Technology transfer of concentrated bulk preparation comprises the upstream process technology and quality control of seasonal influenza vaccine, i.e. seed preparation and virus cultivation up to the inactivation processes.

3.1. Pandemic influenza—product characterization and optimization

In July 2009, following the onset of the A(H1N1) influenza pandemic, Bio Farma switched its attention to the development of a vaccine against this novel strain and by November 2010 a total of 20 lots had been produced (Table 1). Of the latest nine batches of A(H1N1) derived from A/California/7/2009 (H1N1)v-like NYMC 179A, the first three were used to familiarize Bio Farma operators with the process. Thanks to this experience and hands-on guidance from Biken experts, the next batches showed increasing consistency (Table 2), and it is expected that by early 2011, three consecutive and consistent batches will have been produced to be formulated as monovalent pandemic ready-filled bulk.

3.2. Construction of an industrial scale antigen production facility

Within its overall influenza pandemic preparedness plan, the Indonesian Ministry of Health decided to set up a manufacturing facility for egg-based influenza vaccines against wild-type influenza virus strains. The project comprises the whole manufacturing process including bulk antigen production, formulation, filling, laboratory quality control facilities, as well as an independent chicken farm to produce embryonated eggs. Significant progress had made in the physical execution of the BSL3+ building within the Bio Farma complex in Bandung. Following a consultative process among all stakeholders, the design, layout and final operating spaces of the three floors of the building were approved and the building is nearing physical completion. Process equipment will then be installed and connected to utility and service distribution points. Following operational and performance qualification, GMP and building monitoring systems and the training