Policy Recommendations on

Thailand Strategy for Pandemic Influenza

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Preface

There are currently reports on epidemics of highly pathogenic avian influenza virus in many regions. A new wave of pandemic seasonal flu is also predicted since it has now been over 30 years from its last incident. These have stimulated concerns about an influenza pandemic globally that is predicted to cause millions of deaths and have a major socio-economic impact on Thailand, which is among the countries affected by the virus, both in animals and humans. The first national strategic plan for avian influenza prevention and control, 2005-2007 was therefore launched.

Since vaccine usage is one of the main strategies in disease prevention, a working team, including the National Center of Genetic Engineering and Biotechnology (BIOTEC, NSTDA) and the Health Systems Research Institute (HSRI, Thailand Ministry of Public Health) was designated to responsible for a feasibility analysis on "National Strategies on Pandemic Influenza Vaccine Preparation for Thailand". The strategic plan is proposed according to the time frame for short-, intermediate- and long- term preparations.

The short-term plan focuses on importing vaccine. The intermediate plan is domestic vaccine production to ensure vaccine availability and accessibility for the Thais.This is to start up the production in the shortest possible time by modification of existing vaccine manufacturing facilities. For long term sustainability of influenza vaccine production, an investment of a new vaccine plant is proposed.

Four avian influenza outbreaks in Thailand were reported in 2004, and caused major damage to the Thai poultry industry. Over 30 millions chicken were killed. The virus crossed the species barrier to infect humans and 17 people died. The Royal Thai Government has taken this threat seriously and put immense resources and efforts into controlling this outbreak and preventing the possibility of a pandemic. The Prime Minister has established a multisectoral public-private National Committee on Avian Influenza Control, chaired by the Deputy Prime Minister Jaturon Chaisaeng. The committee is mandated to tackle the problem in an integrated , holistic and sustainable manner.

The committee thus developed Thailand's National Strategic Plans for Avian Influenza Control and Influenza Pandemic Preparedness, 2005-2007. The plans were endorsed by the cabinet on 25th January 2005. NSTDA was responsible for knowledge generation and management. Subsequently, in 2007, the Deputy Prime Minister Kosit Panpiumrat appointed the working group to formulate a second national strategic plan to ensure the continuity and sustainability of a proper preparedness for an avian influenza pandemic.

This policy recommendation paper is an output of the work on knowledge generation and management. Scientific knowledge and technical developments of influenza vaccine manufacturing in Thailand were previously scarce. The team gathered information from experts and organizations, both national and international, in forms of both tacit knowledge and explicit knowledge, and then a feasibility analysis was performed for policy recommendations on an influenza vaccine preparation that is suitable for Thailand.

It is our hope that this paper will be of value and benefit to policy decision making for Thailand's pandemic influenza vaccine preparation.

Acknowledgement

The authors and working group of the project including the National Center for Genetic Engineering and Biotechnology(BIOTEC of NSTDA), and the Health Systems Research Institute (HSRI, Thailand Ministry of Public Health) would like to express utmost thank to our project advisor, Dr. Somsak Chunharas, General Secretary of the Thai Health Foundation for his generosity and valuable advice for this project. We would also like to express our deepest gratitude to all contributors to this attempt including,

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- Vaccine Manufacturers, four in Thailand and four in China: Thai Red Cross, Government Pharmaceutical Organization (GPO), GPO-Merieux Biologicals,Co.Ltd, the Bureau of Veterinary Biologics; Shenzhen Neptunus Interlong Biotech Holding Co. Ltd., Shanghai Institute of Biological Product (SIBP), Sinovac Biotech Co. Ltd. and Hualan Biological Engineering Inc.). Many thank for their hospitalities and generosity in sharing their vaccine expertises and experiences during our visit. Also,we would like to thank Prof. Sumana Khomwilai and Pharmacist Surasak Nantawiriyakul for their kind help organizing the excellent and effective field-trip to China.
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Executive Summary

"National Strategies on Pandemic Influenza Vaccine Preparation for Thailand"

The 2004 unprecedented epidemics of highly pathogenic avian influenza H5N1 among poultry starting in Asia and later spreading to many regions has stimulated concerns on global pandemic influenza. Thai government has taken this threat seriously. In May 2005, Thailand has launched National Strategic Plan for Avian Influenza Control and Influenza Pandemic Preparedness in Thailand, 2005-2007. Research and development is a sub-component of one of seven preparing strategies. Four sub-committees were set up to take care of Pandemic influenza vaccine. One of these committees is responsible for conducting a feasibility analysis of pandemic influenza vaccine preparation.

A working group comprising researchers from various institutions has collaborated to carry out this study. Many approaches were applied for this study such as literature reviews, series of brainstorming, consultation meetings with internal and international experts, mapping facilities, and field visits. A mapping of facilities related to vaccine research and production both for humans and animals covering both private and public organizations indicated that universities had high capacity in research and development phase. The process of influenza vaccine production in pilot and industrial scale was not available locally. However, there are some facilities that can be modified to do some production.

The working group has proposed four strategies on pandemic influenza vaccine preparation as follow :

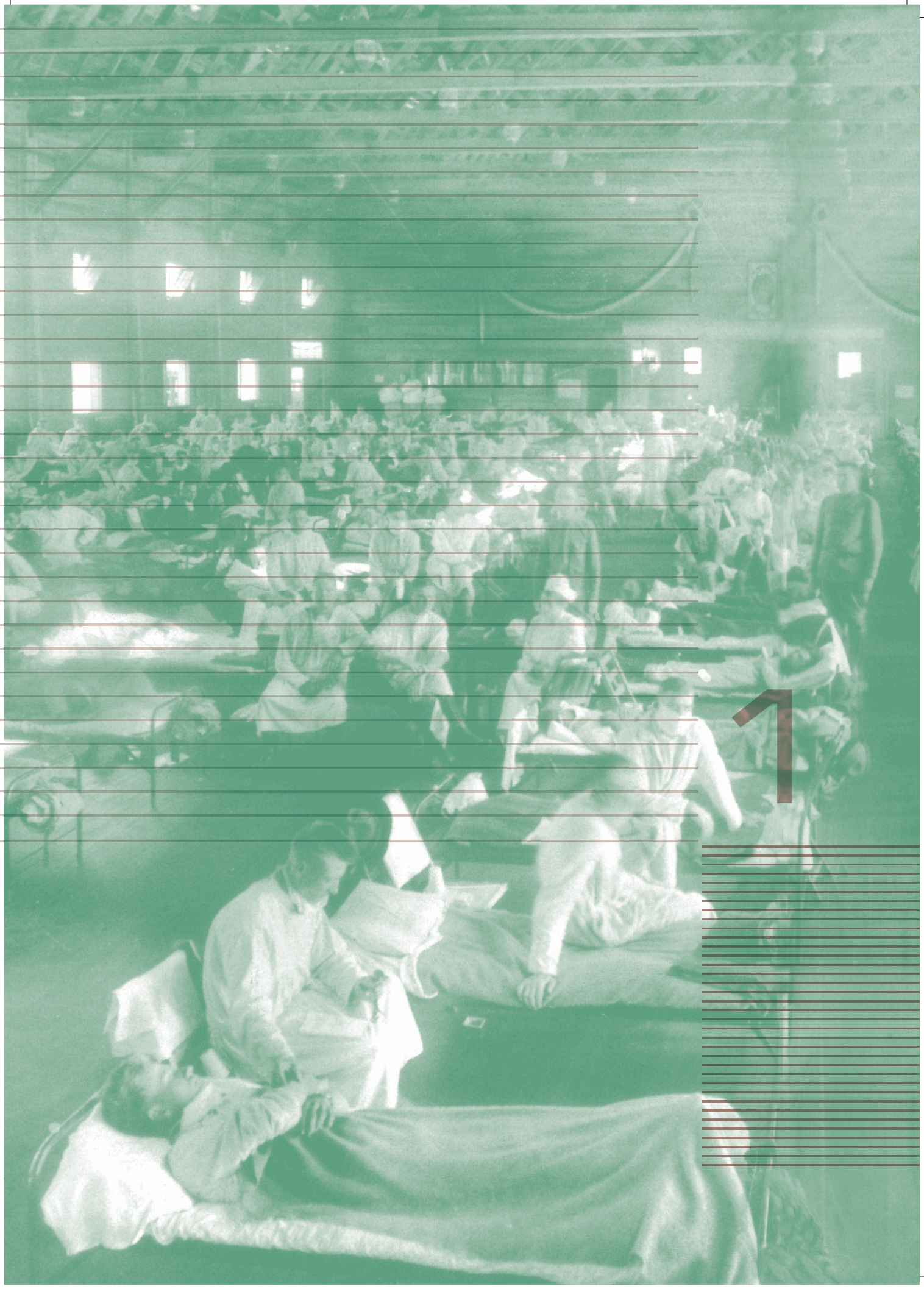
Strategy A: Purchasing finished vaccine
Strategy B: Filling vaccine from bulk stock
Strategy C: Modifying available vaccine plants
Strategy D: Building a new vaccine plant:

Strategy A and Strategy B are immediate preparing for pandemic by stockpiling. The coverage of these strategies is to cover frontline national protection. Strategy B was proposed to reduce the bottle-neck problem of vaccine production, to have some cost saving and to promote available filling capacity in the country. However, both strategies may not be applicable in pandemic situation with concerns on the mismatch issue between stockpiled strain and pandemic strain, the unavailability of vaccine supply globally, and the inability to cover all population.

Strategy C is on modification of Bureau of Veterinary Biologics (BVB) plant. Similar technology platform (egg-based technology), good infrastructure, skill and experience personnel, shortest time for start-up production, and limited investment are main reasons to propose this plant as a contingency plan for emergency production as global vaccine supply is limited. This plant needs upgrading on downstream process and detailed production process. The potential limitations of this strategy are bureaucratic will and perception, not technical issues. This option is valued for thorough evaluation as a security back-up while a new production plant is not available.

Strategy D on building a new vaccine plant is a long-term strategy for national security on pandemic influenza vaccine self-reliance. With available information and accessibility of technology, egg-based technology was proposed to be technology platform for this new production plant. Scale of production was proposed based on the number of doses needed during the pandemic situation, economy of investment scale, and economic evaluation of seasonal influenza vaccine. Issues on management, organization structure and staffing, main equipments of production process, crude estimation of investment and timeframe of establishing new plant were discussed. Critical success factors including continuous supply chain of raw material (eggs), research and development, human resource preparation, and preparation for technology transfer were proposed.

In additional to this, key issues on Good manufacturing Practice (GMP) and Fast Track Registration were herein discussed in detail. Lastly, the report was finalised on issue of the relationships among the four strategies. Strategy A on purchasing finished vaccine and Strategy B on filling the bulk stock was temporary strategy for short-term period. Strategy C was the plan for medium-term period while waiting for Strategy D to be ready to be long-term security tool for the country. However, after the new plant was available, Strategy C could also function as a back-up capacity to Strategy D to increase vaccine availability for the whole population of in emergency period. As none of the four strategies was a perfect strategy for all periods of time, therefore selecting the right combination of all four strategies was the critical point for Pandemic vaccine preparation. All strategies shall be implemented in proper timeframe with good coordination from relevant stakeholders in order to achieve mission on the better preparation for protecting Thai people from the coming Pandemics.



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Chapter 1 Introduction and Concepts for Developing Strategies

- Why we need to have influenza vaccine preparedness
- Seasonal influenza vaccine and pandemic influenza vaccine
- Influenza vaccine manufacturing infrastructure in Thailand
- Strategic framework for pandemic influenza vaccine preparedness

Chapter 1 Introduction and Concepts for Developing Strategies

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1.1 Why we need to have influenza vaccine preparedness

Influenza infection is caused by the influenza virus which is in the Orthomyoxiridae family. There are three genera of the influenza virus; influenza virus A, B and C. The influenza virus A commonly causes human illness with a possibility of aggressive symptoms. The clinical symptoms of influenza A infection include sudden high fever, headache, muscle aches and weakness. The influenza B is able to cause an endemic while influenza C infection often leads to asymptomatic or slight presence of clinical signs without transmissibility.

The influenza virus is a negative sense-single stranded RNA. The virus genome is composed of 8 segmented RNA codes for 10 proteins which are PB2, PB1, PA, HA, NP, NA, M1, M2, NS1, and NS2 (see Figure 1.1). Four antigenic proteins are on the virus surface comprising HA, NA, M and NP. Subtype classification is based on Hemagglutinin (HA or H) and Neuraminidase (NA or N) which can be divided into 16 and 9 types, respectively. Only viruses with H1, H2 and H3 strains have been reported to cause human illness. The H5 and H7 strains cause avian infection but recently caused an emergence of human infection. All types of influenza virus are able to infect water birds.

An epidemic of the influenza virus occurs in every 1-3 years as an endemic or in every 10 - 40 years as a pandemic. The occurrence is caused by an antigenic shift of the virus from the mixing of the viruses between those found in human and animals e.g. pigs, poultry and horses. Given that an emergence of the novel influenza virus which transmits from one to others that harms human in combination with lack of human immunity, the transmission would be intensified to infect various aged groups of the population possibly leading to a global pandemic.

Pandemic history and the future trend of influenza pandemic

There were three influenza pandemics in the past century, all of which were caused by the influenza virus A. Each pandemic resulted in great mortalities, social and economic loss. The greatest loss was due to the Spanish Flu (1918 - 1919) caused by the H1N1 strain resulting in 40 million deaths around the world, greater than the number of deaths of the World War I. The second pandemic occurred between 1957 and 1958 commonly known as Asian flu caused by the H2N2 strain. Around 100,000 deaths around the world were reported. The third pandemic was from 1968 to 1969 killing about 700,000 people. This third pandemic was assumed to have been brought about by an influenza virus infection in vertebrates.

For the next influenza pandemic, the World Health Organization classified the pandemic risk of influenza infection into 6 levels as follows:

Level 1: Infection in animals caused by a novel virus not infecting human
Level 2: No human infection but possible to infect human
Level 3: Human infection but no human-to-human transmission
Level 4: Limited human-to-human transmission
Level 5: Increased human-to-human transmission
Level 6: Pandemic

The global situation of H5N1 infection is currently at level 3; however, Indonesia's situation is at level 4 based on a report on limited human-to-human infection. Due to 30 years intermittence of the pandemic, the subtype H5N1 transmission in poultry and limited poultry-to-human infection for the past 2-3 years, there is a great concern over a future pandemic possibility. Due to virus ability to mutate through an antigenic drift mechanism, an influenza vaccine formula must be annually adjusted for effective protection. A vaccine with inappropriate formula adjustment may not induce human immunity to the altered virus whose HA has already changed. In addition, a mutation of the influenza virus through antigenic shift respective to gene exchanges found in various types of virus could boost its potential for global pandemic within several months. With no human immunity to the new virus, the fourth pandemic could happen at global level and at equal chance of infection to all aged groups.

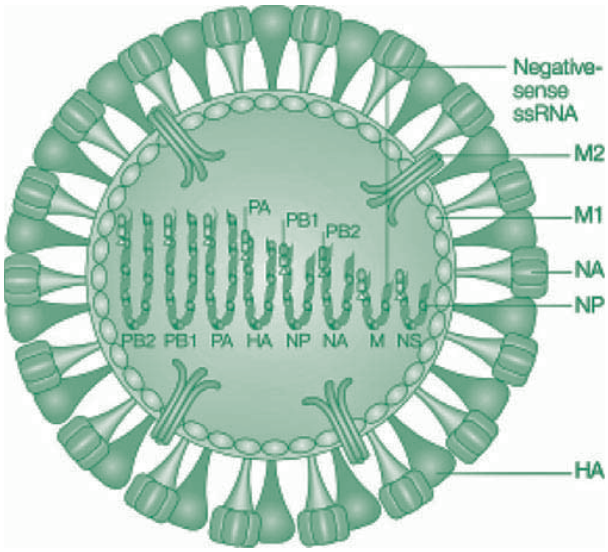

Figure 1.1: Cross section of the influenza virus showing its external antigen and 8 segmented genomes

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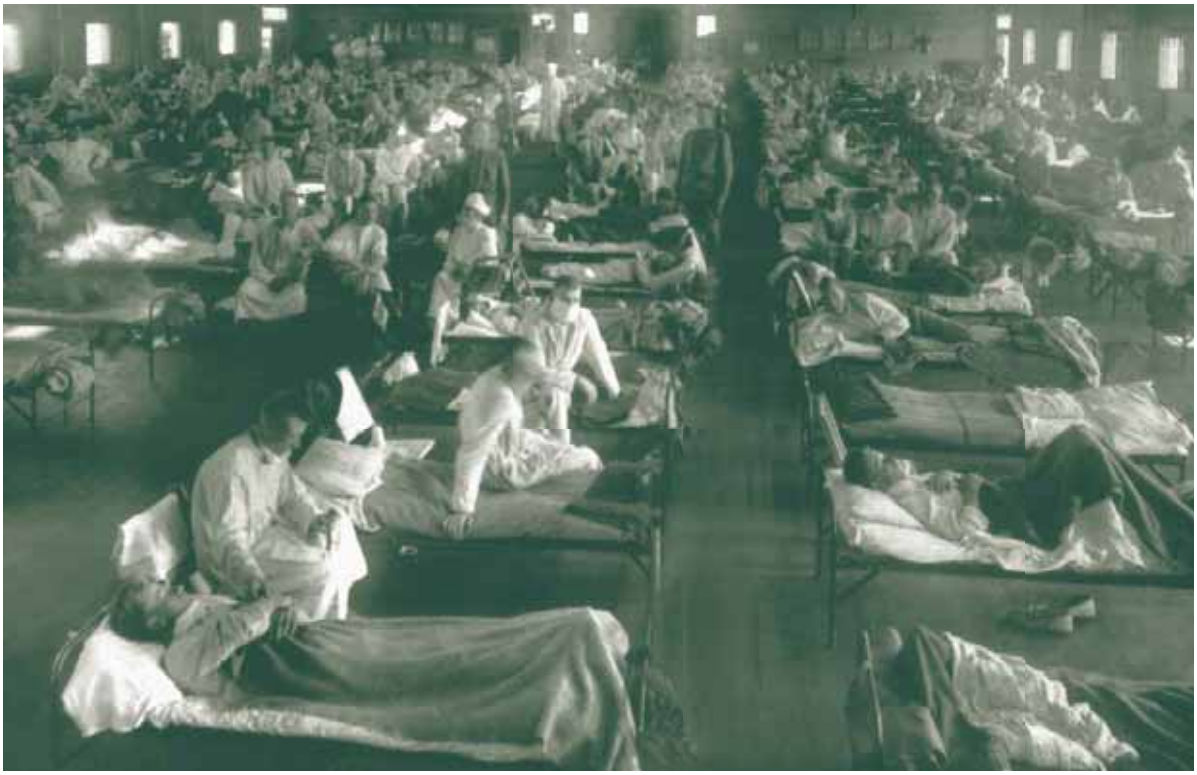

Figure 1.2: Spanish flu (1918 - 1919) causing 40 million fatalities around the world

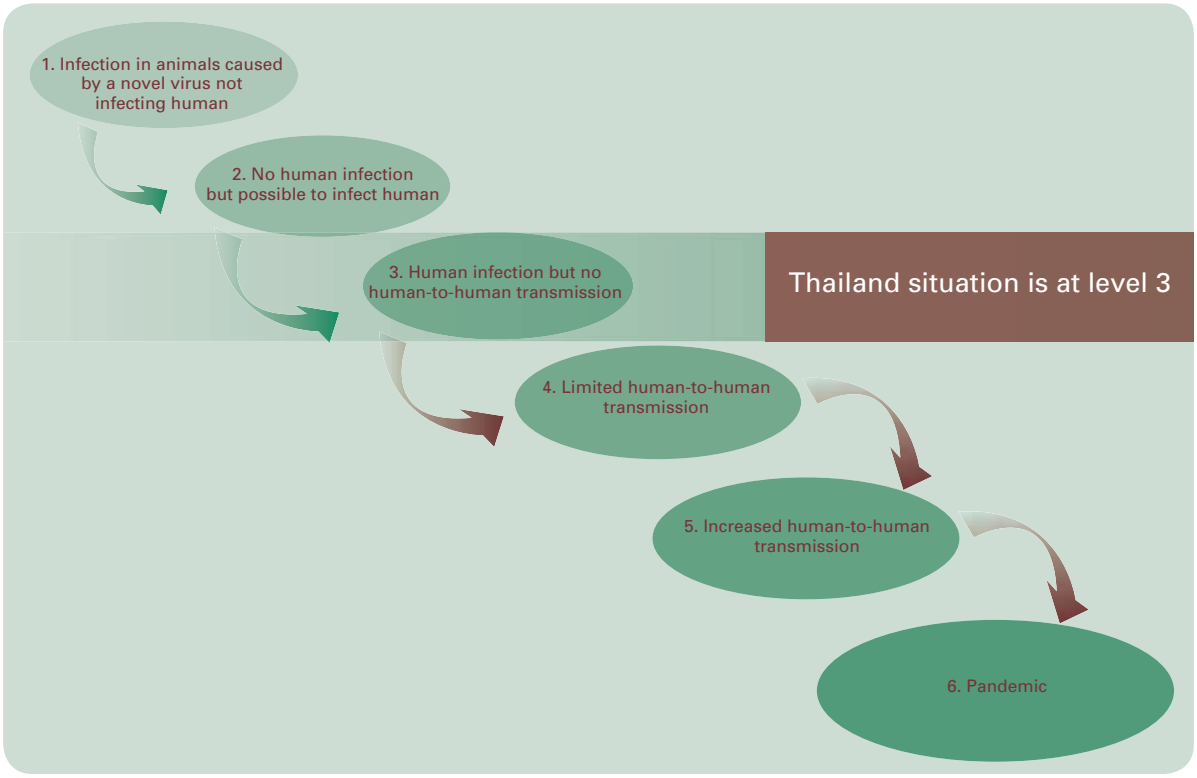

Figure 1.3: Pandemic risk levels of influenza virus infection (from http://www.who.int), and situation is at level 3

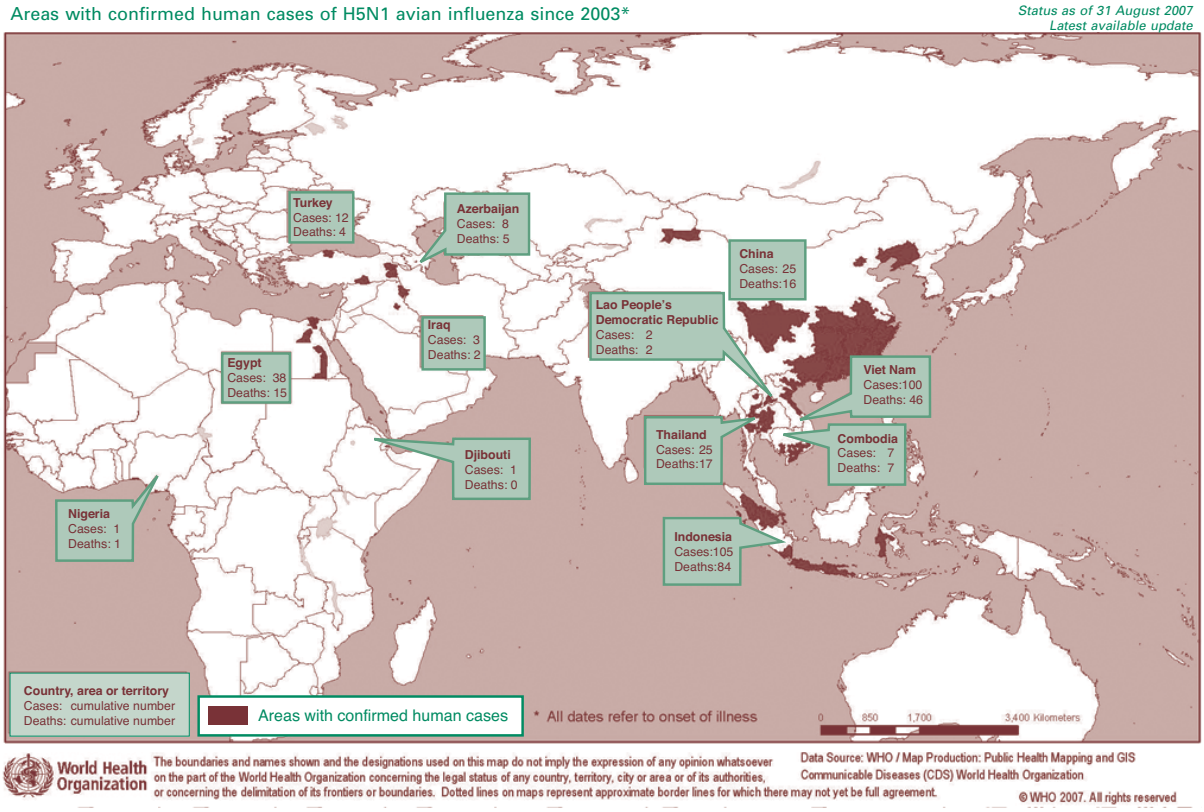

Figure 1.4: Global map reporting H5N1 infection in human since 2003 - 29 August 2007 from http://www.who.int)

Projection of social and economic impacts due to a pandemic of the influenza virus

There would be considerable social and economic impacts due to a pandemic, mostly resulting from the great number of morbidities and mortalities and human resource shortage as a consequence. An epidemiological study on the pandemic projection came out with over 30 million deaths for a 6-month long pandemic. The modern convenience of mass transportation would also aggravate the pandemic. Given insufficient stockpiles of vaccines, antiviral drugs, medical equipment and health personnel some of whom might be dead or incapacitated by illness, a massive loss to the global economy would be reachable. The WHO has warned every country to seriously undertake preparedness for a future pandemic.

In Thailand, the pandemic projection based on a least loss scenario yielded around 6,500,000 (10% of the total population) infected cases with 65,000 mortalities (1%) (Chunsuthiwat, 2006). Comparatively, the SARS (Severe Acute Respiratory Syndrome) pandemic in 2003 in China, Vietnam, Hong Kong and Toronto, Canada caused around 8,000 morbidities and 800 mortalities and made business disruptions in many sectors e.g. tourism, transportation, hotels and food with estimated loss of 18 billion US dollars or about 0.6% of the GDP (Global Development Finance, Development of Global Financial Sector).

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A study of the Asian Development Bank (ADB) based on the best scenario of influenza pandemic indicated that the morbidity and mortality rates would be about 20% and 0.5% of the population, respectively (Asian Development Bank, 2006). The economic loss in Asia would be between 110 and 300 billion US dollars and risk of economic stagnation which would also reduce global market value by 14%, equal to 2.5 trillion US dollars. The Fiscal Policy Office, Thailand, an analysis on Thai economic impacts of an avian flu epidemic with respect to two categories: animal-to-human infection and human-to-human infection. The assumptions were based on the 2005 value of chicken exportation reported by the Thai Association of Chicken Exportation and the Thai tourism impact due to human-to-human transmission of SARS epidemic in 2003. The impacts are shown in Table 1.1.

Table 1.1 Overall economic impacts in Thailand (Fiscal Policy Office, 2005)

Impact	Category I (2005)	Category II (2005)
1. Economic expansion rate	0.2 - 0.25% reduction	0.25 - 0.35% reduction
2. Domestic chicken consumption expansion	Stagnation	Similar to that of category I
3. Chicken exportation	Exportation of manufactured chicken instead of frozen one	Similar to that of category I
4. Service sector (tourism)	Not affected numbers similar to SARS situation	Reduced tourist
5. Net financial support (financial aid and compensation)	Financial aid from the government's contingency fund	Similar to that of category I

The Avian and Human Pandemic Influenza - Economic and Social Impacts forum organized by World Bank at the WHO (8 November 2005) addressed that since there were not enough studies on impacts of global pandemics, the US study of socio-economic impacts caused by the pandemic of influenza virus in 1999 could be taken as a reference (with reference to epidemiological data of other pandemics after World War II). With this approach, there would be about 1000-2000 fatalities in the US and an economic loss of 100-200 trillion US dollars (using the 2004 US dollar value). Both social and economic loss value in the US would reach 71.3-166.5 trillion US dollars. In consideration of all developed countries impacts, the loss value would be about 550 trillion US dollars which would be less than the loss incurred in all developing countries where greater mortalities and morbidities would be tangible because of their poor public health infrastructures.

The International Health Policy Office, Thailand, expected that if an influenza pandemic occurs in Thailand during 2008-2010, the Thai medical cost would be 4.4-47.2 billion Baht. The loss estimation excluded indirect impact on domestic and international tourism impact, social impact, mortalities in young aged group and elderly including increasing chronic illness. Such expected impacts have an implication for Thailand to undertake pandemic preparedness and ensure ample influenza vaccine for domestic use (Tangcharoensathien, 2005).

Pandemic preparedness and prevention measures

Realizing the peril of influenza pandemic, the WHO developed the WHO Global Influenza Preparedness Plan in order to minimize or prevent consequent impacts. Currently, many countries including Thailand have their national strategic plans and measures for influenza pandemic.

Thailand has had national strategic plan for avian flu control and national strategic plan for influenza pandemic for 2005 - 2007. The plan includes activity and financial plans which need the cooperation of various agencies. This preparedness plan is composed of:

1. Strategy for strengthen influenza surveillance system
2. Strategy for preparedness of essential medical supplies and equipment
3. Strategy for preparedness for Pandemic Responses
4. Strategy for public relation and education,
5. Strategy for development of sustainable and integrated management systems

The influenza vaccine is the most important and effective tool to prevent infection concerning a strategy for preparing the necessary medical supplies. However, the pandemic influenza vaccine is in fact different from the seasonal influenza vaccine because its production can only be started once the virus causing the influenza is identified. The vaccine manufacturing usually takes at least six months. Hence, the vaccine would not be available in the initial pandemic phase in which a variety of public health measures and limited and expensive antiviral drug are required. To effectively cope with the possible pandemic, the increasing preparedness of the vaccine and antiviral drugs must be planned.

Roles of an influenza vaccine for curbing pandemic

Immunization by an influenza vaccine is the best means for prevention, and mortality and morbidity reduction especially in risk groups e.g. children, patients with chronic conditions and the elderly. Additional to preventing annual loss of seasonal infection, influenza vaccine will play an important role in controlling disease spreading and decreasing impacts of the coming pandemic. Currently, World Health Organization has promoted the use of seasonal influenza vaccine in order to strengthen the vaccine distributing system, to expand influenza vaccine production, and also to

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The seasonal influenza vaccine is produced annually according to forecasted circulating strains. Each dose of influenza vaccine is composed of three strains of influenza virus (trivalaent vaccine). And the vaccine is mostly manufactured by developed countries in European and North America regions. Their overall current capacity production is about 350 million doses/year which would be insufficient if considering the global population of 6.5 billion.

1.2 Seasonal influenza vaccine and pandemic influenza vaccine

1.2.1 Current situation of technological development of influenza vaccines

The seasonal influenza vaccine has been used for more than 60 years. It has high safety to humans only causing muscle ache at injection site for about 1-2 days. Because the vaccine is mostly produced in eggs, it is not recommended for those allergic to egg proteins. The antigenic drift of the influenza virus causes an annual change of the virus strain. The effectiveness of the influenza vaccine ranges between 70-80% (in a possible range of 50-95%). The more well-matched the virus strain contained in the vaccine against the strain causing the epidemic, the more effective the vaccine is. Its effectiveness is also subject to the vaccine recipient's age and immunity level.

High risk group populations are normally suggested for seasonal influenza vaccine immunization. The short lived immunity given by the seasonal vaccine prevents a chance of virus mixtures between human influenza virus and avian influenza virus. Such a mixture could result in a novel virus by antigenic shift and may cause a pandemic. Thus, immunization with a seasonal influenza vaccine could prevent the seasonal flu and the creation of new strains of pandemic influenza viruses. However, it should be emphasized that the seasonal influenza vaccine itself cannot prevent infections of avian virus or future pandemic of the influenza virus because the virus stain of the vaccine is different from both.

A report on H5N1 infection to humans in Hong Kong in 1996 addressed a human infection via poultry interface without a mediator e.g. pig. This suggested a possibility of a pandemic of avian influenza since humans lack or have little immunity against it. Vaccine prototypes from the virus isolated from the infected patients in Vietnam and Hong Kong have been developed.

In January 2004, the H5N1 human infection was reported in Vietnam. The virus was isolated by laboratories in Hong Kong and Japan for studying its genes and antigens. The WHO emphasized that, with the cooperation from all agencies and laboratories involved together with WHO guidelines, the prototype virus for vaccine manufacturing would be available within four weeks after an outbreak.

In April 2004, the WHO announced the prototype vaccine of H5N1 was made and ready for clinical trials. Only 2 corporations, Aventis Pasteur (Sanofi Pasteur at present) and Chiron asked for seed virus of such vaccine to produce a small scale vaccine ready for clinical trials.

In May 2005, H5N1 was isolated from infected patients and animals. Its antigens and genes which are appropriately used for vaccine production were determined by the WHO. The prototype viruses, A/Vietnam/1194/04, A/Vietnam/1203/04 and A/Hongkong/213/03, were prepared by reverse genetic technique. To encourage the H5N1 studies for vaccine production, the WHO affirmed that the use of reverse genetic process in research would not override intellectual property rights. However, this technique could not be used for commercial manufacturing.

Vaccine manufacturers are able to acquire the seed vaccine for production from the WHO Global Influenza Program or institutions as follows:

- National Institute for Biological Standards and Control in the UK
- CDC in US
- St. Jude Children's Research Hospital in US

Recently, in the US, Sanofi Pasteur has been contracted to manufacture H5N1 vaccine. The vaccine was found to induce human immunity in volunteers at quantity of 90 micrograms of antigens. Two injections are required possibly because of the fact that humans have never exposed to avian influenza virus before.

1.2.2 Types of vaccines:

There are 2 types of influenza vaccine; inactivated and live-attenuated influenza vaccine.

1.2.2.1 Inactivated influenza vaccine (IIV)

Inactivated influenza vaccine is the most globally distributed seasonal vaccine (90%). The vaccine is composed of inactivated virus and each dose contains three influenza virus stains; influenza A (H3N2), influenza A (H1N1) and influenza B at 15 ug each strain. Inactivated vaccine can be produced by four approaches as follows:

- **Whole-cell influenza vaccine** is developed by inactivating the whole virus, but has no longer been produced since 2001 due to its side effects,
- **Subvirion (split virion)** vaccine is composed of various components of the virus produced by fragmenting the virus,
- **Purified surface-antigen vaccine** is produced by purifying Haemagglutinin (H) and Neuraminidase (N) surface antigens of influenza virus for vaccine purpose,
- **Virosomal vaccine** is produced by removing the viral genetic materials and then using only its envelope. The envelope, called a virosome, is incapable of reproducing or infecting cells but it is able to induce immunity. It is also reported to be used as an adjuvant.

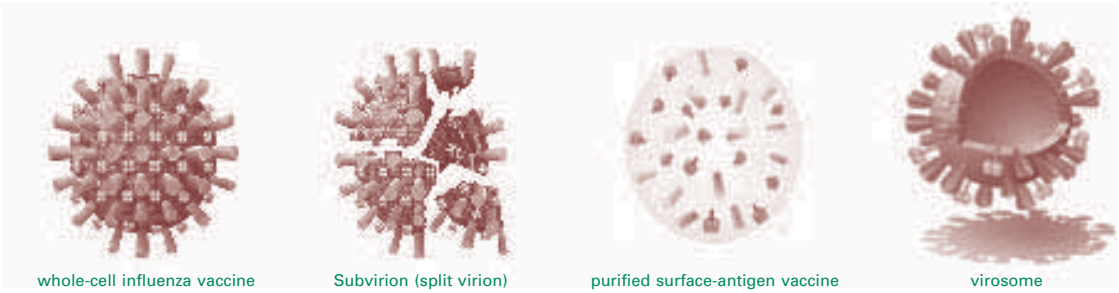

Figure 1.5: Inactivated Influenza vaccine

1.2.2.2 Live-attenuated influenza vaccine (LAIV)

Live-attenuated influenza vaccine is the vaccine developed to alleviate an inconvenience of the inactivated vaccine which needs 1-2 injections for immunizations per year. The LAIV is administered intranasally by imitating a natural infection of the influenza virus. The vaccine contains three Influenga virus strains similar to those of the inactivated influenza vaccine. However, they are cold-adapted strains (unable to reproduce at high temperature e.g. at the lower respiratory tract) and said to be live-attenuated strains.

LAIV has been used in Russia for more than 50 years and it is marketed in the US under the brand name "Flumist®" by MedImmune Corporation. The LAIV has not currently been marketed in Thailand. The advanatages and disadvantages of IIV and LAIV is presented in Table 1.2.

Table 1.2: Comparison of inactivated and live-attenuated influenza vaccine

Vaccine types	Advantages	Disadvantages
IIV	1. 70-80 % effectiveness 2. High safety	1. Not applicable to those allergic to egg proteins
LAIV	1. Convenient administration into body 2. Batch productivity 30% higher than that of inactivated vaccine 3. high local immunity (local IgA) 4. Vaccine effectiveness lasting longer than 1 year	1. High price 2. Applicable to people aged between 5 to 49 years 3. Not recommended for those with low or lack of immunity caused by any illness

1.2.3 Influenza vaccine manufacturing

After analysis the global pool of influenza viruses, the scientists forecast the dominant strains of next influenza season. Then the selected strains are modified to be the appropriate seed for influenza vaccine production. In influenza vaccine plant the seed viruses reproduce in appropriate host cells e.g. hatching eggs or mammal cells. All the activities involved in virus reproduction are said to be in the upstream process which will be followed by the downstream process regarding vaccine purification, formulation and packaging. Both upstream downstream processes take about 3 months. After the downstream process, the vaccine will be tested for the lot release, which takes 2-3 months (see Figure 1.6).

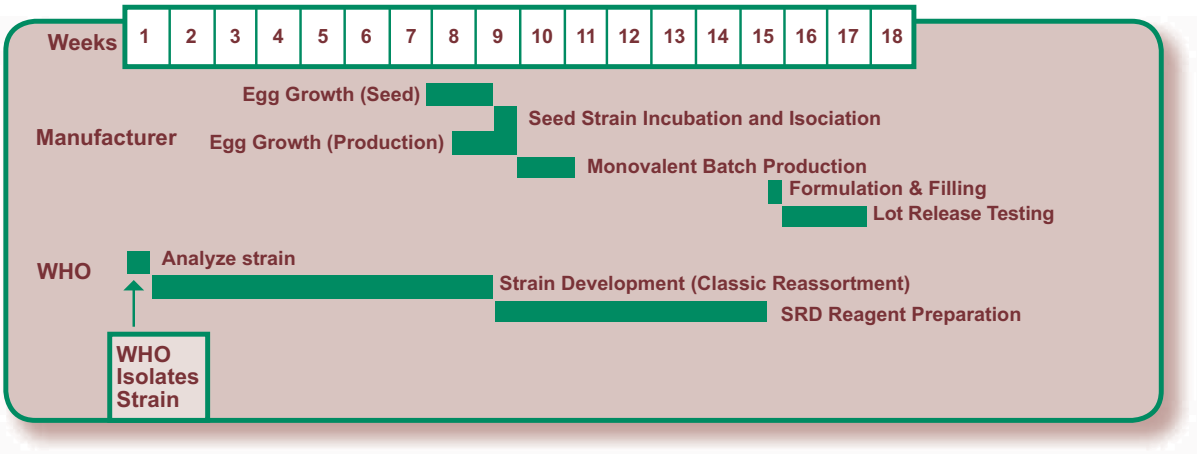

Figure 1.6: Egg-based manufacturing of influenza vaccine and production timeline

Both seasonal and pandemic influenza vaccine are manufactured by the same process. Thus, the production capability of seasonal influenza vaccine also indicates that of avian influenza vaccine in the pandemic situation.

1.2.3.1 Seed lot production

The virus strains, provided by the WHO, are used for producing seed lots in chicken eggs. Many production passages are undertaken to acquire sufficient virus seed for actual manufacturing. The produced virus titer is determined and seed lot release testing performed. Due to the fact that a spread of avian influenza (H5N1) has been caused by many subtypes, there is a certain risk of preparing the pandemic influenza vaccine in advance. The manufactured vaccine may be incompatible of subtypes to the causing subtype. In addition, the HA antigen of H5N1 has lower effectiveness than the HA antigen of H1N1 and H3N2 on account of inducing varying human immunity. Therefore, study on the production of effective vaccine is necessary to ensure timely response to a pandemic.

In Thailand, the Faculty of Medicine, Siriraj Hospital, Mahidol University, is now able to produce the seed virus for both inactivated vaccine and attenuated vaccine (cold adapted seed strain) by reverse genetics method. If a pandemic should occur in Thailand, the seed virus subtype causing the national pandemic can be prepared. In addition, the NIBSC (National Institute for Biological Standards and Control) is another institution able to provide the seed virus.

1.2.3.2 Reproduction of virus or its subunit (upstream process)

The current production of the virus or its subunit for vaccine production is based on 3 technologies;

1) Egg-based technology
2) Cell-based technology
3) Alternative technologies e.g. recombinant HA vaccine using the Baculovirus Expression Insect Cell System, M2: Universal vaccine, DNA-based vaccine

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1) Egg-based technology

Egg-based technology has been employed for over 50 years. This technology is reliable in terms of the quality of the manufactured vaccine. The vaccine production starts with an inoculation of the seed virus into a hatching egg aged between 9-11 days. The inoculation can be manually or carried out by an automatic machine. The egg is then incubated for 3 days and checked by light. If the egg remains in good condition, it will be cooled down to 2-8^{o}C to kill the embryo. The allantoic fluid of the infected egg containing virus will be harvested (see Figure 1.7). The egg-based technology is well established and influenza vaccine manufacturers are familiar with the process. However, the technique relies heavily on the egg supply. In the case of avian influenza pandemic in which most of poultry will be infected, there might be a shortage in egg supply for vaccine manufacturing.

2) Cell-based technology

Most vaccine manufacturers view that virus reproduction by cell culture is more appropriate for the future. After culturing the cell, the cell will be inoculated by the seed virus to multiply in the cell. The whole process takes about 37 days (see Figure 1.8).

Cell lines used for producing seasonal influenza vaccine are;

1. MDCK (Madin-Darby canine kidney) cells are able to produce large number of virus. This cell line is allowed for vaccine manufacturing in the Netherlands but prohibited in the US as to concern over a possibility to cause human tumor,
2. Vero (African green monkey kidney) cells are already approved on safety but yielding little virus number,
3. PerC.6 (Human fetal retinoblast) cells are under the license of Crucell Corporation.

Cell culture technology supports large scale virus production without the barrier of host supply as found in the egg-based technology. A limitation of this technology is a lack of certain information on cells and culture methods suitable for producing the influenza virus. The current vaccine based on this technique is either in experimental phase or clinical trials. The cell-based vaccine has not yet been marketed.

In Thailand, the cell-based technology is in experimental stage. The accessibility to the technology to promote a large scale manufacturing is really limited. For technology transfer, it is estimated that over 160 million US dollars may be required irrespective of other additional costs and royalty fees paid when the vaccine hits the market. A country interested in getting such a technology must be a previous customer of the technology owner at a purchase amount over 10 million doses per year in continuity. Only 300,000 - 400,000 doses of the influenza vaccine are

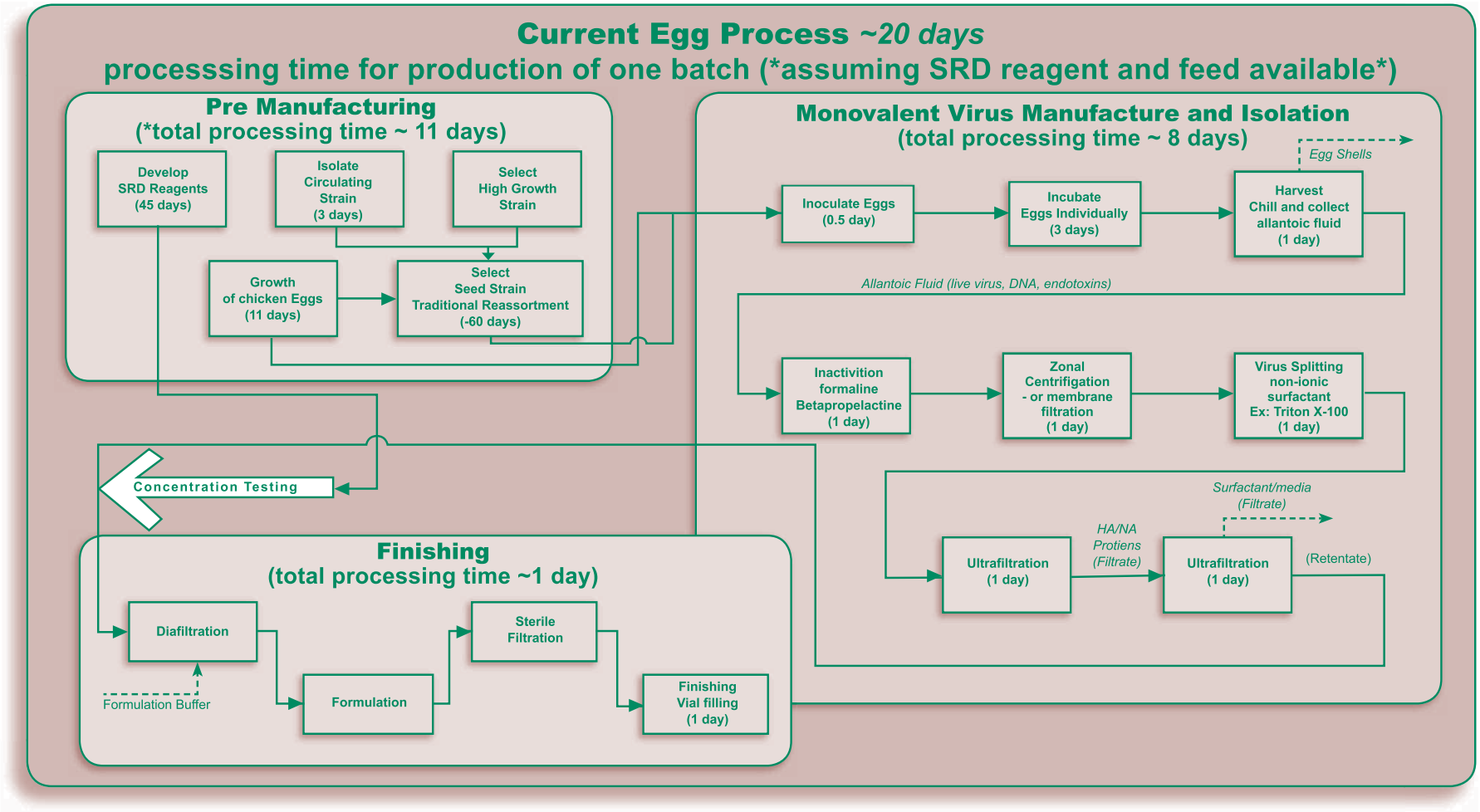

Figure 1.7: Influenza vaccine production with egg-based technology

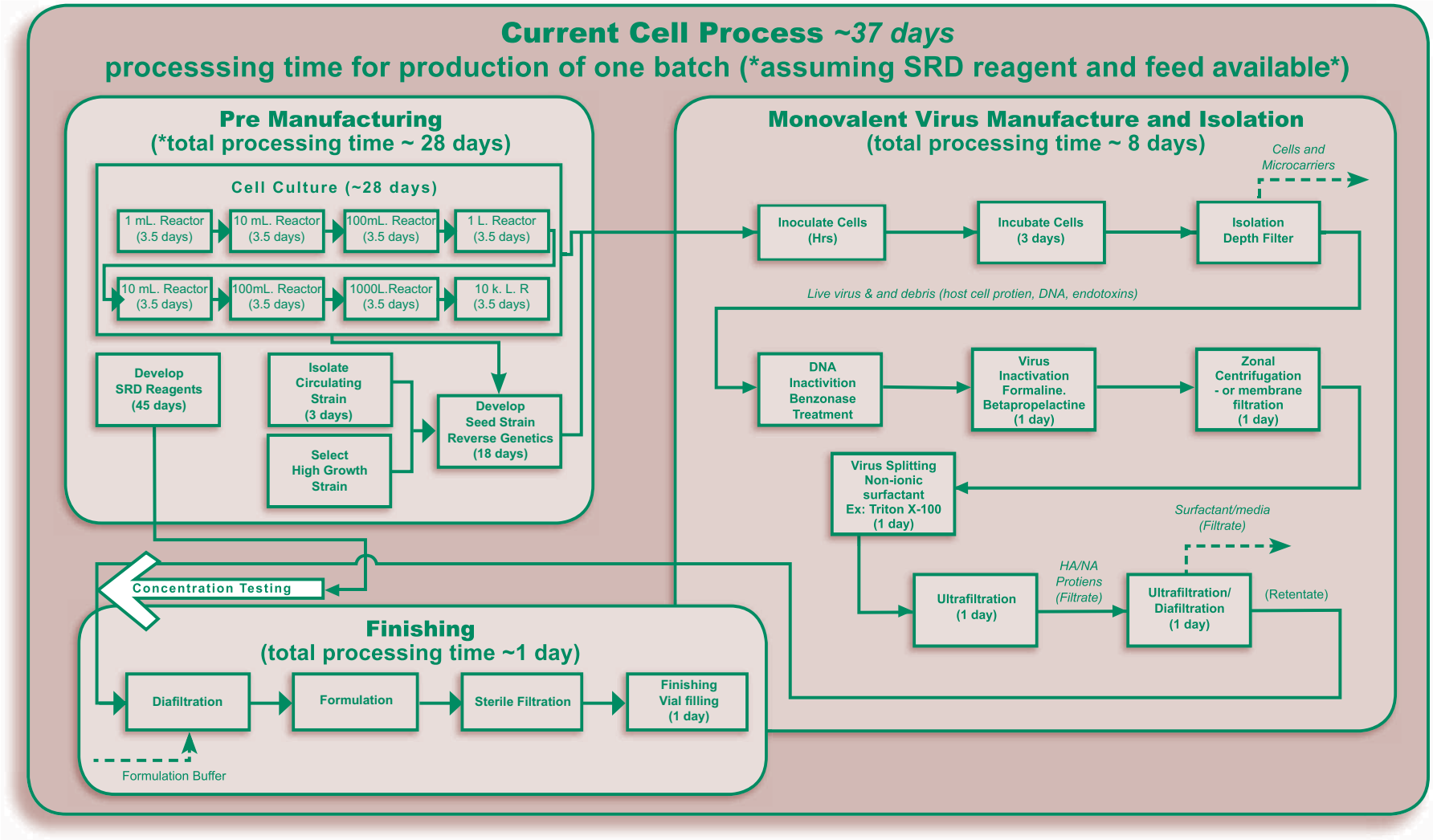

Figure 1.8: Influenza vaccine production with cell-based technology

3) Alternative technology: Baculovirus expression insect cell system

This technology is used to produce only the protein antigen of the virus for example hemagglutinin or neuraminidase. Genetic engineering is used to clone the influenza gene into the baculovirus genome. The engineered baculovirus will then be taken to infect the baculovirus hosts, insect cells. The infected cells will reproduce recombinant protein of the influenza virus strains that were subjected to genetic engineered. The recombinant protein will be used for vaccine manufacturing (see Figure 1.9 and Annex 1).

This technique supports safety to the operation staff and environment because of no direct contact with the influenza virus. Hence, the design of the vaccine plant is normally consistent with the general standards of pharmaceutical manufacturing. An important concern over this technology is the safety and quality of the vaccine produced through insect cells on account of little information of the technology, no vaccine license registration in Thailand and inaccessibility to the technology at a manufacturing scale. A US company, Protein Sciences, is the owner of the technology under the brand "FluBlok". The stage of the vaccine production is in the registration stage in the US. There is also a technology transfer agreement between Protein Sciences and UMN, Japan.

The three technologies are compared as shown in Table 1.3.

Thailand presently does not have any influenza vaccine manufacturing plant. There are limited production of some vaccines used for human both upstream and downstream process by the GPO (Government Pharmaceutical Organization) and the Thai Red Cross. However, the processes used are different from the manufacturing of influenza vaccine.

A more similar process to influenza vaccine production using egg-based technology is performed at the vaccine center of Bureau of Veterinary Biologics (BVB), Department of Livestock Development for animal vaccine manufacturing (New Castle vaccine). The cell-based and baculovirus based technology are carried out at some Thai academic institutions and the Ministry of Public Health's research centers but not yet reaching a pilot and industrial scale.

1.2.3.3 Downstream process

The downstream process determines what types of vaccine would be produced e.g. inactivated vaccine, whole cell vaccine, split vaccine or subunit vaccine (see Figure 1.10). The downstream process involves virus inactivation, purification of whole virus particle or subunit, virus concentration, filter sterilization, formulation by addition of adjuvant and packaging. Numbers of steps involved in downstream processes should be kept to a minimum for each vaccine type since there is certain loss of virus yield at each step.

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Table 1.3: Comparison of influenza vaccine production technologies

Technology	Advantages	Disadvantages
Egg-based technology	1. higher virus number than that of cell-based technology 2. no external antigens 3. no carcinogens 4. good antigenicity vaccine	1. technique is limited only for virus strains able to grow in eggs 2. requirement of eggs supplies and manpower used 3. possible changes of virus HA protein 4. side effects to those allergic to egg proteins
Cell-based technology	1. ease of culturing the cells 2. ease of controlling the production and expanding the production scale 3. elimination of the use of thimerosol 4. good antigenicity vaccine	1. low number of virus produced 2. risk of increasing adventitious agents due to serial passages of culturing 3. requirement of microcarrier or equipment facilitating cell attachment with the use of trypsin and FBS 4. possibility to cause tumors by agents produced from MDCK cells
Baculovirus-based technology	1. baculovirus and insect cells are safe to human, no BSL3 system required 2. purified recombinant proteins are harmless to those allergic to egg proteins 3. ease of production of recombinant protein of virus as subunit vaccine rather than the whole virus particle production 4. possibility of scale up to industrial scale as this process has been used to produce other recombinant proteins, 5. no genetic heterogeneity 6. inactivation process is not required (no chemical added)	1. high price of insect cell medium (the same as cell based technology) 2. possibility of insect cells post translation modification different from mammalian cellsñ however, clinical trials on the recombinant influenza vaccine showed good immunogenicity.

Live attenuated influenza vaccine

The downstream process of the live attenuated influenza vaccine is not complicated. The quantity of vaccine produced is therefore higher than that of the inactivated influenza vaccine. The process starts with the harvesting of allontoic fluid followed by a low speed centrifugation as a clarification process. An additional purification of the vaccine may be performed by ultracentrifugation for separation of egg proteins from virus. Sterile filtration is required prior to adding the stabilizer and packaging. It is reported that one hatching egg can produce 30-100 doses of the live attenuated influenza vaccine compared with inactivated influenza vaccine for which 0.5-2 doses are produced for each hatching egg used.

Inactivated influenza vaccine

The manufacturing of the inactivated influenza vaccine from allantoic fluid starts with concentration of the virus by methods such as filtration using cross flow filtration to concentrate the vaccine (see Figure 1.7 and 1.10). Then, zonal ultracentrifugation is commonly used for purification of virus from egg proteins. Addition of inactivation agents such as ß-propiolactone or formalin is included in the process. The consequent steps are different as to types of vaccine needed. For inactivated split vaccine type, chemicals e.g. Triton-X100 are used for splitting the virus. Eliminating the contaminating substances such as using diafiltration method for medium exchange is therefore necessary in the following steps.

For subunits vaccine, viral antigens (hemagglutinin (HA) and neuraminidase (NA)), are further purified from other protein components by Chromatographic methods e.g. gel filtration or ion exchange chromatography. The last step is sterile filtration to get the vaccine ready for packaging. The whole process takes 2-3 days. Sequences and techniques for each process may be different among manufacturers. All batches of the vaccine must be tested to ensure their virus inactivation and quality.

An important component in inactivated vaccines is the adjuvant. Adjuvants are been used to improve immune response to the vaccine. Thus, antigen quantity (dose level) may be reduced when some adjuvant is included. Two adjuvants which have been proved safe for influenza vaccine are aluminum salts and MF59 (oil-in-water emulsion).

The aluminum salts works better with seasonal influenza vaccine. However, it does not minimize the H5N1 antigen dose unless higher amounts of aluminum salts are used. MF59 induces antibodies that last longer than the aluminum salt and promote cross neutralization of pathogens. However, the MF59 is patented.

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Some alternative adjuvants have also been developed e.g. AS03 owned by GSK. AS03 is reported to potentially reduce the dose antigen as much as 30 times (DCVM 2006). Access to new adjuvants is limited due to their patent availability. The WHO has established a working group to explore the advujant issue. However, it is in the early phase of research.

When comparing the downstream process between the virus produced from egg-based technology and cell-based technology, the later contains less contamination than that in the egg. The lower complexity of the virus purification process is then evident for cell-based technology. The whole process of the cell-based virus production is shown in Figure 1.8. The final forms of the vaccine can be either the whole, split or subunit vaccine.

The virus antigen produced from Baculovirus and insect cells are the recombinant HA protein and recombinant NA protein of influenza virus. The recombinant protein is harvested from the insect cell culture and then purified by methods such as chromatography to get the subunit protein of the virus (see Figure 1.9). As the vaccine contains the protein (not the whole virus), the virus inactivation process is not necessary.

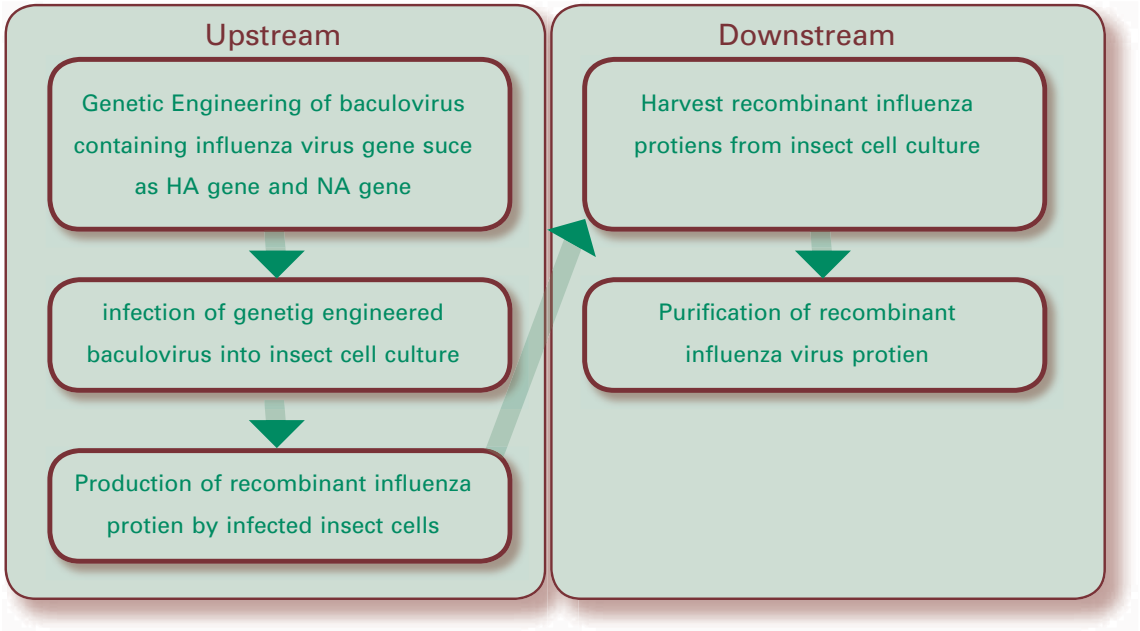

Figure 1.9: Process of producing the protein antigen of influenza virus by using Baculovirus Expression insect cell system

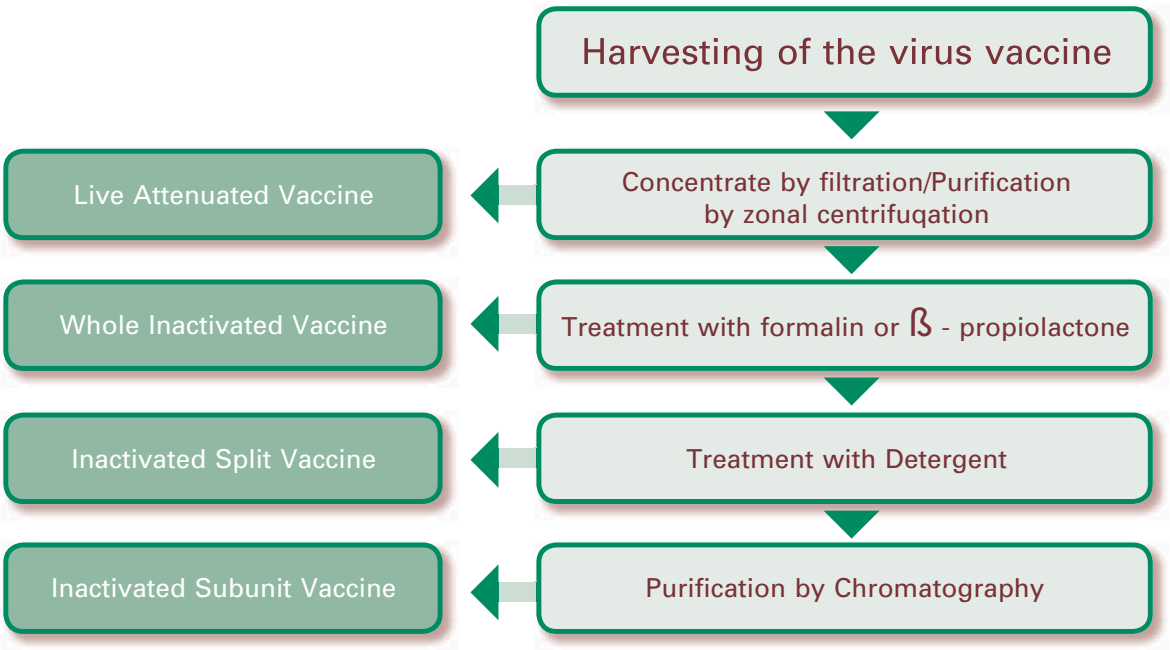

Figure 1.10: Downstream process of Influenza vaccine

1.2.3.4 Vaccine testing

Standard tests on the influenza vaccine is usually a measurement of the Haemagglutinin (HA content) by Single Radial Immunodiffusion (SRD) assay in which the reference HA antigen is prepared and determined by the National Control Laboratory (NCL). It is reported that the reference HA antigen produced by the chicken egg is only suitable for testing the HA content of the egg-based vaccine. The testing on the cell-based vaccine needs the WHO's recommendation. Likewise, the HA measurement of the pandemic vaccine requires support from the WHO and NCL because the manufacturers may not have the reference HA antigen for testing. As the adjuvant contained in the vaccine may affect the SRD testing, the HA measurement may be performed prior to adding the adjuvant or using the other direct measurement or testing of the immunogenicity in animals.

Immunogenicity test

Effectiveness and safety assessment of the vaccine requires the clinical trials. The clinical trials will determine appropriate administration routes and antigen quantity for each dosage. The assessment also includes a testing of the human immunity level.

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Haemagglutination inhibition (HI) antibody assay generally tests the vaccine effecacy on stimulation of human immunity. An antibody specific to the influenza HA antigen in serum is measured after immunization. Effective influenza vaccines must stimulate human immunity to reach an HI antibody titer ⩾ 40 which should also be considered as standard criteria for a pandemic vaccine. In addition, sero-conversion rate must reach four times higher after immunization and attention should also be paid to the geometric mean titer (GMT) of the samples.

The HI titer from each laboratory may be varied due to virus strains, types and sources of red blood cells, etc. Some agents may be contaminated with inhibitors. Hence, validation of haemagglutination inhibition (HI) antibody assay must be undertaken. Other immunity tests such as microneutralization assay could also be employed in parallel with HI assay.

Stability testing

The stability testing on the vaccine while stored under the recommended temperature is very important. The vaccine manufacturer has to prove at least three lots of vaccine have consistent shelf life. Division of Biological products under Department of Medical Sciences, Thailand's NCL, is generally the responsible unit for the stability test. Generally, an influenza vaccine lasts for one year from the manufacturing date with respect to the possibility of a change in the virus strain in the following year. In some countries, the HA content level which is measured on the expiry date must be shown on the vaccine label to ensure its stability.

1.3 Influenza vaccine manufacturing infrastructure in Thailand

It is expected that the industrial countries where most influenza vaccine plants are located would prohibit the vaccine exportation until certain that their vaccine stockpiles were sufficient for domestic use. Thailand's neighboring countries e.g. Vietnam, Indonesia and India are now developing their own influenza vaccine plants. To prepare for a pandemic influenza situation in Thailand where there is no pandemic vaccine for Thais, the influenza vaccine manufacturing in Thailand should be encouraged.

The development of vaccine production can be divided into 3 levels: the experimental level, semi-experimental level and the manufacturing level.

According to the mapping of Thailand's vaccine capacity, many Thai universities and research groups are currently carrying out research and development of the influenza vaccine for both poultry and humans at the experimental level. The semi-and manufacturing level do not yet exist in Thailand. However, in an emergency situation, there are some vaccine manufacturing facilities, which are currently used for producing other vaccines available that could modified for influenza vaccine production.

There is the fact that only the influenza virus strain causing the pandemic is used for producing the pandemic influenza vaccine. The production process takes several months to produce the prototype vaccine. It is practical that the pandemic vaccine would be produced by the manufacturers currently producing the seasonal influenza vaccine. The seasonal influenza vaccine production capacity therefore determines the capacity of pandemic influenza vaccine production.

1.4 Strategic framework for pandemic influenza vaccine preparedness

After analyzing basic information, meeting with both national and international experts and brainstorming in the working group, 4 strategies for influenza vaccine preparedness to cope with the pandemic situation recommended are:

Strategy 1: Strategy for stockpiling finished vaccine
Strategy 2: Strategy for stockpiling the bulk vaccine
Strategy 3: Strategy for modifying vetenary vaccine plant to produce human influence vaccine in an emergency situation
Strategy 4: Strategy for establishing a new human vaccine plant

Strategy 1: Strategy for stockpiling finished vacine

The strategy is suitable prior to the pandemic occurrence. The purchase of potentially pandemic vaccine must be done immediately due to uncertain arrival of the pandemic. The strategy could be performed within 3-6 months. However, there is a risk that the virus strain contained in the purchased vaccine may not be the same as the strain causing the pandemic.

Strategy 2: Strategy for stockpiling bulk vaccine

This strategy, similar to the first strategy, is only possible prior to a pandemic. Importation of bulk vaccine for filling is an alternative to purchasing finished product and would reduce the vaccine price. There are several vaccine and drug plants which is capable to filling vaccine. Presently, the GPO-Merieux Biological Products Co, Ltd. imports the seasonal influenza vaccine for filling in Thailand but has not yet imported the potentially pandemic vaccine. One major concern for this strategy is that it might be difficult to get the bulk vaccine in a pandemic situation.

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Strategy 3: Strategy for modifying vaccine plant to produce the pandemic influenza vaccine in an emergency situation

The Veterinary Biologics Division, Department of Livestock Development of Ministry of Agricultural and Cooperates currently manufactures animal vaccine using egg-based technology. The plant was built in a standard modular system which is convenient for any adaptation. Staffs of the department also have expertise in the technology. It is therefore proposed that this plant may have potential to be the manufacturing plant for human influenza vaccine in an emergency situation. The plant modification would take about 1-2 years and would not require much investment. It would have to be modified before the emergency situation occurred.

Strategy 4: Strategy for establishing a new human vaccine plant

As a long term strategy, a new plant for human influenza vaccine is proposed. The plant should manufacture both seasonal influenza and the pandemic influenza vaccine at the manufacturing level. The plant establishment would take at least 5 years and a lot of investment is required. This strategy guarantees the best preparedness for self-reliance of influenza vaccine production provided that the other strategies have also been reinforced for an emergency.

The details of the strategies 1 - 3 will be discussed in chapter 2 - 4. The strategy 4 discussion will be divided into two parts, the strategy description in chapter 5 and the vaccine production capacity in chapter 6. In addition, the vaccine production standard, the legislative and regulation framework which should be considered prior to vaccine registration in an emergency situation will be discussed in chapter 7. A comprehensive discussion on the relationships of the four strategies and policy recommendations will be given in chapter 8.

Chapter 2: Strategy 1: Strategy for stockpiling finished Vaccine

- Vaccines strains, manufacturers and distributors
- Vaccine prioritization to target population groups during influenza pandemics
- Vaccine stockpile
- Estimated budget to stockpile vaccines
- Other considerations for vaccine stockpiles for influenza pandemics
- Conclusion

Chapter 2: Strategy for stockpiling finished Vaccine

2

Since 2004, there have been four avian influenza epidemics in Thailand. Over 30 million of poultry have been infected and destroyed. The human death toll was 17 (WHO, 3 February 2007). From these epidemics, the virus is believed to spread in the country. Intermittent influenza epidemics are therefore predicted. Changes of virus strains by antigenic shift may be the cause of the next pandemic, which is considered as a public emergency (Wanchai, 2006).

Epidemiological modeling showed that early containment of influenza outbreaks is important for preventing and delaying a pandemic. Despite an uncertain timing of the next pandemic, recent influenza outbreaks in many countries including Thailand indicated the likelihood of an influenza pandemic.

The method of choices for influenza prevention is a vaccine. Presently, Thailand does not have the influenza vaccine production capacity, thus preparation by stockpiling of vaccine of the virus strain causing the outbreak is therefore necessary. However, the pandemic vaccine can only be produced after the outbreak and the causing strain identified. This takes a certain period of time for manufacturing. Stockpiling is thus possible only for pre-pandemic influenza vaccine[1]. Pre-pandemic influenza vaccines purchased from other countries at appropriate level and in a continuous manner would help to mitigate the impact from the influenza outbreak. The strategy for purchasing pre-pandemic influenza vaccines like the H5N1 vaccine is not similar to the purchase of seasonal influenza vaccines because of the different purposes of use and different target groups for vaccination. This will be discussed in more details in this chapter.

It should be emphasized that stockpiling of vaccines is similar to that of purchasing insurance as to the fact that the insurance premium must be paid every year to cover the loss if occurring.

Considerations for purchasing influenza vaccines for national stockpiles

Pre-pandemic influenza vaccines are not in the marketplace since no manufacturers have performed complete clinical trials in humans. Therefore, the stockpiled vaccine could not be approved by the Thai Food and Drug Administration, Ministry of Public Health. The pre-pandemic influenza vaccines are prepared only to be stockpiled and used only in an emergency situation.

The importation of pre-pandemic influenza vaccines for stockpiling would not be an ordinary vaccine purchase. A number of considerations for importation are as follows;

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[1] *Influenza vaccines mentioned in this report are classified into seasonal Influenza vaccines, pre-pandemic Influenza vaccines and pandemic Influenza vaccines. The vaccine for pandemic preparedness is the pandemic Influenza vaccine which can be produced only after the pandemic emergence. Thus, vassines which will be stockpiled prior to the pandemic are the pre-pandemic Influenza vaccines. Recent research and development on the pre-pandemic Influenza vaccines has focused on many virus strains e.g. H5N1 which has infected intermittently and is able to change to a new strain that has potential to cause the pandemic.*

2.1 Vaccine strains, manufacturers and distributors

At present, there are many influenza vaccine manufacturers carry out research and development on production and clinical trials of pre-pandemic influenza vaccines from different influenza virus strains e.g. the H5N1, H9N2, H5N3, H2N2, H7N7 and H7N1. These manufacturers are Baxter (Czech Republic), Berna Biotech-Crucell Company (Switzerland), Biken (Japan), Chiron (UK, Italy), CSL (Australia), Denka Seiken (Japan), MedImmune (US), Nobilon International BV (The Netherlands), Sanofi Pastuer (France, US) and Solvay Pharmaceuticals (The Netherlands). In addition, a universal strain vaccine based on the M2 protein was also being investigated by Merck&Co, Inc. (USA). The vaccines are produced both as the inactivated and live attenuated influenza vaccine. Manufacturing technologies are mostly based on egg-based production. Only six companies are using the cell-based technology. The latest information (17 October, 2006) from the International Federation of Pharmaceutical Manufacturers and Associations on details of the influenza vaccine manufacturers is shown in Table 2.1.

The decision on buying a vaccine is based on the clinical trial results on humans, the virus strain used to produce the vaccine, limitations of the vaccine, manufacturing standards, production technology, purchasing conditions e.g. price, timing for vaccine delivery, the vaccine return policy, the new vaccine purchased and other consequent benefits e.g. technology transfer, etc.

Pre-pandemic influenza viruses such as the H5N1 virus have the potential to cause severe human illness and a high death rate of about 50%. There has been a concern that the next pandemic may be caused by this virus. The pandemic influenza vaccines can be exclusively produced by some manufacturers producing seasonal influenza vaccines. However, it is assumed that once a pandemic emerges, the countries where the vaccine manufacturers are located would not export the pandemic vaccines and would build up their pandemic vaccine stockpiles to be sufficient for their own consumption before exporting. Thailand would thus have to purchase and stockpile the prepandemic vaccines before a pandemic during the period in which the manufacturers are still able to export the vaccines.

The establishment of a influenza vaccine new manufacturing plant would take about five years. Since the production capacity is currently not available, prepandemic influenza vaccine stockpiling for Thailand is therefore inevitable and should start immediately. Continuous changes in influenza virus strains also prompt for the new or annual purchase of prepandemic vaccine.

Pre-pandemic influenza vaccines are currently being studied by several laboratories in Thailand e.g. The Faculty of Medicine at Siriraj Hospital, Mahidol University, King Mongkut's University of Technology Thonburi and the National Center for Genetic Engineering and Biotechnology (BIOTEC). A portion of the stockpiled vaccines in Thailand may be taken from these researches for emergency preparedness providing that all necessary tests have been carried out on these home made vaccines.

2

Table 2.1: Information of vaccine manufacturers producing pre-pandemic influenza vaccines from the International Federation of Pharmaceutical Manufacturers and Associations (http://www.ifpma.org/influenza/content/pdfs/Table)

R&D for Avian / Pandemic Influenza Vaccines by IFPMA Influenza Vaccine Supply International Task Force (IVS ITF) members
(Updated 17 October 2006)

#	Company (Site Location)	Strain	Type	Culture	Adjuvant	Doses (μg)	Trials	Timing	Additional Information
1	Baxter (Czech Republic)	H5N1 Wild type (A/Vietnam/1203 /2004)	Inactivated Whole virion	Cell Vero	Alum	3.7 / 7.5 / 15 / 30 / 45	Ph I&II* Adult**	Start: Jun 2006	* with NIID ** 18-45 year olds
2	Berna Biotech - Crucell Company (Switzerland)*	H9N2	Inactivated Whole virion	Egg	Alum	1.7 / 5 / 15 / 45***	Ph II	Start: 2006 End: Q4 2006	2 doses * with Leicester University ** Formulated with Virosomes as a carrier/adjuvant system *** Intramuscular **** Intradermal
			Inactivated Whole virion	Egg	None	5 / 15****			
			Virosome**	Egg	**	1.7 / 5 / 15 / 45***			
3	Biken (Japan)*	H5N1 (NIBRG-14)	Inactivated Whole virion	Egg	Alum	1.7 / 5 / 15	Ph I Adult**	Start: Mar 2006 End: Sep 2006	2 doses Intramuscular + subcutaneous Ph II & III Q3-4 2006 * with NIID ** 20-40 year olds
4	CSL Limited (Australia)	H5N1 (NIBRG-14)	Inactivated Split virus	Egg	$AlPO_4$	7.5 / 15 (1st set*) 30 / 45 (2nd set**)	Ph II Adult***	1st Start: Oct 05 1st End: Feb 06 2nd Start: Mar 06 2nd End: Jun 07	* 1st set results announced Feb 2006 ** 2nd set testing in broader population *** 18-64 year olds for 2nd set
5	CSL Limited (Australia)	H5N1 (NIBRG-14)	Inactivated Split virus	Egg	$AlPO_4$	30 / 45	Ph II Child*	Start: 2006	* 6 months to 8 year olds
6	CSL Limited (Australia)	H5N1 (NIBRG-14)	Inactivated Split virus	Egg	$AlPO_4$	30 / 45	Ph II Elderly*	Start: 2006	* > 65 year olds
7	Denka Seiken (Japan)*	H5N1 (NIBRG-14)	Inactivated Whole virion	Egg	Alum	1.7 / 5 / 15	Ph I Adult**	Start: Mar 2006 End: Jul 2006	* Intramuscular + subcutaneous Ph II & III Q3-4 2006 * with NIID ** 20-40 year olds
	GSK Biologicals (Germany)	H2N2	Inactivated Whole virion	Egg	Alum	1.9 / 3.8 / 7.5 / 15	Ph I&II	Trials finished in 2005	Mock-up file submitted to EMEA Dec. 2005
	GSK Biologicals (Germany)	H9N2	Inactivated Whole virion	Egg	Alum	1.9 / 3.8 / 7.5 / 15	Ph I&II	Trials finished in 2005	Mock-up files submitted to EMEA Dec. 2005
8	GSK Biologicals (Canada & Germany)	H5N1	Inactivated Whole virion	Egg	Alum	3.8 / 7.5 / 15 / 30	Ph II Adult*	Start: Mar 2006	2 doses * 18-60 year olds
9	GSK Biologicals (Canada & Germany)	H5N1	Inactivated Split virus	Egg	yes*	3.8 / 7.5 / 15 / 30	Ph I&II Adult**	Start: Mar 2006	2 doses * Novel adjuvant ** 18-60 year olds
10	GSK Biologicals (Germany)	H5N1	Inactivated Split virus	Egg	yes*	15	Ph III Adult	Start: May 2006	2 doses * Novel adjuvant
11	Kaketsuken (Japan)*	H5N1 (NIBRG-14)	Inactivated Whole virion	Egg	Alum	1.7 / 5 / 15	Ph I Adult**	Start: Mar 2006 End: Jul 2006	Subcutaneous Ph II & III Q3-4 2006 * with NIID ** 20-40 year olds
12	Kitasato Institute (Japan)*	H5N1 (NIBRG-14)	Inactivated Whole virion	Egg	Alum	1.7 / 5 / 15	Ph I Adult**	Start: Mar 2006 End: Jul 2006	Intramuscular + subcutaneous Ph II & III Q3-4 2006 * with NIID ** 20-40 year olds
13	MedImmune (USA)*	H5N1 (A/Vietnam/1203 /2004)	Live attenuated	Egg	None	Intranasal	Ph I	Start: 2006	* CRADA with NIAID (Collaborative Research & Development Agreement)
14	MedImmune (USA)*	H5N1 (A/HongKong/49 2/1997)	Live attenuated	Egg	None	Intranasal	Ph I	Start: 2006	* CRADA with NIAID

Table 2.1: Information of vaccine manufacturers producing pre-pandemic influenza vaccines from the International Federation of Pharmaceutical Manufacturers and Associations (http://www.ifpma.org/influenza/content/pdfs/Table) (continued)

#	Company (Site Location)	Strain	Type	Culture	Adjuvant	Doses (μg)	Trials	Timing	Additional Information
15	MedImmune (USA)*	H9N2	Live attenuated	Egg	None	Intranasal	Ph I	End: 2005 Expanded Ph I start in 2006	* CRADA with NIAID
16	MedImmune (USA)	H5N1	Live attenuated	Cell	None	Intranasal	Pre-clinical		
17	Merck & Co. Inc (USA)	M-2	Conserved Protein	Cell	None		Ph I	Start: 2006	
18	Nobilon International BV (Netherlands)	H5N1 (NIBRG-14)	Inactivated Whole virion	Cell	Alum	3.8 / 7.5 / 15 / 30	Ph I&II	Start: Q4 2006	
	Novartis Vaccines & Diagnostics (V&D) (Italy)	H5N3 (A/duck/Singapore/1997, NIB 40)	Inactivated Surface antigen	Egg	MF59	7.5 /15 / 30	Ph I	Trials finished in 2000	• Lancet 2001 357: 1937-1943 • Vaccine 2003 21: 1687-1693 • JID 2005 191: 1210-1215
	Novartis V&D (Italy)	H9N2 (G9/PR8)	Inactivated Surface antigen	Egg	MF59	3.75 / 7.5 / 15 / 30	Ph I&II* Adult**	Trials finished in 2005	2 doses Mock-up file submitted to EMEA Jan. 2006 * Trial conducted by NIAID ** 18-34 year olds
19	Novartis V&D (UK)	H5N1 (A/Vietnam/1203 /2004)	Inactivated Surface antigen	Egg	None Alum MF59	7.5 / 15 / 30 / 45 7.5 / 15 / 30 7.5 / 15	Ph I&II* Adult**	Start: Mar 2006 End: Jul 2006	2 doses * Trial conducted by NIAID ** 18-64 year olds
20	Novartis V&D (Italy)	H5N1 (NIBRG-14)	Inactivated Surface antigen	Egg	MF59	7.5 / 15	Ph II* Adult-Elderly	Start: Mar 2006 End: Sep 2006	* Trial conducted by Novartis V&D
	Novartis V&D (Italy)	H5N3 (NIB 40) H3N2 (Panama) B/Guandong	Inactivated Surface antigen	Egg	LTK63 MF59	7.5* 15	Ph I	Trial finished in 2002	* Intranasal J. Virol. 2006 10: 4962–4970
21	Novartis V&D (Italy)	H5N1	Inactivated Surface antigen	Egg	MF59	7.5 / 15	Ph II Adult*	Start: 2006	2 doses followed by a 6 month booster dose * 18-60 year olds
22	sanofi pasteur (France)	H5N1 (A/Vietnam/1194 /2004-NIBTG14)	Inactivated Split virus	Egg	Alum	7.5 / 15 / 30	Ph I* Adult*	End: 2005	2 doses * 18-40 year olds Lancet 2006 367:1657-1664
							Ph II Adult* Elderly**	Start: Q2 2006	2 doses * 18-60 year olds ** > 60 year olds
23	sanofi pasteur (USA)	H5N1 (A/Vietnam/1203 /2004)	Inactivated Split virus	Egg	None	7.5 / 15 / 45 / 90	Ph I&II* Adult**	Start: Apr 2005 End: Feb 2006	2 doses * Trial conducted by NIAID ** 18-64 year olds
24	sanofi pasteur (USA)	H5N1 (A/Vietnam/1203 /2004)	Inactivated Split virus	Egg	None Alum	45 / 90 (Study 1) 3.75 / 7.5 / 15 / 45 (Study 2)	Ph I&II* Elderly**	Start: Oct 2005 Start: Mar 2006	* Trial conducted by NIAID ** > 65 year olds
25	sanofi pasteur (USA)	H5N1 (A/Vietnam/1203 /2004)	Inactivated Split virus	Egg	None	45	Ph I&II* Child**	Start: Jan 2006 End: Feb 2007	* Trial conducted by NIAID ** 2-9 year olds
26	sanofi pasteur (USA)	H5N1 (A/Vietnam/1203 /2004)	Inactivated Split virus	Egg	Alum	7.5 / 15 / 45	Ph I* Adult	2006	* Trial conducted by NIAID
27	sanofi pasteur (USA)	H5N1 (A/Vietnam/1203 /2004)	Inactivated Split virus	Egg	None	3 / 9* 15 / 45**	Ph I*** Adult	2005	2 doses * Intramuscular ** Intradermal *** Trial conducted by NIAID
28	sanofi pasteur (USA)	H7N7	Inactivated Split virus	Egg	Alum		Ph I* Adult	Start: 2007	* Trial conducted by NIAID
29	sanofi pasteur (France)*	H7N1	Inactivated Split virus	Cell**	Alum	12 / 24	Ph I Adult***	Start: Sep 2006	2 doses * with EU Flupan Project http://www.nibsc.ac.uk/spotlight/fluplan/ ** PER.C6(R) cell-Crucell *** 20-40 year olds
30	Solvay Pharmaceuticals (Netherlands)	H5N1	Inactivated Surface antigen	Egg	Alum	To be determined	Ph I Adult*	Start: 2007	* 18-49 year olds
31	Solvay Pharmaceuticals (Netherlands)	H5N1 (NIBRG-14)	Inactivated Surface antigen	Cell MDCK	Alum & *	To be determined	Ph I Adult**	Start: 2007	* Novel adjuvant ** 18-49 year olds

2

2.2 Vaccine prioritization in an emergence of a pandemic

The objective of prioritizing population groups for influenza vaccination is to use limited resources efficiently. Vaccination prioritization is usually based on the efficiency for prevention and control of infection, and to prevent any chaos in society. Risk exposure levels and public service responsibility are the key criteria to prioritize population groups for vaccination, however each country has different priority lists. It should also be emphasized that the priority lists for vaccination in an emergence of a pandemic are different from seasonal influenza vaccination.

The policy for both seasonal and pandemic influenza vaccine for Thailand is discussed in Appendix 2.

2.2.1 Priority groups for pandemic influenza vaccination in the US

The National Vaccine Advisory Committee (NVAC) and the Advisory Committee on Immunization Practices (ACIP) made the priority list of population groups for pandemic influenza vaccination on 19 July 2006 (Temte, 2006) as shown in Table 2.2. The Department of Health and Human Services (HHS) is currently undertaking a broad public hearing on such a list in order to meet the increasingly public demand (HHS, Request for Information (RFI): Guidance for Prioritization of Pre-pandemic and Pandemic Influenza Vaccine, http://aspe.hhs.gov/PIV/RF/).

2.2.3 Priority groups for pandemic influenza vaccination in Thailand (MOPH, 2006)

The Thai priority lists are as follows:

1. Health care workers involved in the treatment of influenza infection,
2. Health personnel working on controlling the influenza infection,
3. Health care workers treating infected patients in emergency rooms and out-patient service areas and patients with high risk for seasonal flu,
4. Persons involved in security services e.g. governance authorities, police and armed forces,
5. Utility workers working in pubic transportation, electricity, water and public telephone services,
6. Persons aged ≥ 64 years old with complications caused by seasonal flu,
7. Persons aged from 6 months old to 64 years old with at least two high-risk conditions, for seasonal flu with complications,
8. Pregnant women, persons with the low immunity, persons who are unable to get vaccinated,

Table 2.2: Priority groups for pandemic influenza vaccination in the US (http://www.aafp.org/fpm/20060100/32prep.pdf)

Group	Population
1A	Health care workers • Health care workers with direct contact to patients and supporting staffs • Vaccine and antiviral manufacturing personnel
1B	Highest-risk groups • Patients aged ≥ 65 years old with at least one high-risk condition • Patients aged between 6 months to 64 years old with at least 2 high-risk conditions • Patients hospitalized in the past year because of pneumonia, influenza or another high-risk condition
1C	Household contacts and pregnancy • Household contacts with children aged under 6 months old • Household contacts with severely immuno-compromised individuals • Pregnant women
1D	Pandemic responders • Key government leaders and pandemic public health responders
2A	Other high-risk groups • Patients aged ≥ 65 years old with no high-risk conditions • Patients aged between 6 months to 64 years old with one high-risk condition • children aged between 6 to 23 months old
2B	public personnel • emergency units worker, security personnel, utility workers, transportation workers and telecommunications workers
3	• Other key government health care decision-makers • Individuals providing mortuary services
4	• Healthy people aged between 2 to 64 years old without any high-risk conditions

2

2.2.2 Priority groups for pandemic influenza vaccination in Canada

The prioritization for pandemic influenza vaccination in Canada is illustrated in Table 2.3.

Table 2.3: Priority groups for pandemic influenza vaccination in Canada (http://www.phacaspc.gc.ca/cpip-pclcpi/ann-d_e.html)

Group	Population
1	Health care workers, public health responders and key health decision makers involve in; • Hospital care for treatment of infection • Medical equipment and patient rooms • Ambulance and paramedic services • Pharmacies and vaccines • Laboratories
2	Key decision makers and pandemic responders; • Police • Fire fighters • Armed forces • Emergency personnel • Utility workers e.g. electricity, water, communication systems • People working in funeral and mortuary service • Personnel working in public transportation and transportation of essential goods e.g. food
3	Persons at high risk and develop serious illness if infected with seasonal influenza; • persons living in nursing homes, homes for elderly • Persons with high-risk for serious illness • Persons aged ⩾ 65 years old and not in the two groups above • Children aged between 6 to 23 months old • Pregnant women
4	Healthy adults e.g. individuals aged between 18-64 years old
5	Children aged between 24 months old to 18 years old

2.2.4 Comparison of priority groups for pandemic influenza vaccination in three countries and remarks for Thailand

Health personnel are in the first rank priority group given by the three countries. Thailand and Canada are similar in placing persons involved in security services and utility works in the second group. Thailand, however, does not indicate a priority level of persons involved in policy decision making as it has been done for the US and Canada. This could prompt problems in practice for Thailand. The prioritization that includes the policy decision makers therefore should also be made.

High-risk infected patients are ranked the second group in the US which is prior to pandemic responders and persons involved in public works. The group priority implies the vaccine stockpile level each country must prepare. A country where priority group is infected patients would need to stockpile a larger amount of the vaccine than would the countries giving health care workers as the highest group.

Public involvement in group prioritization in the US helps to provide public understanding on how the practical prioritization would be and public awareness that could prevent panic when a pandemic emerges. This process would also support a real expectation from the public and promote self care management in a pandemic occurrence.

Apart from the suggestion of including policy decision makers in the priority group, Thailand should also add persons involved in vaccine manufacturing and distribution to correspond with a plan for setting up a vaccine plant. In addition, public involvement in the process for group prioritization should not be left out. The right of access to fundamental health care as indicated in the Thai constitution must also be considered. A rationing resource concept is important in a situation of insufficient stockpile level which would commonly happen. The amount of vaccine to provide for each priority group and center for vaccine distribution should also be identified and kept in the database of the preparedness plan.

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*Note: * high risk conditions are;*

- *persons with chronic illness e.g. asthma, chronic obstructive pulmonary disease, restrictive pulmonary disease, coronary heart disease with normal blood pressure*
- *persons who have been hospitalized in the previous year with diseases such as chronic metabolic disease including diabetes mellitus, renal dysfunction, hemoglobinopathy, persons on immunosuppressive drugs and HIV infected patients*
- *persons with mental and muscle illness causing compromised respiratory function including cognitive dysfunction, spinal cord injuries, epilepsy and neuromusculardiseases*
- *persons aged 6 months to 18 years continuously on aspirin*
- *pregnant women*
- *children aged 6 to 23 months*

2.3 Vaccine stockpile levels

The objective of stockpiling of the prepandemic vaccine is to control an initial outbreak of the virus by preventing or delaying the pandemic. With the limited resources, the stockpiled vaccine would first be used for health personnel including persons involved in disease control. The remaining would be rationed to persons as indicated in the prioritizing group. The amount of vaccine for each prioritization group for pandemic influenza vaccination is therefore an input to determine the vaccine stockpile for each country.

Due to the fact that there is no definite conclusion of which virus strain would cause the next pandemic, the current manufacturing of the pandemic strain vaccine is impossible. A practical activity is then to stockpile pre-pandemic vaccines. The H5N1 strain is globally of most interest as the pre-pandemic vaccine strain. However, there is also a possibility of changes in the H5N1 strain to be considered as an uncertainty in stockpiling.

The currently limited productivity of influenza vaccine manufacturing in the US has made the US government plan to boost its domestic production capacity in order to acquire ample stockpiles by 2011[2]. The US Federal Government has made contracts with two vaccines manufacturers, Chiron and Sanofi Pasteur, to provide 62.5 and 100 million US dollars, respectively for researching and manufacturing 20 million doses of bulk vaccine for stockpiling.

Japan depends upon four local vaccine manufacturers potentially producing the pandemic influenza vaccine. Its action plan for Phase 3A, in which there is no national outbreak, includes the manufacturing of the prototype vaccine and the stockpiling eggs used for vaccine production. In Phase 4A, in which there are some incidences but no national outbreak, Japan will start manufacturing the known strain vaccine. In Phase 4B when a national outbreak starts, the prototype vaccine must be ready to distribute to health personnel, public service workers, staff involved in vaccine distribution and at-risk people.

P.R. China's plan is to start stockpiling the finished vaccines of about 600,000 doses and the bulk vaccines of about 24 million doses for WHO influenza pandemic level 3-4. At level 5, China would have about 6 million doses of the finished vaccines and 24 million doses of the bulk vaccines (Duanthanom et al., 2006).

[2] The US Fedral Government plans to spend 2.1 billion US dollars to purchase 20 million doses of the H5N1 vaccine and 2.8 billion US dollars to research the vaccine manufacturing so to speed up its production and to improve the vaccine's reliability.

On an account of unknown virus strain causing the pandemic and limited information of vaccine efficiency, there is no clear guideline on the appropriate level of the stockpile each country should pursue. This is different from a stockpiling of antivirus drugs. The WHO recommended stockpiling of antivirus drug at 25% of the total population as an appropriate level of stockpiling. The stockpiled vaccines would generally be first rationed to health care workers, persons controlling the disease and persons providing public services. The amount of vaccine for these groups would vary from country to country causing a difficulty to determine the appropriate level of the stockpile. In addition, the price of the vaccine would partly take control over a decision of stockpiling level. Hence, the appropriate level would be basically subject to a country's context.

Thailand's appropriate level of the vaccine stockpile has not yet been determined. If applying P.R. China's context to that of Thailand irrespective to scale effect, while in WHO pandemic level 3-4, it is estimated that Thailand should prepare to have approximately 150,000 doses (meeting 0.23% of the entire population) comprising of 30,000 doses of the ready to use (finished) vaccines and 120,000 doses of the bulk vaccines. At level 5, its stockpiled vaccine level should reach 1.5 million doses (2.3% of the population) comprising 300,000 doses of finished vaccines and 1.2 million doses of the bulk vaccines.

Table 2.4: Estimated influenza vaccine stockpile for Thailand based on P.R. China

WHO Phase	P.R. China				Thailand	
	Finished vaccine		Bulk vaccine		Finished vaccine	Bulk vaccine
	Million (doses)	%	Million (doses)	%	Million (doses)	Million (doses)
3-4	0.6	0.046	2.4	0.185	0.030	0.120
5	6	0.462	24	1.846	0.300	1.200

Note: *To facilitate the calculation, the vaccine proportions to the population are based on the approximate 1,300 million Chinese and 65 million Thais (information from Chinese at a Glancestating 1,296.1 million Chinese in 2004 and 64.2 million Thais in 2005) and the use of the proportion of vaccine doses per Chinese population, applicable to the dose Thailand should stockpile.*

The estimated figures of vaccine prepared for WHO pandemic level 3-4 is similar to the number in the budget plan determined by Thailand's Public Health Infrastructure Plan (2006 - 2009). Over the past 1-2 years, the Department of Disease Control has purchased seasonal influenza vaccines for health personnel of approximately 200,000 doses per year[3]. The vaccines were administered at one dose per person for effective protection of seasonal flu and the numbers of vaccines purchased covered the requirement for the existing number of health personnel.

[3] *Department of Disease Control purchased seasonal influenza for health personnel 400,000 doses in 2007*

In consideration of the administration of one dose per person for effective protection, Thailand's stockpile level prior to the pandemic for health personnel would range from 30,000 - 200,000 doses. However, for the new pandemic strain, the administration of two doses per person for effective protection of individuals who had not been exposed to the new virus might be required. The stockpile level would range from 60,000 to 400,000 doses.

2.4 Budget estimation for purchasing stockpiled vaccines

The estimation is based on two inputs which are the number of vaccine doses and the price per dose for the stockpile. The first input is derived from the estimated figure stated above while the price is based on the reference prices of the H5N1 vaccine that Indonesia was offered to purchase at 20 US dollars/dose[4] or 700 Baht/dose (based on exchange value of 35 Baht/US dollar) during the first three years (2007 - 2009). Decreasing prices to 500 Baht and 300 Baht/dose[5] is expected in 2010 and 2011, respectively. The price reduction in the following years is estimated on the assumption that many vaccine manufacturers would increase their production capacity and more varieties of completely studied vaccines would be available, creating price competition. The budget estimation should be based on annual purchase of vaccine to guarantee vaccine quality and its effectiveness against the disease causing strain.

An estimation of the budget for stockpiling the finished vaccines for front line workers in Thailand is illustrated in Table 2.5. If 60,000 doses per year are purchased for five years, the budget would be approximately 174 million Baht. In the case that the stockpile level is increased to 200,000 and 400,000 doses per year, the 5-year budget would be 580 million and 1,160 million Baht, respectively.

The stockpile levels for pandemic prevention may depend on different situations. The minimum stockpile level is expected in a situation that no conclusive information on human-to-human transmission of the virus. In contrast, higher stockpile level would be required if there is a pertinent report of human-to-human infection. A purchase agreement with the vaccine manufacturer should cover the vaccine price in advance for the incidence of human-to-human transmission because the vaccine price would expectedly be increased.

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[4] *Input from Dr. Triono, the Indonesian representative in viral sharing session, WHO Geneva, 19-20 April 2007*

[5] *The prices seasonal influenza that the Department of Disease Control has agreed in the purchase contract for 200,000 doses.*

Table 2.5: Estimated budget for purchasing and stockpiling pre-pandemic influenza vaccines (million Baht)

Population number for vaccination	Vaccine stockpile level (doses)	Estimated budget (million Baht)					
		Year1	Year2	Year3	Year4	Year5	Total
30,000	60,000	42	42	42	30	18	174
100,000	200,000	140	140	140	100	60	580
150,000	300,000	210	210	210	150	90	870
200,000	400,000	280	280	280	200	120	1,160
Vaccine price (Baht/dose)		700	700	700	500	300	na

Note: Estimation based on 2 doses/person for effective protection

Uncertain timing of the pandemic emergence discourages the private business sector to invest in the vaccine production. Since prevention of pandemic is regarded as a national security issue, the government sector is therefore responsible for the investment in pandemic preparedness such as vaccine purchase and/or production.

The early phase of pandemic is expectedly to last six months in which a rush in the vaccination for people in both public and private sector would be undertaken to reach the vaccination target as quickly as possible e.g. within one month. The vaccination would be based on priority groups. Any group not previously mentioned in the priority group should be consulted by the national committee in charge of strategic directions for pandemic control.

2.5 Other considerations for vaccine stockpiling for influenza pandemics

2.5.1 Risk from the differences between the stockpiled vaccine strain and the pandemic causing strain

A best means of pandemic prevention and control is to have pandemic influenza vaccine stockpiles or vaccines produced for the same virus strain or close to the pandemic influenza strain. Because of the lack of information of the pandemic causing strain prior to the outbreak, several vaccine strains should therefore be purchased from many manufacturers to reduce some risks. Alternatively, the vaccine that cross protects against several strains is recommended. A likelihood of changes in influenza viruses would also prompt an elimination of previous vaccine stock for a newer strain vaccine stockpile.

In countries where influenza vaccine manufacturers are located such as Canada, the governments may sign a contract with the manufacturers on a condition of reserved production capacity. This is to guarantee the appropriate numbers of vaccines when an outbreak occurs. However, this is not applicable to Thailand since there is no influenza vaccine manufacturer. The only alternative is to purchase vaccines both as the finished products and bulk influenza vaccines for filling. Vaccine bulk for filling is discussed in the next chapter.

2.5.2 Vaccine deployment approval in a pandemic situation and compensation resulting from vaccination

The prepandemic influenza vaccines are unlikely to completed clinical trial Phase 3 due to the fact that there has been no infected patient for testing. In addition, safety and research ethical considerations would also be raised to prevent the real testing in humans. The effectiveness and efficiency of the vaccine will not therefore have been thoroughly tested before being used in an influenza pandemic situation.

During the emergence of a pandemic, the vaccination must be immediately provided. Using the incompletely tested pandemic vaccines previously described is subject to some certain risks of complications. Thus, a launch of such a vaccination must be decided by the National Committee. In UK, the vaccine regulator and the vaccine manufacturers have gathered all the information about pandemic vaccines ready to facilitate decision making for the vaccination in a pandemic emergency. They have also prepared for the registration of prototype dossiers (new vaccines) to speed up the approval of a new pandemic vaccine.

Because there are some risks involved in the vaccination, budget for compensation given to those affected by the vaccine which has not been passed all required processes, must be included in the plan. The government or public agencies should take this issue into consideration.

2.5.3 Regional or global stockpiling

The stockpiling may be undertaken at either regional or global level. Although developing countries may not have full access to the vaccines reserved at those two levels, this will probably raise their chances for vaccine accessibility. This could facilitate global cooperation in an influenza surveillance system, especially information of intermittent outbreaks, influenza virus changes, and virus resistance to antiviral drugs. The WHO held a brainstorming meeting on vaccine stockpiling at global level in April, 2007. Currently, there has been no regional stockpiling of influenza vaccines in the South-east Asian region although it is an active and risk area for the next pandemic.

2.6 Conclusion

Due to the unknown nature of the pandemic causing virus strain, this strategy thus aims at stockpiling of pre-pandemic vaccines for front line persons involved in health care, disease control, utility and security services. Initially, the stockpiled vaccines would not target all people but purposively control the outbreak or delay the pandemic. This strategy would take about 3-6 months for preparation if there was sufficient budget. Factors needed to be considered to purchase vaccine for stockpiling are:

1. The strains of virus used for vaccine production, vaccine distributors and the amounts of vaccine ordered from manufacturers,
2. Priority groups for vaccination in a pandemic situation,
3. Levels of vaccine stockpiles,
4. Budget estimation for purchasing vaccines to stockpile,
5. Other considerations e.g. risk from the mismatch between the vaccine strain and the pandemic causing strain, approval of vaccine deployment, compensation resulting from complications caused by vaccination, and global and regional stockpiling.

The priority groups for Thailand are health personnel directly treating infected patients and controlling the outbreak, and persons involved in utility and security services. Approximately 18-42 million Baht per year would be needed for 60,000 doses per year (300-700 Baht per dose). If the stockpiles were raised to 400,000 doses per year, the budget would reach 120-280 million Baht per year. Thailand also needs to prepare a budget for purchasing new vaccines annually due to the likelihood of changes in influenza viruses.

To stockpile 400,000 doses per year for 5 years, Thailand must commit an enormous budget of 1,160 million Baht for only the high priority groups. This strategy is therefore a temporary strategy only whilst local vaccine production capacity does not exist. For long term plan, the government should consider other strategies to put into practice e.g. purchasing of bulk vaccine for filling (Strategy II) and/or development of vaccine production capacity in Thailand (Strategy III and IV) to reduce budget which would be needed in long term.

3

Chapter 3

Strategy 2:
Strategy for stockpiling bulk influenza vaccines

- Vaccine filling concept
- Potential agencies for filling bulk vaccines
- Filling target
- Budget estimation
- Conclusion

Chapter 3: Strategy 2: Strategy for stockpiling bulk influenza vaccines

3.1 Vaccines filling concept

Filling is the last process of vaccine manufacturing and the least complex process. In the filling process, bulk vaccines in large amount usually greater than 10 litres are prepared for formulation and filled to become finished products which could be in vial or pre-filled syringe form. The finished product can be either single dose or multiple dose vaccine. For the influenza vaccine, 0.5 ml vaccine for one dose is generally used in adults and children aged 3 and over. The filling of pre-pandemic and pandemic vaccines can be performed at the manufacturers which fill seasonal influenza vaccines or other vaccines[1] or at the standard manufacturers able to produce injection syringe medicines. The standard of the manufacturers potentially filling influenza vaccines will be described in the following part.

The production capacity of vaccine manufacturers is subject to filling capacity. In other words, the vaccine manufacturing productivity in both up-stream and down-stream process and the filling capacity should be compatible for production maximization. Although not having influenza vaccine production plants, Thailand has an ability to fill bulk vaccines to be finished products. The possession of this ability helps reduce the vaccine price by about 20%[2]. In addition, stockpiling as bulk vaccines can prolong vaccine-life which is normally shortened after formulation and filling. Therefore, the bulk vaccine is suggested for stockpiling pre-pandemic vaccines which remain uncertain to deploy. This could be an additional strategy worthy of implementation.

However, the filling strategy, the same as strategy 1, is not applicable in the pandemic situation in which there would be no bulk vaccine to purchase because of globally limited influenza vaccine production capacity. The mismatch of stockpiled vaccine strain and the pandemic causing strain also dampens protection effectiveness. Though able to reduce vaccine price, this strategy is still far from reaching the vaccination levels for all groups of people. The objective is to stockpiling pre-pandemic vaccines for front line persons to control or delay the outbreak.

3.2 Potential agencies for filling bulk vaccine

At present, Thailand does not have plants for filling pre-pandemic influenza vaccines. There are however four agencies having the potential to expand their filling productivity during a pandemic situation by changing the filling process to be able to fill 0.5 ml[3] for influenza vaccine as described below (see Table 3.1).

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[1] *Except for manufacturing producing foot-and-month disease vaccine.*

[2] *In Thailand, price of seasonal influenza vaccine as finished product is 300 Baht/dose while bulk vaccine priced at 250 Baht which is about 17% reduction.*

[3] *Based on influenza vaccine adult dose (0.5 ml/doses) and for children age 3 years old and younger (0.25 ml/dose).*

1. The Government Pharmaceutical Organization-Merieux Biologicals Co.Ltd. (GPO-MBP) is a private company with filling machines and experience in filling seasonal influenza vaccine. The company is willing to expand its productivity for filling pre-pandemic influenza vaccines to 22 million doses per year if requested. Some limited additional expenditure for cleaning and validating its filling machines would be required prior to starting the influenza vaccine filling

2. The Thai Red Cross Society has already ordered a filling platform to fill 2-10 million vials of seasonal influenza vaccines per year. If it fills 10 doses per vial, the maximum productivity would be about 100 million doses per year. The platform will be set up and ready for filling by 2008. In the pandemic situation, the Society would be able to switch to filling the pandemic vaccine immediately.

3. Three private pharmaceutical manufacturers: M&H Manufacturing, Thai Nakornpathana, and Bilolab Corporation, Limited, have cooperated well in providing information to the report working group. These three companies are currently filling pre-filled syringes medicines. They could change to fill the pandemic influenza vaccine once a pandemic occurs. Their total productivity is about 24 million vials per year (1-3 ml per vial). If filling 6 doses (3 ml) influenza vaccine per vial, they could produce 144 million doses per year. These companies have been suggested by GMP experts of the Thai Food and Drug Administration (FDA), to fill influenza vaccines because their plants are found to comply with national standards.

4. The New Castle Plant, Veterinary Biologics Division, Department of Livestock Development, Ministry of Agriculture has filling machines but has not yet acquired GMP. The plant needs some modifications to meet GMP standards and re-adjustment of its filling head and filling process to be suitable for influenza vaccine filling. The Thai FDA's approval is also needed to certify for filling human influenza vaccines. The plant currently has two filling machines. One with maximum productivity of 12,000 vials per hour (1-3 ml per vial) is expected to fill the vaccine at about 40 million vials (3 ml) or 240 million doses per year (6 doses/vial) and it is not presently utilized. The other has the maximum productivity of 8,000 bottles per hour (bottle 5-250 ml) and is used for filling the New Castle vaccine. To minimize its impact on the plant's routine production of its vaccines, the first machine would only be used for filling influenza vaccines.

Table 3.1: Comparison of agency potential for increasing their filling productivity

Agency	GMP standard	Seasonal influenza vaccine filling capacity	Current Preparatory (dose/yr)	Maximum filling productivity if increased (dose/yr)	Preparatory measures to face with the pandemic	Plant adjustment time needed	Budget needed for plant modifications (Baht)
Government Pharmaceutical Organization-Merieux Biologicals Co.Ltd.	✓	✓	500,000 (0.5 ml/dose)	10 million (in parallel with other vaccine filling) 22 million (if stopping other vaccine filling)	No plant modification with work round increase from 1 to 3 rounds	2 weeks (for cleaning and validation)	Cleaning expenditure, (20,000 Baht for cleaning agents)
Thai Red Cross Society	✓	✓	600,000 doses/yr for ampoules and 600,000 doses/yr for vials (1-2 ml/dose) (if halting the solvent and vaccine production)	1. 2 million doses/yr if stopping current vaccine and solvent production and switching to work 3 rounds (without new filling machine) 2. 10 million doses/yr (0.5-5 ml/dose 1 yr) if purchaseing new automatic compact filling line (ready in 2007)		-	80 million

Table 3.1: Comparison of agency potential for increasing their filling productivity (continued)

Agency	GMP standard	Seasonal influenza vaccine filling capacity	Current Preparatory (dose/yr)	Maximum filling productivity if increased (dose/yr)	Preparatory measures to face with the pandemic	Plant adjustment time needed	Budget needed for plant modifications (Baht)
Private manufacturers (M&H Manufacturing, Thai Nakornpathana, and Bilolab Corporation Limited)	✓	✗	5.1 million vial (1-3 ml)	24 million vial/yr (1-3 ml) = 144 million doses/yr	Filling improvement to accommodate the filling of pandemic influenza vaccine	6 months	1 million
New Castle Vaccine Plant, Veterinary Biologics Division, Department of Livestock Development	✗	✗	200 million doses/yr (0.1 ml/dose)	40 million vials/yr (1-3 ml) = 240 million doses/yr	Not yet meeting GMP so requiring improvement and Thai FDA approval needed on switching to filling human vaccine	6 months after getting GMP	1 million

These are some agencies with potential for filling influenza vaccines in Thailand. Some modifications to the plants would be necessary. Their total productivities of vaccine filling after plant improvement would also be increased. Each plant would need a different budget size for improvement and different supportive measures. If such improvements are carried out according to the plan, all plants would be ready for filling influenza vaccines within 1 year.

3.3 Filling target

The existing high potential vaccine filling capacity in Thailand and advantages of filling bulk vaccines has made this strategy an interesting option which should be included in the pandemic influenza preparedness plan. Based on the information from the previous chapter on Thailand's stockpile levels needed (60,000 - 400,000 doses) and China's proportion of H5N1 stockpile levels between the level of finished vaccine and bulk vaccine, which is 1 to 4, the estimation of Thailand's stockpile levels for bulk vaccine would be 48,000 - 320,000 doses (Table 3.2).

3.4 Budget estimation

Stockpiling the bulk vaccines would reduce the budget needed compared to stockpiling the finished vaccines as shown in Table 2.5. Both of the bulk vaccines and finished vaccine for stockpile are likely to be ineffective for prevention if changes in the virus occur. The stockpiling of bulk vaccines which are priced cheaper would however help reduce the budget.

The budget needed for stockpiling finished and bulk vaccines is estimated on two scenarios. The first scenario is based on the assumption that the influenza viruses change themselves rapidly and the stockpiled vaccines become no longer effective after 1 year. Hence, both finished and bulk vaccines must be purchased annually.

The second scenario is based upon the assumption that some minor changes of virus occur but the stockpiled vaccines remain effective. The vaccine-life for finished vaccines are effective for only one year[4] while the bulk vaccines have longer vaccine-life, as previously described, and could be effective for two-years (providing that the vaccine strain is still protective against the disease causing strain). Thus the purchase of finished vaccines and bulk vaccines may be performed every year and every two years, respectively. The purchase plan subject to the two scenarios is shown in Table 3.3.

Other assumptions:

1. Proportions and doses of finished and bulk vaccines derived from Table 2.4
2. Price of pre-pandemic influenza vaccines derived from Table 2.5
3. Price of bulk vaccines in Thailand plus filling expenditure is 20% lower than that of finished vaccines

[4] *Expiration time of seasonal influenza vaccines lasts longer than one year but one year is indicated due to virus changes. For expiration time of pre-pandemic vaccines there is no conclusive evidence.*

Table 3.2: Thailand's stockpile levels of finished vaccines and bulk vaccines

Stockpile level (doses)	Finished vaccine (doses)	Bulk vaccine (doses)
60,000	12,000	48,000
200,000	40,000	160,000
300,000	60,000	240,000
400,000	80,000	320,000

Table 3.3: Annual purchase of influenza vaccines based on 1st and 2nd scenario

	1st scenario		2nd scenario	
	Finished vaccine	Bulk vaccine	Finished vaccine	Bulk vaccine
Yr1	✓	✓	✓	✓
Yr2	✓	✓	✓	✗
Yr3	✓	✓	✓	✓
Yr4	✓	✓	✓	✗
Yr5	✓	✓	✓	✓

Note: ✓ purchasing, ✗ not purchasing

Table 3.4: Budget estimation based on 1st and 2nd scenario (million Baht)

Stockpile level (doses)	1st scenario					2nd scenario				
	Yr1	Yr2	Yr3	Yr4	Yr5	Yr1	Yr2	Yr3	Yr4	Yr5
60,000	35	35	35	25	15	35	8	35	6	15
200,000	118	118	118	84	50	118	28	118	20	50
300,000	176	176	176	127	76	176	42	176	30	76
400,000	235	235	235	168	101	235	56	235	40	101

Table 3.5: Budget estimation and budget reduction (million Baht) of both scenarios compared with the budget used for only stockpiling finished vaccines with respect to different stockpile doses

Stockpile doses	Only stockpiling finished vaccines	1st scenario: annual purchase (20% of finished and 80% of bulk vaccines)		2nd scenario: annual purchase of finished vaccine and every 2-year purchase of bulk vaccines	
	Budget used	Budget used	Budget reduction	Budget used	Budget reduction
60,000	174	146	28	100	74
200,000	580	487	93	334	246
300,000	870	731	139	500	370
400,000	1160	974	186	667	493

Based on the above budget estimation assumptions subject to the 1st and 2nd scenarios, the budget estimation is shown in Table 3.4. The total budget and the budget reductions are illustrated in Table 3.5. If the proportion of finished vaccines and bulk vaccines are stockpiled at 1 to 4, in the 1st scenario, 28 - 186 million Baht would be saved overall over five years (Table 3.5), or about 16% saving, compare to the case of making annual purchase of finished vaccine only. Similarly for the 2nd scenario in which virus changes are not rapid, the finished vaccine must be purchased while the bulk vaccine is purchased every 2 years, 100 - 667 million Baht would be needed. Between 74 - 493 million Baht less budget would be needed (about 42.5% saving).

The possibility that the 2nd scenario should happen is still doubtful in terms of actual occurrence. The tendency of virus changes has indicated a greater likelihood of the 1st scenario. In this report, the working group decided to propose the estimated budget which is based on the 1st scenario for both first and second strategy of pandemic influenza preparedness in stockpiling influenza vaccines for the best coverage of all the pandemic risks.

3.5 Conclusion of strategy II: Strategy for filling influenza vaccines in Thailand

The influenza vaccine filling strategy prior to a pandemic is considered as a supplementary strategy by purchase of bulk vaccines instead of exclusively buying finished vaccines. In Thailand, there are a number of agencies whose plants have high potential to fill enough influenza vaccines for Thais. Some modifications at some places are required before starting filling influenza Based on the assumption of stockpiling 80% of bulk vaccines and 20% of finished vaccines for 5 years, the estimation showed 16% reduction (28 - 186 million Baht), relative to the budget used for totally purchasing finished ones. The budget could possibly be reduced if changes in the influenza viruses were slow.

The strategy of stockpiling both bulk and finished vaccines is however a short term and uncertain strategy largely because Thailand cannot produce its own vaccine. If a pandemic occurs, the vaccine accessibility from international countries could become difficult and the stockpiled vaccines would be only deployed to high priority groups. A majority of the population would not have access to the vaccine. Therefore a more permanent strategy should be available for Thailand, especially the development of influenza vaccine manufacturing capacity.

Chapter 4

Strategy 3:
Strategy for modifying veterinary vaccine plant to produce human influenza vaccine in an emergency situation

- Rationale of modifying veterinary vaccine plants to produce human vaccine in an emergency situation
- Current status and capacity of the veterinary vaccine plant at the Bureau of Veterinary Biologics (BVB's), Animal Health Department
- BVB's poultry vaccine plant
- Modification of BVB's poultry vaccine plant to produce human pandemic influenza vaccine
- Estimated capacity of BVB's poultry vaccine plant for human pandemic influenza vaccine production
- Budget Estimation
- Operational plan
- Conclusion

Chapter 4: Strategy 3: Strategy for modifying veterinary vaccine plant to produce human influenza vaccine in an emergency situation

4.1 Rationale of modifying veterinary vaccine plants to produce human vaccine in an emergency situation

On 27th April 2006, the WHO/OIE/FAO discussed the feasibility of using veterinary vaccine production facilities for human influenza vaccine production to increase vaccine production capacity. At that meeting, potential veterinary vaccine producers such as those in China and Mexico also attended and agreed that this idea was technically plausible since many veterinary vaccine production facilities in some countries have already been certified to the GMP standard.

The strategy for modifying veterinary vaccine plants to produce human influenza vaccine in a pandemic situation was proposed as one of the national strategies for Thailand. Firstly, at this time, Thailand does not have an industrial-scale facility to produce influenza vaccine for humans. Secondly, this option is technically feasible. The veterinary plant at the Bureau of Veterinary Biologics (BVB), Animal Health Department has long experience of vaccine production. However, for the production of human influenza vaccine, this plant requires improvement on downstream processes, especially the purification process. Moreover, the plant needs to achieve the GMP standard similar to that required for human vaccine production.

The strength of this strategy is that it requires marginal investment and short start-up time (1 year), compared with building a new production plant which would take at least 3-5 years and a lot more cost for the investment. Furthermore, the BVB plant is a platform for producing animal vaccines using egg-based technology which is the current technology used for influenza vaccine production. With the expertise and facilities available, if a pandemic occurs before a new human vaccine plant is ready for production, veterinary can be an important alternative to obtain vaccine additional to importing vaccine from the limited global supply of global influenza vaccine.

4.2 Current status and capacity of the Bureau of Veterinary Biologics, (BVB), Animal Health Department

BVB has an area of 11.04 million square meters and 425 staff. It has produced animal vaccines for 47 years, starting with foot and mouth disease. The current production capacity is 630 million doses per year of cattle, swine, and poultry vaccines. Currently, it is in the process of development for GMP standard.

Currently, BVB has three plants for virus vaccine production. The first and the second ones produce Foot and Mouth vaccine with cell-based technology for cattle and swine (Table 4.1). The third is producing poultry vaccine using egg-based technology. The third plant has potential for being modified to produce human influenza vaccine in an emergency situation since it was constructed with German standards as a modular system which is simple for modification.

Table 4.1 Status and capacity of veterinary vaccine production of the Bureau of Veterinary Biologics

Main product	Main equipments	Technology Platform	Production capacity (doses/ year)	GMP Certified	Production period
1. Plant for Foot and Mouth Disease vaccine for cattle	1. Fermenter size 5000 litres, 2 tanks (in 2008 another two fermenters sized 2,500 and 2,000 litres will be installed) 2. Ultrafiltration MW 100,000 D/cutoff with filtration rate 350-400 litres/ hour, 2 sets (in 2008 another two sets will be installed) 3. Continuous centrifuge 6,000 rpm with 480 litres/hour, 2 sets (in 2008 another 2 sets will be installed) 4. High speed centrifuge 4 set, 2 sets for size 1Lx6 and 2 sets for size 0.4 Lx6 (in 2008 another 2 sets size 0.4Lx6 will be installed) 5. Filling and packaging with filling capacity 4,000 bottles/hour, 1 set	Cell-based technology	17 million doses	In the development process for GMP standard	1 year
2. Plant for Foot and Mouth Disease vaccine for swine	1. Fermenter size 3200 litres, 3 tanks and 1400 litres, 1 tank 2. Ultrafiltration MW 100,000 D/cutoff size 350-400 litres/hour, 2 sets 3. Continuous centrifuge maximum speed 6,000 rpm with centrifugation rate 480 litres/hour, 2 sets 4. High speed centrifuge 2 sets (size 1Lx6) 5. Ultracentrifuge for centrifugation with sucrose gradient, 1 set 6. Filling and packaging machine with speed 3,000 bottles/hour, 1 set	Cell-based technology	20 million doses	In the development process for GMP standard	1 year
3. Plant for poultry vaccine	Detail in Table 4.2	Egg-based technology	200-250 million doses	In the process of application for GMP and expected to be certified in 2008	1 year

4.3 BVB's poultry vaccine plant

The BVB's poultry vaccine plant produces vaccines using egg-based technology. The plant was designed by TAD Pharma Company, Germany. It was constructed in 1995 and started production in 1997. This plant has 20 staff and it is composed of 4 buildings including:

1. Administration building that covers an area of 487.5 square meters.
2. Production building that covers an area of 1,161 square meters. The production has two production lines i.e. live attenuated vaccine production and inactivated vaccine production. The proportion of area of the two production lines is 50:50. Equipment in both production lines is presented in Table 4.2.
3. Building of supporting facilities such as water preparation, HVAC system that covers an area of 240 square meters.
4. Building for quality control of vaccines and eggs that covers 406 square meters.

The vaccines produced from this plant include:

1. New Castle vaccine, both live attenuated and inactivated vaccine. Current capacity of producing live attenuated vaccine is 30 million doses/year,
2. Gumboro vaccine, both live attenuated and inactivated type,
3. Fowl Pox, live attenuated type, 20 million doses per year,
4. Infectious Bronchitis vaccine, live attenuated type, 20 million doses per year

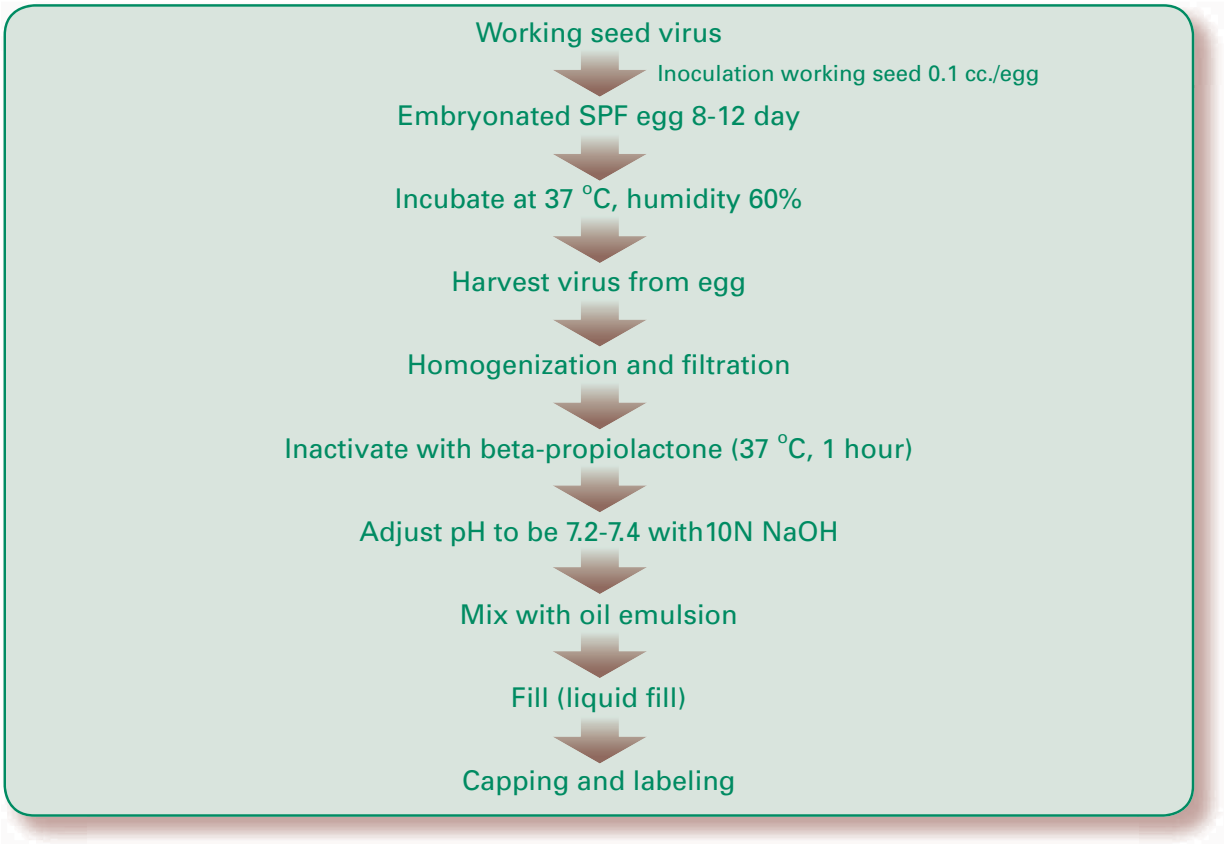

Figure 4.1 Process for production of inactivated poultry vaccine

According to infrastructural and other relevant information, the BVB's poultry vaccine plant has potential for being modified to produce human influenza vaccine in an emergency situation for the following reasons.

1. The currently most used technology for influenza vaccine production on the industrial scale is egg-based technology. Although cell-based technology has an increasing role, it has been estimated that 5-10 years are required before cell-based technology could become the main production technology.
2. The BVB poultry vaccine plant's existing platform is similar to one used for influenza vaccine production (Figure 4.1-4.4). However, some equipment for the purification process of human vaccine production has to be added to the BVB plant.
3. Currently, the BVB plant is improving bio-safety standard to BSL2 and is in the process of application for the GMP standard with the Thailand FDA. This biosafety level is suitable for producing influenza vaccine with reverse genetic strain. There is also potential to improve this plant to meet the BSL3 standard for producing vaccine of wild type viruses.
4. The available equipment in BVB's production processes are in good condition for human vaccine production.
5. The supporting utilities such as WFI preparation, HVAC system, kill tank system, and incinerator meet the standards for human vaccine production.

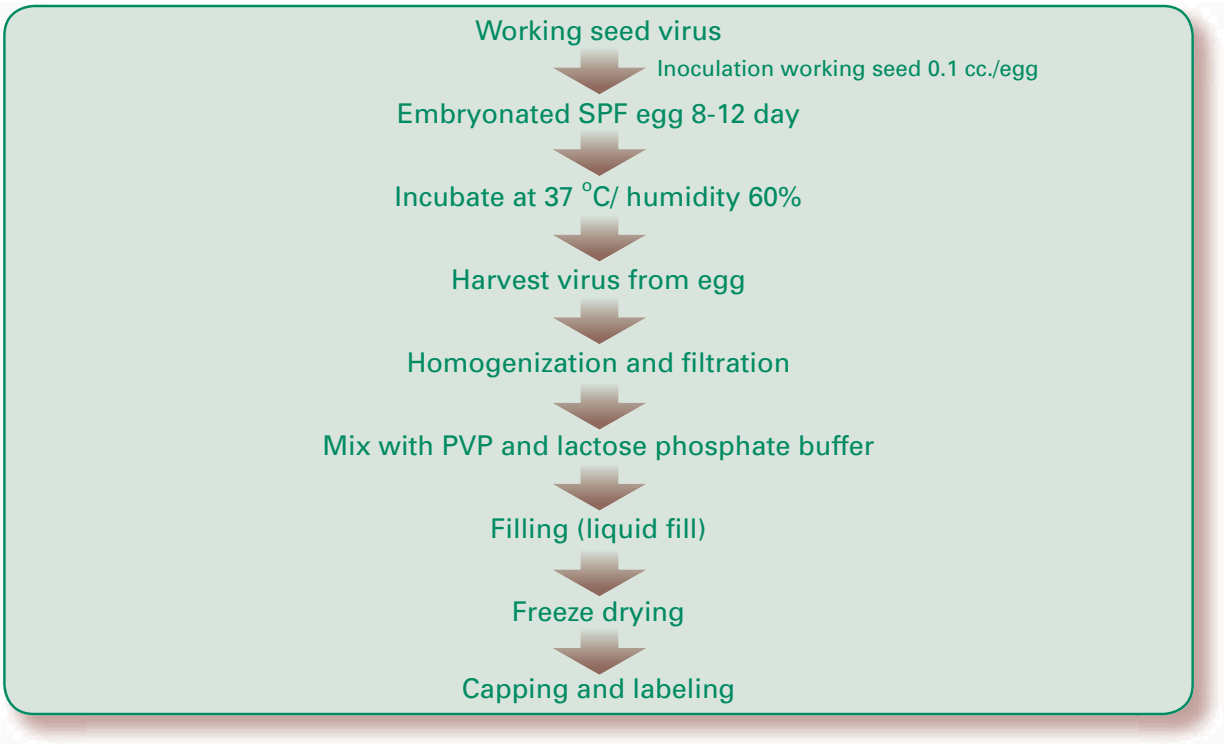

Figure 4.2 Process for production of live attenuated poultry vaccine

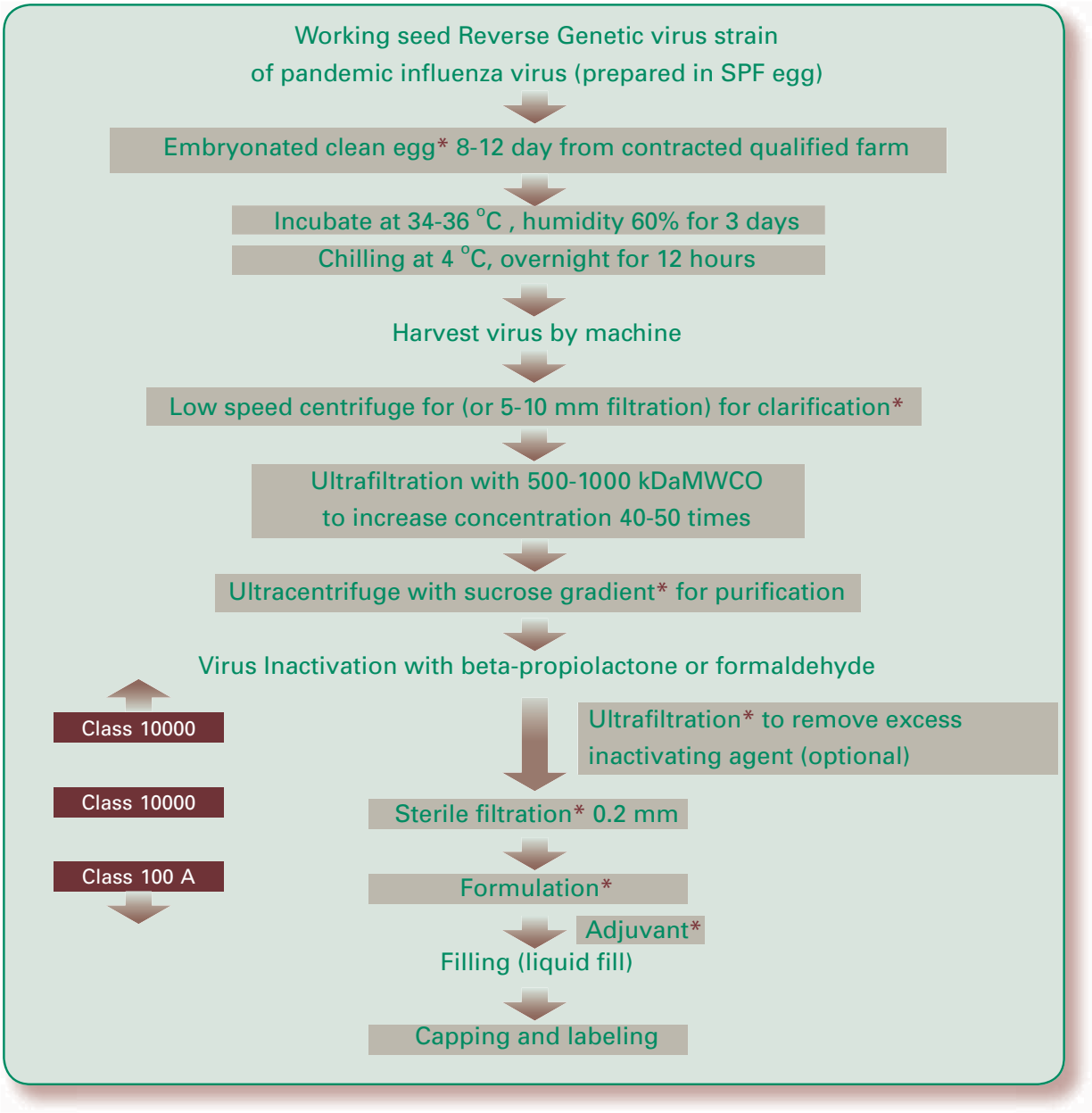

Figure 4.3 Production process of human Pandemic Inactivated Influenza Vaccine (PIIV).
* = steps required to be added into existing poultry vaccine production process

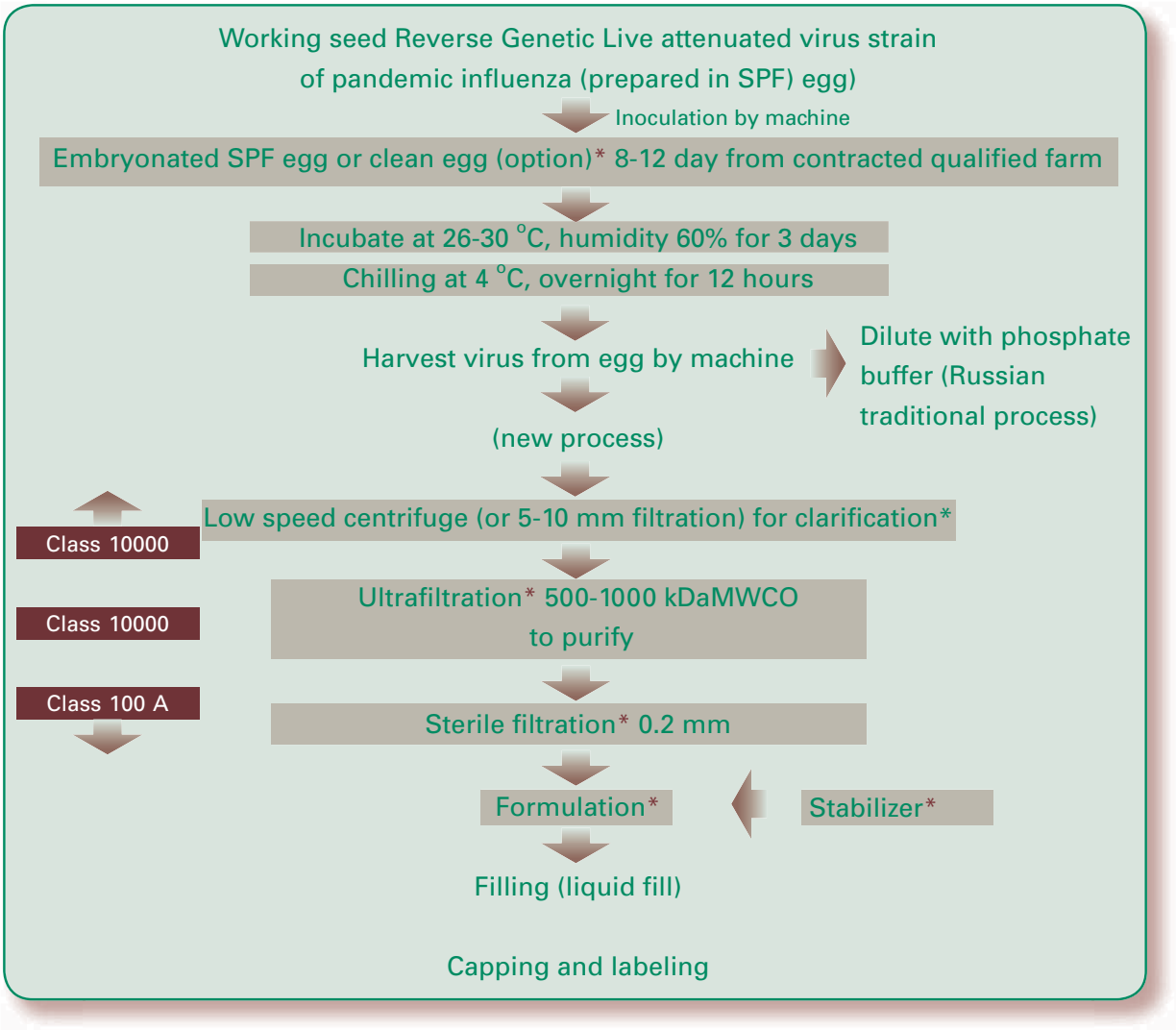

Figure 4.4 Production process of human Pandemic Live Attenuated Influenza Vaccine (PLAIV)
* = steps required to be added into existing poultry vaccine production process.

Table 4.2 Equipment and production capacity of BVB egg-based plant

Equipment /production step	(company) / production capacity	
	Live attenuated line	Inactivated line
Inoculator / Harvester	Manual Inoculate 2,000 eggs / 5 staff/4 hr Harvest 2,000 egg / 4 staff / 4 hr	(TKA cod.600618, Italy) inoculate 8,000 eggs/ hr, (56 M eggs/yr) harvest 6,500 eggs/hr, (45.5 M eggs/yr)
Incubator	(Petersime Co. Ltd., USA) 1 room (20,000 eggs) for 3 days or 2.33 M eggs/ yr	(Petersime Co. Ltd, USA) 2 rooms (40,000 eggs) for 3 days or 4.66 M eggs/ yr
Homogenizer	(Harrislee, Germany) 100 Liters tank / 200 Liters tanks	(Harrislee, Germany) 100 Liters tank
Filter	(Gelman, Australia) 100 micron filter	na
Inactivation	na	(Harrislee, Germany) 200 Litres tank / 2 tanks
Hot air oven tunnel	(Groninger, Germany) STS 5538 65 kg glass/hr, size 150x280x55 cm, temp raised to 300°C in 3 mins.	Double door autoclave (Consolidated Stills+Sterilizers, USA), 679 liters
Filling / Stoppering	(Groninger, Germany) DFVK 4000 Max 12,000 vials/hr for 3 cc vial Current cap 8,000 vial/hr - fill volume 1 cc, 128,000 vials/d (16 h operation) or 44.8 M vials/ yr	(Groninger, Germany) DFV 8000 Max 8,000 bottles /hr 250 ml bottle Current cap 3,000 vial/hr - fill volume 5-250 cc.
Lyophilizer	(Heto, Denmark) FD 150-12, 96-2RS, Max 30,000 vials eachx2 Current cap 28,000-30,000 vials /batch 2 batch/wk or 3 M vials/yr	na
Labeling/ Capping	(Groninger, Germany) HER 010 -Max 15,000 vial /hr KVK 108 B -Max 18,000 vial /hr	Within filling machine

Production capacity calculated from 350 working days/year

*** The gray portion is the equipment to be used to produce human vaccine in an emergency situation*

With these existing facilities, the BVB's poultry vaccine plant has high potential for being modified to produce human influenza vaccine in emergency situations. This option provides the shortest time to prepare influenza vaccine production on an industrial scale in Thailand, by improving efficiency of resource utilization of available assets.

4.4 Modification of BVB's poultry vaccine plant to produce human pandemic influenza vaccine

The strategic plan for modifying BVB's poultry-vaccine plant to produce human pandemic influenza vaccine has been carried out by using information obtained from site visits, consultations with experts in vaccine production, influenza vaccine production, scientists and engineers, FDA's officers, and BVB's staff. The prime objective of modifying BVB's plant is to prepare the plant to be able to produce human vaccine in emergency situations. The modification of the plant should introduce minimum impact to the current production of poultry vaccine. As the BVB line currently produces only live attenuated poultry vaccine, the modification of the plant should focus on the modification of the other unused production line for inactivated poultry vaccine.

Of the two types of influenza vaccines (Live Attenuated Influenza Vaccine-LAIV and Inactivated Influenza Vaccine-IIV), LAIV production requires less steps than the IIV (Figure 4.4). The yield of vaccine per egg used for LAIV production is 30 doses/egg whereas only 3-6 doses/egg can be produced for the IIV process (information from Dr. Eric D'Hondt). In addition, the WHO's meeting on January, 2007 suggested that LAIV would be an important tool during the pandemics as it is more efficient in preventing infection and it can induce immune response faster than IIV. LAIV is applied via nasal route which is similar to natural infection. Although the current indication of seasonal LAIV is for population aged between 5 to 49 years old, in May 2005, the USFDA allowed the use of this vaccine for children of age 2 years or older. Russia has widely used this vaccine for the elderly for a long time and no significant side effects have been reported from this vaccine. From the production point, LAIV production is much more efficient than producing IIV as the yield per egg of LAIV is 30-100 times of that of IIV (information from Dr. Eric D'Hondt). In a pandemic situation, high surge capacity is very critical as we wish to have the highest possible amount of vaccine in the shortest of time in order to prevent the infection. In other words, in an emergency situation, the production should therefore focus on the production of LAIV rather than IIV. The BVB's plant should be prepared as follows.

4.4.1 Preparation of the building

The plant was designed to meet bio-safety level 2 which is adequate for safely when producing vaccine from reverse genetic seed viruses. However, it is possible to improve the plant to meet bio-safety level 3 for production vaccine with more lethal seed viruses. The building should be improved in the following points:

- The clean standard of most of production areas is class 10,000 which complies with the standard requirement for human vaccine production. The clean standard should be improved in some areas only.
- The production of LAIV including seed preparation, egg inoculation with virus, egg incubation, virus harvest, separation and purification, formulation and filling can be carried out in the area of the poultry inactivated vaccine line. However, in order to avoid the sensitivity on public perception of vaccines produced in an animal vaccine plant, the bulk vaccine can be filled in other places such as the GPO-Merieux Biologicals Co. Ltd., private drug companies, and the Thai Red Cross which is in the process of installing a new filling line and will be ready for filling vaccine within this year (2007). Details of potential fillers were presented in Chapter 3.
- From detailed assessment it was found that the incubator room is the bottleneck for production capacity of BVB's poultry plant. Currently there are two incubators in the in activated vaccine-production line. To increase the production capacity, we propose to increase to eight incubating-chilling rooms (dual function) by extend working space on one side of the current wall (see Figure 4.6). Each room can incubate or chill 20,000 eggs at one time. Two rooms containing total 40,000 eggs will be used to produce one batch of vaccine, and two rooms can be reserve capacity for any errors during the surge production.
- To adjust the current production line of poultry inactivated vaccine (Figure 4.2) to comply with production of human pandemic LAIV (Figure 4.4), the following adjustments are required (Figures 4.5, 4.6):
    - To remove the seed preparation room (1.8) to increase space for centrifuge and modify the incubator room (1.6) to be a new seed preparation room,
    - To modify the incubator room (1.7) to be a media and buffer preparation room,
    - To modify the inactivation room (2.1) to be a sterile filtration room; this is needed to upgrade the room cleanliness level to be 100A in 100B,
    - To modify the cold room for vaccine storage (2.2) to be the room for formulation; this needed to upgrade the cleanliness to be 100A in 100B,
    - The homogenization room (1.10) and vaccine storage room (1.9) will be kept for storage of poultry vaccine. After modifying the plant, the plant would be used for practicing human vaccine production and for the real production during pandemics.

During these periods, the production of poultry vaccine would be stopped and these rooms would not be used,

- To remove the wall next to the fumigation room up to the vaccine storage room including the corridor to increase the production space and to install an ultrafiltration unit and decontamination autoclave (the cleanliness level will be upgraded to class 10000),
- To install 8 incubating and chilling rooms at the side of the current production plant (this plant can be extended up to 6 meters towards the QA/QC building),
- To improve the cleanliness of the filling room (2.5) to meet class 100B if the vaccine needs to be filled in this plant,
- The inoculators and harvester for the poultry inactivated vaccine can be used for human LAIV production,
- To improve the air flow pattern in each room to have an air inlet in the upper part of the room and air outlet in the lower part of the room,
- The vaccine produced would be in the bulk form to be filled in other places or to be filled in the filling room (2.5),
- To install air quality monitoring units to monitor quality of air in every operating room.

4.4.2 Preparation on process and equipment

(production process presented in Figure 4.4):

- Numbers of trolleys should be increased to carry 160,000 eggs (8 incubator rooms X 20,000 eggs in each room),
- To avoid contamination with other organisms, LAIV is recommended to be produced from SPF eggs. However, there is a concern that SPF eggs may not be available during a pandemic situation. Currently, the WHO is considering the feasibility of using of cleaned eggs instead of SPF eggs in LAIV production.
- The following equipment for purifying the harvested allantoic fluid should be added:
  - Biosafety cabinet in the seed virus preparation room,
  - Low speed centrifuge e.g. Sharples centrifuge for clarification (5-10 micron filtration may be an alternative),
  - Ultrafiltration (molecular weight cut-off 500-1000 kDa) with capacity of more than 1,000 Litres/hr,
  - Sterile filtration system (0.2 micron) with capacity of more than 1,000 Litres/hr
- More cold rooms for LAIV storage since all available cold rooms are currently used for poultry vaccine. A -15^{o}C room might be required for the storage of LAIV (depends on the vaccine formula). With the limitation on space, the freezer may be installed in an extension of the building.

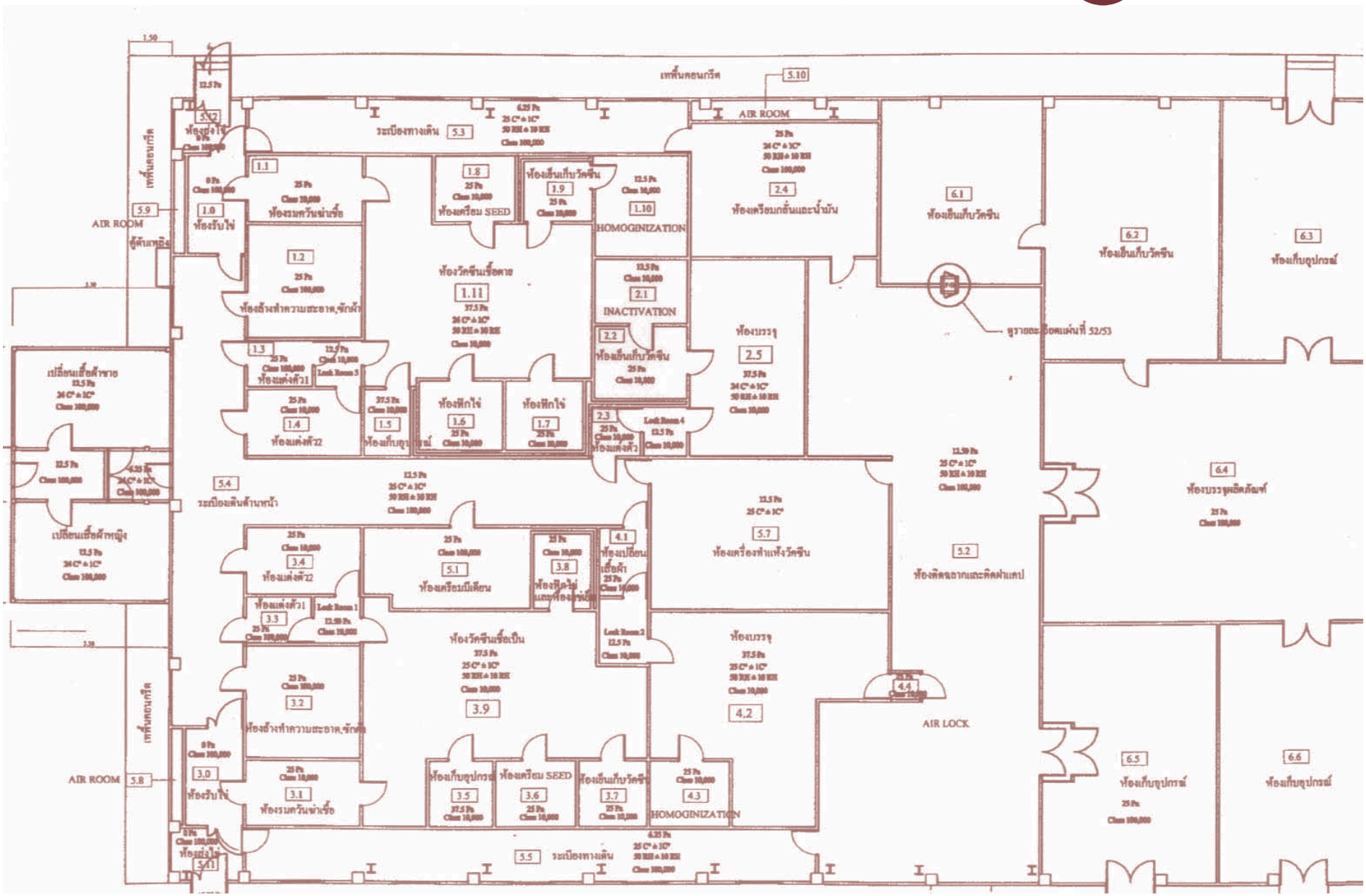

Figure 4.5 Layout of BVB's poultry vaccine plant before the modification

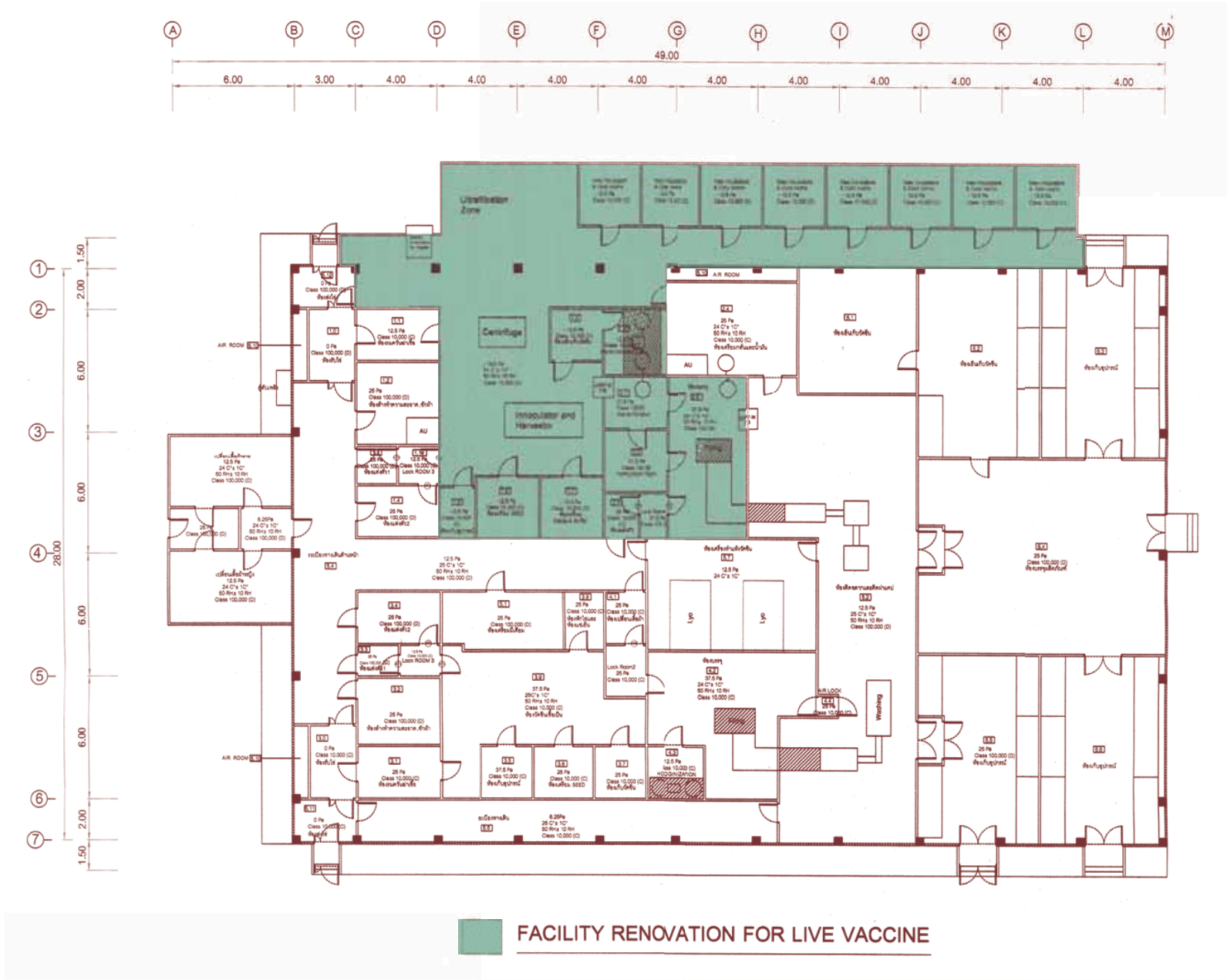

Figure 4.6 Layout of BVB's poultry plant to be modified to produce human Pandemic Live Attenuated Influenza Vaccine (PLAIV)

4.4.3 Preparation on other issues:

4.4.3.1 Obtaining a production expert

Although BVB has long experience in producing poultry vaccine from egg-based technology, they do not have knowledge and skill of human influenza vaccine production, especially in the downstream processes. Although producing LAIV has fewer steps in the downstream process, it is different from animal vaccine production. In Thailand, there are some staff in working vaccine production and other industries that have skills in operating equipment in purification steps such as the Sharples centrifuge, ultrafiltration, sterile filtration and ultracentrifugation. However, none of these staff have experience of the whole production process of both LAIV with egg-based technology in industrial scale operation. Therefore assistance from international experts in the early phase of operation will facilitate the start-up and efficient production of LAIV.

4.4.3.2 Obtaining and training staff

BVB's staff have skills in upstream processes of egg-based technology however they have limited know-how in both downstream and quality control of human vaccine production. In order to have both adequate quantity and quality of staff for producing human influenza vaccine there is some preparation of human resources required. The preparation of human resources includes:

- Recruitment of additional staff for vaccine preparation and organizing training with GMP in each section consistently. The training should be classified into two levels i.e. basic courses (examples of the course presented in Annex 9) and advance courses. This will require trainers from both domestic (such as GPO-Merieux Biologicals Co. Ltd) and international sources.
- The training should cover both theory and practice aspects of LAIV production and quality control.
- Training staff in SOP preparation.

4.4.3.3 Preparation on SPF eggs

BVB's SPF hatchery can supply SPF eggs with a capacity of 120,000 eggs/three months while the expected demand will be three million SPF eggs/three months (in the case where LAIV production requires only SPF eggs as the raw material). Supply of SPF eggs can be increased by expanding the capacity of BVB's SPF hatchery and/or importing SPF eggs from other countries such as China or Taiwan. The eggs can be procured in an 8-12 days pre-incubated form or in an unincubated form. Proper transportation is required especially for pre-incubated eggs to reduce damage to the embryo.

4.4.3.4 Storage of live attenuated vaccine

Effectiveness of the LAIV will decrease significantly if it is kept at room temperature. This type of vaccine requires -15 °C storage. Therefore cold-chain custody during transferring the vaccine is crucial. Collaboration with experienced private sector in cold chain delivery will assist the transferring of vaccine in an emergency situation.

4.4.3.5 Preparation on miscellaneous issues

- In order to avoid shortage of poultry vaccine, a contingent plan for stocking poultry vaccine is required when the BVB's poultry plant is used to produce human vaccine,
- To stock main spare parts for equipment and supporting systems to be ready for use,
- To have a maintenance plan for equipment both in the production and QC lab, and supporting systems (WFI, AHU),
- To prepare adequate numbers of vials and caps of appropriate size,
- To prepare proper containers for LAIV.

4.4.3.6 Collaboration of other organizations

Additional to strong ministerial collaboration between the Ministry of Public Health and the Ministry of Agriculture and Cooperation, both in policy and operational levels, collaboration with the following organizations is essential to ensure the effective and efficient production of human influenza vaccine in an emergency situation.

- The National Center for Genetic Engineering and Biotechnology (Biotec) in partnership on human resources, and research and development,
- The Government Pharmaceutical Organization (GPO) in partnership of human resource development and vaccine research and development at both laboratory scale and pilot scale production, which is currently supported at the GPO by the World Health Organization (WHO),
- The Food and Drug Administration (FDA) on designing standards and details of modifying plant,
- The Department of Medical Science on human resource development, research, and standards for vaccine quality assessment.
- The Thai Red Cross Society on human resource development,
- Universities on human resource development both in production process development and virus strains for seed preparation (in collaboration with the WHO),
- The private sector for
  - The modification of vaccine plant to meet the acceptable standards,
  - The timely process of procurement, importation, installation and testing of equipment,
  - SPF and clean egg preparation at private standard farms to obtain an adequate supply of eggs on-time,
  - GPO-Merieux Biologicals Co. Ltd on human resource development relating to vaccine formulation and filling and maintenance of supporting systems,

4.5 Estimated capacity of BVB's poultry vaccine plant for human pandemic influenza vaccine production

The production capacity for human influenza vaccine produced by modified BVB's plant is estimated based on the following information and assumptions:

1. Incubators: 8 incubating-chilling rooms (capacity 20,000 eggs each); 6 rooms will be used for incubating and 2 rooms will be used for chilling,
2. incubation period: 3 days after inoculating working seed into embryonated eggs
3. Chilling period before harvesting: 12 hours
4. Operation period: 2 cycles/week
5. Yield for LAIV (minimum): 30 doses/1 egg (information from Dr. Erik D'Hondt)

Production capacity was calculated based on following formula:

Production capacity (doses/week) =
Number of incubator rooms x 20,000 eggs/room x cycles/week x yields doses/egg

After modification of BVB's plant, the production capacity of human pandemic LAIV would be:

7.2 million doses/week or
86.4 million doses/3 months (12 weeks) or 360 million doses/yr (50 weeks)

With good management, the maximum capacity that could be achieved is:

9.6 million doses/week or
115.2 million doses/3 months (12 weeks) or 480 million doses/yr (50 weeks)

The budget estimated above excludes the cost of management, cost of the preparation for filling and packaging, cost of egg preparation, cost of system validation, cost of laboratory and pilot scale production, and cost of QA/QC preparation. It is estimated that these costs would be approximately 30 million Baht. Therefore the preparation towards this strategy would require initial cost around 100 million Baht in the first year and the cost of system maintenance and practicing production in campaign at around 10 million Baht per year.

4.6 Budget Estimation

Resources required for preparation of the BVB poultry plant can be divided in two parts i.e. for improving building and procuring equipment (Table 4.3) and for the human resource development (Table 4.4).

Table 4.3 Estimated budget required for preparation of building and equipment to produce human pandemic LAIV

Items	Budget (million Baht)
1. Building modifications[1]	37.0
3. Incubators/chilling rooms	1.5 x 8 = 12.0
4. Biosafety cabinet Class 2 (2 sets)	0.8 x 2 = 1.6
5. Low speed centrifuge (Sharples)	2.0
6. Ultrafiltration (1 set)	3.0
7. Decontamination autoclave (1 set)	5.0
8. Sterile filtration 0.2 um (2 sets)	0.2 x 2 = 0.4
9. Vaccine storage room	1
Total	**62.0**

Note:
[1] List of contractors, and dealers for related equipment and devices is presented in Annex 2.

Table 4.4 Estimated budget required for human resource development

Items	Budget (Baht)
1. Training GMP basic 2 week course by WHO expert	800,000
2. Consultation fee for expert in production process for 6 months (400,000 USD/yr)	8,000,000
Total	**8,800,000**

4.7 Operational plan

The plan to improve BVB's poultry-vaccine plant to produce human pandemic influenza vaccine would take one year of operation to cover four action parts (Table 4.5).

1. Improvement of the plant's infrastructure to comply with the GMP standard including cleaning and validation,
2. Production process development for LAIV at laboratory and pilot scale,
3. Development and validation of QC methods
4. Procurement, installation and validation of equipment from pilot scale to production scale.

The preparation above may be done in partnership with the Government Pharmaceutical Organization which is carrying out similar work on laboratory and pilot scale practices, QA/QC tests, and the preparation for industrial scale production. The partnership and information sharing will improve the efficiency of both projects.

Table 4.5 Action plan for preparing BVBís poultry-vaccine plant to produce human influenza vaccine in an emergency situation

Action	month 1	2	3	4	5	6	7	8	9	10	11	12
1. Establish GMP facility												
Renovation of existing plant (6 months), Cleaning Validation	←	—	—	—	—	—	→					
Commissioning and validation							←	—	→			
GMP Facility fully operation (BSL3)								←	—	—	—	→
2. Develop process for LAIV												
In collaboration with WHO for obtaining cold-adapted seed virus for seasonal influenza vaccine	←	—	—	—	—	→						
Establish laboratory and pilot procedures for producing LAIV							←	—	—	—	—	→
Obtain access to cold-adapted pandemic strain									←	—	→	
Establish SOP on production											←	→
3. Develop and validate QC Method												
Introduce influenza specific test methods	←	—	—	—	—	—	—	—	→			
Develop and validate QC release test for LAIV and IIV						←	—	—	—	—	—	→
SOPs on QC release test available											←	→
4. Purchase , install, validate equipment												
4.1 For laboratory purpose	←	—	→									
4.2 For Pilot Production purpose	←	—	—	—	—	→						
4.3 For GMP facility						←	—	—	—	—	—	→

4.8 Conclusion

From study on mapping facilities relating to vaccine production in Thailand, BVB's virus vaccine plants covering both cell-based and egg-based technology have the most potential for the whole process of human influenza vaccine production in an emergency situation. Further investigation indicated that cell-based plants are not suitable to produce human vaccine because production of foot and mouth disease vaccine is technically incompatible with human vaccine production. The current technology used most for industrial production of influenza vaccine is still egg-based technology. The cell-based technology is in the process of development and it is expected to replace the egg-based platform in the future. From assessments by local and international experts, BVB's egg-based plant has high potential to be modified to produce human pandemic influenza vaccine in an emergency situation. This plant was designed to international standards which are applicable for modification to meet human vaccine production standards such as the GMP standard and Biosafety level 3 (BSL 3). Equipment used in this plant is similar in standard to that in human influenza vaccine plants in other countries (as compared with 5 currently constructed influenza-vaccine plants in China). Furthermore, BVB's plant has experienced staff in the upstream process of egg-based production.

Further analysis indicated that the BVB's plant needed to be improved in terms of modifying buildings, adding some equipment, and developing production processes and human resources. It was estimated that the preparation of BVB's plant would require around only 1 year of preparation and 100 million Baht of investment. Although this report presents some analysis of the modification, it is recommended that a detailed technical and operation analysis by an influenza vaccine expert is required.

After the modification, it is estimated that the production capacity of LAIV by this plant would be 7.2 million doses/week or 86 million doses in 3 months (expandable to 9.6 million doses/week or 115 million doses in 3 months). The high yield of LAIV supports it role as a pandemic vaccine. The lower yield of IIV and the space limitation of BVB's plant directed the idea that the modified BVB's plant would focus on human LAIV production in an emergency situation.

Many logistic preparations to provide a continuous supply chain of raw materials such as eggs need to be undertaken, and collaboration with the FDA on production standards and quality assurance, including public communication on importance of this strategy for national security. Partnership with various public and private organizations, and a strong collaboration and commitment of major stakeholders i.e. the Ministry of Public Health and the Ministry of Agriculture and Cooperation are crucial success factors for implementing this strategy.

In summary, the strength of this strategy is that it is the shortest way to have the whole process of influenza vaccine production with a marginal investment. After the preparation is completed, this plant will work as a main strategy of pandemic influenza-vaccine preparation. The human resource developed under this strategy will assist the long-term human vaccine production in the future. When a new human influenza-vaccine plant is ready for production, this plant will work as the back-up facility. This strategy can work hand-in-hand with other strategies as an effective tool to prevent and respond to a pandemic influenza, the major threat to our nation and our world. Strengths and weaknesses of this strategy are summarized in Table 4.6.

Table 4.6 Strengths and weakness of the strategy on modification of BVB's poultry vaccine plant to produce human pandemic influenza vaccine in an emergency situation

Strength
1. Long experience in egg-based technology 2. Site in remote area 3. Basic utilities such as water and electricity 4. Good supply of SPF eggs both in terms of quality and quantity 5. Designed to international standards, modular system- applicable for modification to produce human vaccine 6. Equipment has similar standards to those in other human vaccine plants 7. Take less time and resources than building a new plant
Weakness (need preparation and improvement)
1. Need improvement in production process and additional equipment especially the downstream process to purify vaccine 2. Improvement to meet standards of human vaccine production such as GMP, (+/- Biosafety level 3) 3. Preparation on human resource including training in GMP and SOP development 4. Improvement of QC Lab (with support from the Department of Medical Science) 5. Preparation for importing animal vaccine which the plant routinely produces in case the modified plant will be changed to produce human vaccine, 6. Contracting egg suppliers to ensure continuous supply chain of raw material 7. Preparing quality assurance and standards of production 8. Public communication about the necessity and assurance system on good quality of vaccine 9. Collaboration between the Ministry of Public Health with the Ministry of Agriculture and other public and private organizations

Chapter 5

Strategy 4: Strategy for establishing the human vaccine plant

- Concepts for establishing the vaccine plant for Thailand
- Establishing the human influenza vaccine plant
- Summary

Chapter 5 Strategy 4: Strategy for establishing the human vaccine plant

5.1 Concepts for establishing the vaccine plant for Thailand

Scientists around the world have predicted that a pandemic influenza will be widespread and that the massive death that will arise will be as much as the pandemic influenza in 1918 that caused 25-50 million deaths (The Economist, 2005). A mathematical model by Anderson (2006) also indicates the difficulty in controlling the spreading of the influenza virus and the pandemic is assuredly going to occur in the future. Restriction of traveling or providing medication after infection needs to be implemented, but other than these, launching of an influenza vaccine is the best solution for pandemic control.

Nowadays, many vaccine plants all over the world are producing vaccine to prevent seasonal influenza virus infection. However, the current vaccine production capacity is not enough to supply to the world population if an influenza pandemic occurs. The vaccine production requires 5-6 months while the early pandemic stage takes around 6 months (Heuer, 2006). An egg-based influenza vaccine production technology has been used for over 50 years and is still the current technology used. However, the production process is time consuming since enough seed viruses must be firstly prepared by inoculation of the virus into SPF embryonated eggs. The seasonal influenza vaccines are made from trivalent vaccines. The three cold-adapted influenza virus strains are cultured in separate eggs and dilute to obtain lived attenuated influenza vaccine (LAIV). The other type of vaccine, inactivated influenza vaccine (IIV) can be produced from the influenza virus which has been purified and inactivated. If its inactivated virus particles are further split by chemical, the IIV split vaccine will be obtained. The three strains are then formulated all together with an adjuvant to strengthen the vaccine efficacy. The production process of the pandemic influenza vaccine is similar to the seasonal influenza vaccine but made from a single pandemic influenza virus strain. Handling of the pandemic virus needs strictly control, standardization and validation of the vaccine to ensure safety.

When all the facilities for producing pandemic influenza vaccine are allocated, the global capacity to produce influenza vaccine is around 300 million doses per year for seasonal influenza (trivalent vaccine), or 900 million doses per year for pandemic influenza (monovalent vaccine). The 900 million doses are adequate to supply for only 10-15% of total population at a single dose (Heuer, 2006). Most production capacity is in developed countries and 70% of the global production capacity is in Western Europe (The Economist, 2005). The current vaccine production cannot cover the demand even in the countries that have their own production capacities. It is likely that the countries lacking vaccine production ability will be insufficiently supplied with the vaccine during a pandemic. Therefore, preparing a pandemic influenza vaccine to accommodate a possible pandemic in Thailand must be immediately implemented.

[1] *Generation of vaccine from Baculovirus/insect cell system is considered as one of the cell-based technologies.*

5.2 Establishing the human influenza vaccine plant

5.2.1 Basic information

Many factors need to be considered to build the vaccine plant, but the priorities are as follows;

- Vaccine production technology

Two production technologies are the egg-based technology and cell-based technology[1]. The egg-based technology has been successfully used for over 50 years and is being employed by almost all vaccine plants. The automated machine technology is standardized and efficient, however, the limitation of egg-based technology is that the production process takes 5-6 months, 3 months for producing the vaccine after obtaining virus seed (e.g. from the WHO) and another 3 months for tests and lot release (International Information Programs, 2006). Obtaining clean eggs is a limiting factor and will be a major obstacle for the production during a pandemic. Cell-based technology is a promising alternative but its production process is still in research and development and the vaccine product is also in the process of the testing by standard regulations (Rappuoli, 2006). The egg-based technology is therefore the best currently available production technology since it has already been implemented for a period of times with automated machines being used in the process, and Good Manufacturing Practice (GMP) has been achieved.

- Production capability

Production capability must be determined before making a plan for the plant construction. It depends on demand, supply, production efficiency, and expected profit (in case of the investment from private sector). Details on determination of vaccine production capacity will be described in the following chapter.

The production capability recommended in this study is that the new plant should start its production capability at 1 million doses per year, and be able to expand to 10 million doses per year by expanding incaubating and packaging units with no demand for new construction. The capability calculation is based on the information obtained from Chinese vaccine plants most of which are in the medium production scale and have production capability around 10 million doses per year (Annex 8) and a plant in the United State with 3 million doses per year (trivalent vaccine) or 9 million doses per year (monovalent vaccine) (Wang, 2006).

- Vaccine types

Egg-based technology can be used to produce both lived attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV). Most seasonal influenza vaccine registered in the market is the inactivated influenza vaccine. For the LAIV, although million doses of this vaccine have been used over the last 30 years in Russia, information on this type of vaccine has only just been disseminated. The WHO has a keen interested in the LAIV since its production efficiency is

higher than the IIV vaccine. One egg can be used to produce only one dose of IIV vaccine while 30 doses of LAIV can be achieved due to its shorter production process. Both live attenuated and inactivated influenza vaccine use the same upstream production process. The downstream process of IIV, however, requires a virus purification process which is not needed for the LAIV. Thus, when a plant is designed for the IIV vaccine which installs more machinery and a more complicated production line, it can be modified for the LAIV production if requested. This chapter focuses on basic structure and equipment for producing inactivated influenza vaccine with the view that the LAIV vaccine is produced in the same plant as the IIV vaccine by adjusting some downstream processes.

The key issue in the production process is to pursue GMP to ensure the safety of the vaccine.The GMP specification must be planned at the beginning of plant construction with international specifications that are usually based on the US FDA or European Union (EU).

Construction of a vaccine plant using egg-based technology takes around 24-32 months from detailed design to finishing process. However, this could be shortened to 11 months (Dempsey and Matzen, 2006). The plant is composed of clean rooms according to US FDA or EU regulations (10,000/100=ISO7/5 and European class B/A). It should be designed to be at least BioSafety Level 2 (BSL 2) with the possibility to be modified to Biosafety level 3 (BSL 3) and its production process must be validated after document submission. The actual production process could be started in 1 year, after the validation process has been completed, and at the same time personnel training on GMP systems should be strengthened to increase their capacities in the GMP system.

The plant and process design can be obtained by a self-developed technology or by transferring technology from well-known manufacturers who are willing to make a contract. Developing our own technology without technology transfer would take longer time and some issues need to be considered such as the vaccine must be firstly prepared at pilot scale with standard procedures to produce enough vaccine for tested in clinical trials from phase I to phase II. This pilot scale has to achieve GMP and be able to reproduce the same quality of vaccine. International consultants may be contracted to design the plant and clean room. Based on information from vaccine manufacturers in China, the plant building size should be around 10,000 square meters. The investment would be approximately 1,800 million baht (for the building, excluding the land). The operating cost would be 200 million baht per year (Annex 8) (Dempsey and Matzen 2006). Figure 5.1 depicts the main equipment in the influenza vaccine production process. Table 5.2 is a work plan for building a vaccine plant in Thailand. With self developed technology, it would take at least 8 years to establish a human influenza vaccine plant with the production capacity of 10 million doses per year.

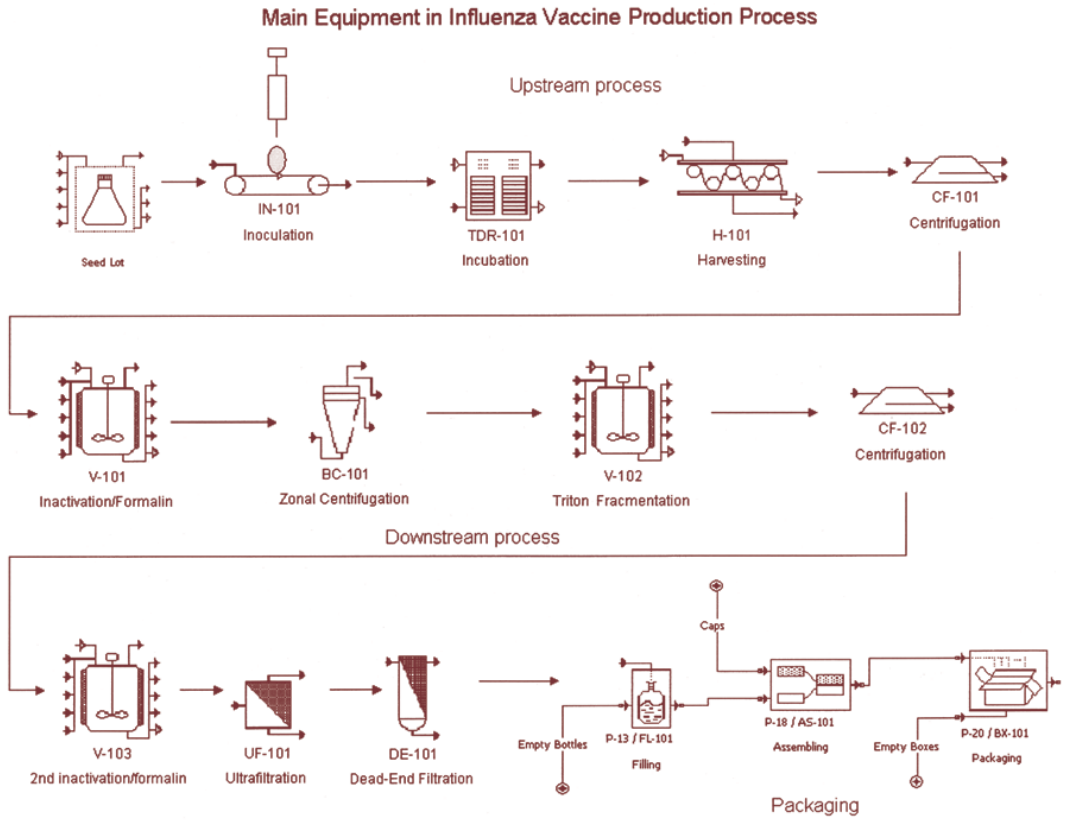

Figure 5.1 Main equipment in an influenza vaccine production process

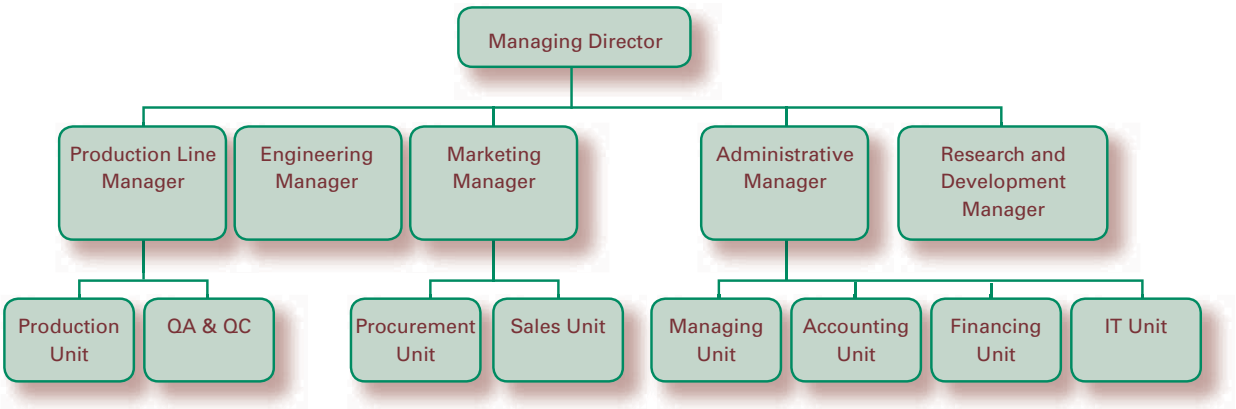

Figure 5.2 Governing structure for a vaccine plant

Table 5.1 Estimated investment and operating expenditure for building an influenza vaccine plant.

1. Budget	Estimated amount (million Baht)
1.1 Buildings and clean room - Water pretreatment system - Water For Injection (WFI) Tank - WFI Loop and system - Clean steam generator - Clean steam system - HVAC and HVAC control system - Waste inactivation system	1,000
1.2 Main production equipment - Automatic inoculation machine - Incubator - Automatic harvesting machine - Centrifugation - Filtration - Blending tank - Filling and packaging - Autoclaves - Holding tanks - Equipment for analysis	800
2. Operation expenses	
- Clean eggs - Seed virus - Clean room operation and maintenance - Salaries	200 per year

Table 5.2 Work plan for a human vaccine plant construction and vaccine production

Action	Year									
	1	2	3	4	5	6	7	8	9	10
Production process development and validation (laboratory scale)	↔									
Define the terms and conditions for the vaccine plant and find a contractor	↔									
Design and construct the vaccine plant		↔	↔							
Production process validation and apply for standard GMP				↔						
Vaccine production at capability of 1 million doses per year					→	→	→	→	→	→
Expand the production capability to 10 million doses per year								→	→	→

5.2.2 Administrative structure of a vaccine plant

The influenza vaccine plant should have semi-private administrative structure, which is flexible and efficient. Figure 5.2 depicts the governing structure for 10 million doses per year production. The administrative structure includes 80 personnel as follows:

- Managing Director 1 position
- Production Line Manager 1 position
  - Production Unit: Engineer 2 positions, worker 30 positions
  - QA and QC Unit: Engineer/biochemist 2 positions and scientist 5 positions
- Engineering Manager 1 position
  - Engineer 1 position and technician 5 positions
- Administrative Manager 1 position
  - Procurement Unit: Front-line Administrator 1 position, worker 3 positions
  - Sale Unit: Front-line Administrator 1 position, worker 5 positions
  - Managing Unit: Front-line Administrator 1 position, workers 5 positions
  - Accounting Unit 3 positions
  - Financing Unit 3 positions
  - IT Unit 2 positions
- Research and Development Manager 1 position
  - Engineer/ Scientist 5 positions

5.2.3 Critical Success Factors

Besides an investment on the plant establishment, another four success factors to produce vaccine for national security during a pandemic, as well as pre-pandemic that should be considered are as follows;

1. **Procurement of raw materials**

   Egg-based technology will be used for vaccine production in this plant. Sufficient clean eggs and Specific Pathogen Free-SPF egg must be continually supplied both in non-pandemic and pandemic situations.

2. **Research and Development (R&D)**

   Since the influenza virus and avian influenza virus continually mutate, research and development on production technology and vaccine efficiency must be constantly carried out to ensure success and sustainable vaccine plant.

   - Follow-up on the mutation of the virus

     Update on the change of virus genetics helps to follow-up the mutation, epidemiology of virus, and overall epidemic trend.

- Follow-up on the shifting of production technology
  Focus on the technology shifting and capacity strengthening on the vaccine production (to reach high surge capacity) as well as follow-up of the production standard to be able to respond to the market requirement on vaccine standard. Examples of R&D are as follows;
  - Improvement of production efficiency such as research on using less SPF egg to produce vaccine, substitution of SPF egg by clean egg in some processes, etc.
  - Development of new process and production engineering
    Cell-based technology should be developed to replace the egg-based technology in future.
  - Research on a new type of adjuvant to reduce vaccine usage with the same (or higher) efficacy.
  - R&D to improve production standards to produce high quality vaccine with better efficiency.
- Efficacy tests of the vaccine
  Both domestic and imported vaccine should be tested on their efficacy. The information obtained may help improvement of vaccine efficacy in the future.

The R&D needs corporation from several organizations, for example the Ministry of Science and Technology, universities, research organizations, granting agencies, the Ministry of Public Health, the Ministry of Agriculture and Co-operatives, etc. The role of the responsible organization is planning and doing some parts of the research according to its own capacity.

3. Human resource development

The vaccine plant and vaccine production at an industrial level require personnel with different areas of expertise. Thailand has insufficient personnel at an industrial level, so there is a need to increase numbers of the following personnel who specialize in different areas for prompt operation as follows;

- Computer engineering and Construction engineering : standard process for vaccine production
- Biochemical engineering: vaccine standard
- Environmental engineering: vaccine standard
- Pharmacist and officers: standards for vaccine production used in clinical trials such as GMP, US FDA or EU
- Pharmacist: vaccine production standards
- Pharmacist and lawyer: fast track registration
- Scientist and safety officer: Bio-safety Level 2/3
- Scientist and Veterinarian: SPF egg specialist
- Scientist: QA/QC

- Scientist: Vaccine efficacy testing
- Researcher in all R&D
- International lawyer: international patent
- Pharmacist: international patent and GMP expert

4. Technology transfer

Thailand lacks the personnel who have the knowledge and experience in vaccine production at the industrial scale. Technology transfer from other countries might be the best approach to strengthen our production capacity. The personnel and preparation for technology transfer are as follows;

- **Coordinator:** a financial analyst who has comprehensive knowledge on establishing a vaccine plant. This person would coordinate with the responsible organization.
- **Coordination plan:** the responsible organization should set a coordination plan be tween the owner of the technology to be transferred and the domestic (Thailand) plant.
- **Legal management:** issuing a confidentiality agreement, allocating a disclosure fee and a royalty fee.

5.2.4 The establishment of a vaccine plant by the Government Pharmaceutical Organization (GPO)

According to the GPO Board of Directors meeting on 26 December 2006, the Minister of Public Health appointed the Board of Directors and Managing Director of GPO to be the responsible party for the pandemic preparedness plan for national security for Thailand. The GPO will be in charge of both production and stockpiling anti-virus medicine and establishment of a human influenza vaccine plant to produce sufficient vaccines for both seasonal influenza virus strain and future pandemic influenza virus. The vaccine plant will have a production capability for both pilot scale and industrial scale with the WHO GMP standard. It is estimated that it will take at least 4 years to finish the plant construction (Minute from the fourth meeting of the GPO Board of Directors, Fiscal Year 2007). Following this, the WHO announced research grants to support countries wishing to establish their own pandemic influenza vaccine production plant, in an amount of 2 million US dollars (around 80 million Baht). Thailand is 1 of the 6 countries that are eligible to submit a proposal. The Minister of Public Health therefore appointed the GPO to be the responsible organization for this project. The GPO submitted the research proposal and was subsequently awarded this grant. The GPO is currently in the process of establishing a vaccine production process at pilot scale to obtain enough vaccine for clinical trials. This surely will accelerate the preparedness of the influenza vaccine production plant.

For construction of an influenza vaccine plant at an industrial level with WHO GMP standards from the previous appointment, the GPO proposed a 5-year plan. The location for the vaccine plant is at Tapkwang sub-district, Kangkoy District, Saraburi Province, with a budget of 1,411.70 million Baht. The proposed production capacity is 2 million doses per year, and the surge capacity is 10 million doses per year. The GPO wishes to produce inactivated influenza vaccine (IIV) for seasonal influenza

vaccine, and lived attenuated influenza vaccine (LAIV) for a pandemic influenza. The production capacity of the LAIV will be 60 doses per year (30 times that of IIV) which covers the whole population, by using egg-based technology or suitable technology (Establishing influenza vaccine project, 2007). When the influenza vaccine project is completed (expected at end of 2011), Thailand will have a vaccine plant at the industrial level with WHO GMP standards.

5.3 Summary

From previous epidemiology data and influenza epidemic situation, it is predicted to have influenza pandemic that causes massive deaths and the best prevention is a pandemic influenza vaccine. However, the current global vaccine production is insufficient for world population, which may cause vaccine shortage during the emergency period. Therefore, Thailand has an urgent need for influenza vaccine pandemic preparedness.

Currently, Thailand does not have an influenza vaccine production plant. There is only some research and development on the virus in various laboratories in university and research institutes. Another activity involved in influenza vaccine is the filling of the imported seasonal influenza by GPO-MBP Biologicals Ltd. at approximately 200,000 doses per year. It is clear that Thailand has little resources for influenza vaccine production. Investment for the infrastructure such as the building, main production equipment and personnel with experience in vaccine production plant at an industrial level is clearly necessary.

Two production technologies for influenza vaccine production have been considered; the egg-based technology and cell-based technology. The egg-based technology is a technology that the vaccine product is approved for use in human and has been employed for the influenza vaccine production for a long period already. However, there is a need for sufficient SPF and clean eggs in the production process, and the downstream process to remove egg protein contaminants, which may cause allergies in sensitive people and may be required for some certain vaccine types. Cell-based technology is a new technology which is in the R&D stage. For pandemic preparedness, the production technology for the new plant must be the well established technology. The egg-based technology fits this criterion. Although the egg-based technology has been selected for the plan of influenza vaccine manufacturing, research and development on cell-based technology in Thailand should also be encouraged since cell-based technology has several advantages compared to the egg-based technology.

The new vaccine plant is recommended to start with a production capability of 1 million doses per year (surge capacity is 4 million doses per year). It will take around 5 years for the design, construction and process validation. The plant should be built with at least Biosafety Level (BSL) 2 to 3, with the pilot plant included. Its production capability could be expand to 10 million doses per year within 8 years. The investment is around 1,800 million Baht with operating cost around 200 million Baht per year with 80 personnel. The key factors for a successful of vaccine plant are to achieve GMP standard and to establish a human resource development program for training specialists in areas such as virology, bioprocess engineering in fermentation, and the downstream processes.

Thailand lacks the experience and human resources in vaccine production at an industrial level. To build the vaccine plant within an acceptable period, there is a need for international technology transfer for plant and process design. This may be accomplished by contracting individual international consultants who have experience in construction of influenza vaccine plants or influenza manufacturers with the technology transfer experience, but the latter will cost more. Although the egg-based production technology may be transferred from one developed from abroad, Thai researchers should continue to develop our own cell-based technology since it is certain that the cell-based method will substitute the egg-based technology in the future.

5

The Minister of Public Health policy through Dr. Mongkol NaSongkla, appointed the GPO to responsible for pandemic influenza preparedness by stockpiling and production of anti-virus medicine and establishing an influenza vaccine plant. The GPO proposed 1,411.70 million Baht to the government for the operation. In addition, Thailand via the GPO has received financial support from the WHO to establish the vaccine production process at pilot plant scale.

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Chapter 6 Scale of seasonal and pandemic influenza vaccine production

- Conceptual Framework
- Scale of production of pandemic influenza vaccine in seasonal influenza vaccine plant
- Economy of scale of investment for seasonal influenza vaccine plant
- Efficient use of seasonal influenza vaccine
- Summary

Chapter 6 Scale of seasonal and pandemic influenza vaccine production

Regards to limitation of information, in some parts, the analysis concepts and scenarios were presented instead of the specific figures as there is no consensus on the most suitable figure.

6.1 Conceptual Framework

It is known that the production technologies for seasonal and pandemic influenza vaccine are similar so that the pandemic influenza vaccine plant can share building, equipment, supporting systems and personnel with the seasonal influenza vaccine. Establishing a vaccine plant for only pandemic influenza vaccine which has uncertainty of when it will take place will induce complicate management plan and inefficient use of resources. Therefore, it is well accepted that vaccine plant for pandemic influenza will produce seasonal or other vaccines during non-pandemic or pre-pandemic phase. To achieve the production standard, vaccine production needs capable personnel consistently practices with production in order to maintain skills, and expertise in vaccine manufacturing processes.

It is clear that the decision to establish a vaccine plant for pandemic influenza is based on national security reason, however, details of establishment should be based on a principle of efficiency of resource used. This concept can be applied for other aspects of national security such as military. Most of the countries need to have reserve military personnel and equipments for military operation. Planning on military defense will depend on risk assessment. Designing appropriate combinations or models of personnel and equipments will be based on capability of the personnel and equipments to manage those risks, and also the resources required to invest and foster these personnel and equipments for prompt operation.

Figure 6.1 depicts the conceptual framework of scale of production capacity of pandemic and seasonal influenza vaccine. The national security is the main reason to establish production of pandemic influenza vaccine. The production capacity of the influenza vaccine plant is based on the principle of efficiency of resource used. The key factors, to determine the production scale of pandemic influenza vaccine, are target population, target coverage, vaccine wastage rate, etc. which will be explained in details in next part. Since both production of pandemic and seasonal influenza vaccine are in the same production unit, the production unit has to have capability to increase vaccine doses such as antigen sparing factor by using adjuvant, and changing the type of vaccine production. Efficiency use of seasonal influenza vaccine will be considered in both demand and supply of vaccine. Concept of economy of scale will be applied for supply analysis. This should cover both capital investment and operating cost. However, due to limitation of information, only capital investment will be considered (section 6.3). Concept of economic evaluation will be applied for the demand analysis (details in section 6.4) to prioritize the target groups for vaccination in terms of the highest social gain or the least social burden. This conceptual framework is an example of analysis of scales for production of both seasonal and pandemic influenza vaccine.

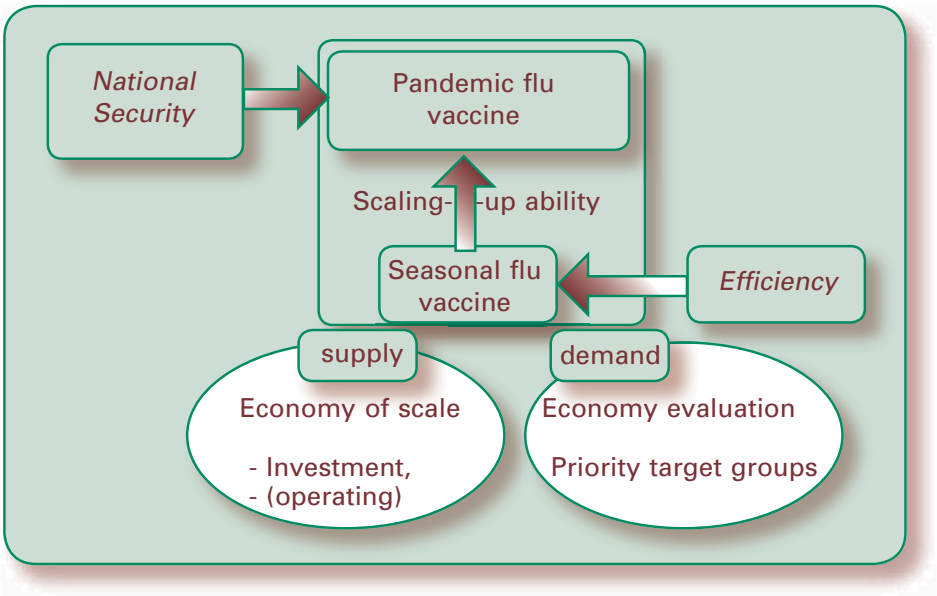

Figure 6.1 conceptual framework

6.2 Scale of production of pandemic influenza vaccine in seasonal influenza vaccine plant

The prime reason to establish influenza vaccine plant is to prepare vaccine for pandemic situation. However, during non-pandemic the seasonal influenza vaccine is the main product from the plant, the scale of production of these two vaccines is interrelated. Factors for determining scale of production capacity of pandemic influenza vaccine are presented as follows:

■ Population

If the pandemics occur, the whole population will be at risk of getting infection. Although the former pandemic's data indicated the different morbidity and mortality rates across different age groups, for example the 1918 pandemic affected the young adult more than the elderly (Schoub and Martin, 2007), there is no such information about the coming pandemics to indicate which group will be worse affected. The target population for vaccination is therefore assumed to be all of Thai population.

According to constitution for Kingdom of Thailand in BE 2550 (2007), the section 30 on the rights and freedom of Thai population;

Article 30 "An individual shall be equal in law and shall receive equal protection under law.

Men and women shall have equal rights.

Discrimination against individual on grounds of origin, ethnicity, language, gender, age, physical or health conditions, personal status, economic or social status, religion fate, education, political opinion which is not contrary to any articles of the constitution, shall not be carried out.

The government measurement that aims to eradicate barrier or to enable an individual to utilize his/her rights and freedom similar to others shall not be considered as discrimination according to the third paragraph."

And article 52 "An Individual shall have equal rights in receiving standard public health services. And the poor have rights to receive free healthcare services from public health care providers, as stated by law.

Public health services which shall be provided thoroughly and efficiently by promoting local administration and private sector to participant in as much as possible.

Government shall provide the prevention and the elimination of serious infectious diseases freely and timely to the population, as stated by law."

The influenza pandemic is life threatening infection. All Thai population has equal rights to access to public health services including vaccine (if available) and other basic life saving services. Therefore, government is responsible to prepare adequate amount of vaccine to provide to all Thai population. Defining target population is, however, different from vaccine prioritization target group which is an administrative issue for controlling disease and national security.

It must be stated that Thai people who are abroad and foreigners who stay in Thailand were not included in the calculation since it is the national security. And if the objective will be extended to be regional security, the target population should be redefined properly.

- The Coverage of target population

In practice, medical and public health services including vaccination usually do not achieve full coverage of all target population. For example, Expanded Program on Immunization (EPI) both the routine program and special campaign can not reach 100% coverage (Porpit, 2003). It is difficult to provide vaccine to all population even during the pandemic when people will be very anxious to get vaccine. Factors such as vaccine logistics, shipping, personnel to provide vaccine, necessary medical suppliers, adequacy and timeliness of the effective vaccine, etc. affect the effective coverage. Without advance preparation, it is impossible to provide vaccine to all population during the pandemic. On the other hand, proper preparing, planning and pro-active strategies can increase the vaccine coverage. The target coverage of providing vaccine during the pandemics is expected to be at 90% of the population (Supamit, 2006).

■ Wastage rate

The vaccine distribution needs good logistics and delivery systems from vaccine manufacturing point to vaccine delivery point. This includes appropriate packaging size, proper cold-chain system, good vaccination skills of personnel, etc. Generally, the wastage rates of EPI program ranged from 5% to 57% (Sirirat, 2007). If wastage rate is high, much more vaccines will have to be stocked than those required. There is an estimation that, during the pandemic, the wastage rate of vaccine distribution will be around 10% (Supamit, 2006).

■ Required doses to activate immunity

For seasonal influenza vaccine, it is generally required one dose of vaccine to stimulate protective immunity, except for the small children. It has been estimated that two doses of vaccine may be required to activate the immunity for the pandemic strain (Stephenson and Nicholson, 2001). Some clinical trial of H5N1 vaccines found that 2 doses with 3-4 week interval can induce immunity (Lin et al., 2006; Bresson et al., 2006; Condon, 2005). Therefore, if two doses are required to stimulate protective immunity for pandemic influenza, the vaccine to be prepared is twice of the population adjusted with the coverage and wastage rate.

■ Capacity to increase the vaccine production

Antigen sparing factor by adding adjuvant or changing the type of vaccine produced is one method for increase of vaccine production capacity. Adding adjuvant will reduce antigen requirement for each dose of vaccine but the vaccine is still able to stimulate immunity. There are many types of adjuvant used in inactivated influenza vaccine such as aluminum hydroxide, MF 59, etc. Generally, total antigen per dose of seasonal influenza vaccine is 45 micrograms (15 micrograms X 3 strains). The pandemic influenza vaccine is only prepared from one pandemic strain. From clinical trial phase 1 in China, it was found that 10 micrograms per dose of whole virion type of the H5N1 vaccine from Sinovac pharmaceutical company can stimulate immunity according to European regulatory requirements for annual licensing of seasonal influenza vaccine (Lin et al., 2006). A European vaccine company was successful with adjuvant system No 3 (ASO3) which can reduce the antigen usage further to 3.75 microgram and vaccine is able to stimulate adequate immunity (private interview with Dr. Johannes Lower, 20th October 2006). Therefore, one dose of seasonal influenza vaccine (45 micrograms) is equal to 12 doses of H5N1 vaccine (3.75 microgram/dose) as calculated by the figures above.

Seasonal influenza vaccine is usually made in form of inactivated vaccine (Inactivated Influenza Vaccine, IIV). With the same amount of raw material (egg), live-attenuated influenza vaccine (LAIV) can be produced with production capacity of 30 times of inactivated influenza vaccine. Changing from producing IIV during pre-pandemic situation to produce LAIV during an emergency period can increase vaccine production capacity around 30 times.

Addition of an effective and efficient adjuvant together with adjusting type of vaccine can have significant impact on increasing production capacity of pandemic vaccine in emergency situation relatively to the production capacity of seasonal vaccine in pre-pandemic phase. If the production capability can be increased by factor of 4, a plant that has its production capacity of 1 million doses per year of seasonal vaccine, will be able to produce pandemic vaccine with capacity of 4 million doses per year. The higher the factor is, the higher the production capacity of pandemic vaccine relatively to the seasonal vaccine will be. In this analysis, we assumed that adjusting adjuvant and type of vaccine has the factor of 4, 6, 12 and 30 times.

- **Timeframe for vaccine production**

Normally, production capacity is defined in terms of number of doses of vaccine produced per year. EPI vaccines do not have strict timeframe. This is different from pandemic vaccine which has to be produced and distributed to people as soon as possible to prevent the infection. From the past pandemics, it was estimated that the first wave of infection would be completed within 6 month period. From an interview with Dr. Supamit Chunsuttiwat, the chief officer of national vaccination program, he indicated that if the production of vaccine can be finished within three month period, it may be possible to distribute the vaccine to the people before the first wave of infection is finished. The shorter the timeframe for vaccine production and distribution is expected, the higher number of vaccine per batch and/or the shorter period of the vaccine production of each batch must be produced. For example, if production of 16 million doses in 3 month period is requested, it indicates that the plant should have the annual production capacity of 64 million doses per year. In this report, the timeframes for vaccine production were assumed to be 3 month, 6 month, and 12 month period.

- **Reserve capacity**

In normal situation, it is generally known that the plant does not produce seasonal influenza vaccine on its maximum capacity as there is limited demand for the products. Reserve capacity indicates the maximal production capacity relatively to the normal operational capacity. This is different from the increase capacity due to adjusting adjuvant and types of vaccine. The reserve capacity is the potential reserve in infrastructure (such as incubators, and capacity of equipments and system) and management (such as increase shift of working) in which the plant can be adjusted to increase production capacity. For example, if the factor for reserve capacity is 2 and the normal production capacity is 1 million doses per years, this plant will be able to increase its production capacity to maximal level of 2 million doses per year. The decision on reserve capacity should be considered since the beginning of concept design and detail design of the plant.

Table 6.1 presents an example of the calculation on production capacity for pandemic and seasonal influenza vaccine for 65 million of Thai population. During the pandemic, if vaccine coverage is 90% and vaccine wastage rate from uncontrolled factors is around 10%, we should prepare for 64 million doses of vaccine assumed that single dose of vaccine can activate immunity. If two doses are needed, there should be a stock of 129 million doses of vaccine.

To produce 129 million doses within 3 month timeframe, the plant should have annual capacity of 515 million doses per year without factor to increase the production capacity.

When adjuvant is used with antigen sparing factor of 12, the plant could reduce its maximum capacity to only 43 million doses of seasonal vaccine annually. To operate at 50% of its maximal level, the plant will only produce 21 million doses of seasonal vaccine per year.

Besides using highly efficient adjuvant, the production process can be modified from producing inactivated influenza vaccine (IIV) to live-attenuated influenza vaccine (LAIV). In order to produce 64 million doses of LAIV within 3 months, it is necessary to establish vaccine plant that has maximum capacity of 8.6 million doses of IIV per year. If the plant has reserve capacity of factor 2, this plant will normally operate with half of its production capacity, or 4.3 million doses of IIV per year. However, in case that the inefficient adjuvant is used or unexpectedly low yield of LAIV production, the maximum capacity of the plant must be kept higher.

The operating cost may be reduced if the normal operation (seasonal influenza vaccine production) is less than 50% of the maximum capacity with the conditions that the plant must maintain production expertise and its ability to expand to maximum capacity if necessary. However, the investment cost for infrastructure can not be cut down since it affects the maximum production capacity.

As mentioned above, the production of pandemic and seasonal vaccines are interrelated. In this section, the technical relationships of scale of production of these two vaccines were discussed. It provided some technical ideas on how large (the scale) of a new vaccine plant should be in order to achieve the prime objective of establishing it. Another viewpoint - economic aspect i.e. on the investment cost by production scale will be discussed in next section and how to make the best of the new vaccine plant will be in the section after next.

Table 6.1 Calculation of productivity of pandemic influenza and seasonal influenza vaccine

	A	B	C	D	E	F	G	H	I	J	K
1	Population	65	million								
2	Coverage	90%									
3	Wastage rate	10%									
4		pandemic flu		seasonal flu		seasonal flu		seasonal flu		Seasonal flu	
5		single dose	two dose	single dose	two dose	single dose	two dose	single dose	two dose	Single dose	Two dose
6	Factors to increase productivity	1	1	4	4	6	6	12	12	30	30
7	Timeframe	Maximum annual capacity									
8	within 12 months	64	129	16	32	11	21	5	11	2	Na
9	within 6 months	129	257	32	64	21	43	11	21	4	Na
10	within 3 months	257	515	64	129	43	86	21	43	9	Na
11	normal operational capacity	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
12	Timeframe	Annual operating scale									
13	within 12 months	32	64	8	16	5	11	3	5	1	Na
14	within 6 months	64	129	16	32	11	21	5	11	2	Na
15	within 3 months	129	257	32	64	21	43	11	21	4	na

Note: 1 dose of LAIV is required for immunization.

6.3 Economy of Scale of Investment for Seasonal Influenza vaccine plant

This part presents several investment costs by scale of seasonal influenza vaccine production. The main data were drawn from two sources. The first was "Global Pandemic Influenza Vaccine Action Plan: Moving Forward", held on 20th October 2006 at Quebec, under supports by WHO and Canadian government. In that meeting, there were presentations on progress of increase global influenza vaccine production in Brazil and Mexico. The second was from a study visit to four vaccine plants in China during 5-11 November, 2007. The information on meeting and study visit were in Annex 8.

It was found that most of the Chinese plants started the production capacity at 2 million doses per year. The plants were dedicated for influenza vaccine production both seasonal vaccine and other strains. Except the plant in Mexico which adopted cell based technology, all other plants used egg-based technology.

The investment cost for influenza vaccine production plant is based on the cost for producing the vaccine which was estimated around 1 US dollars per dose of vaccine (Dr. Marie-Paule Kieny WHO meeting 20th October, 2006). However, this is an average figure, which does not specify the scale of production. Investment cost varies with scale of production as follows:

- Sinovac Company made estimation that investment would cost around 10 million US dollars for establishing a 2 million dose of influenza vaccine per year plant (Sinovac, 2006).

- Neptunus Company has spent 25 million US dollars to establish the plant with normal operation capacity of 1 million doses per year with maximal capacity of 10 million doses per year. It was estimated that an additional investment for 12.5 million US dollars would be required to expand the production to the level of 30 million doses per year (Neptunus, 2006).

- SIBP spent 50 million US dollars to modify an old building to be a production plant of 8-10 million doses per year for seasonal influenza vaccine (SIBP, 2006).

- Hualan Company spent 50 million US dollars to establish a new plant, which is expected to have production capacity of 20 million doses per year.

- Instituto Butatan in Brazil spent 27 million US dollars to establish vaccine plant with production capacity of 30 million doses per year. The agreement on technology transfer from Sanofi Pasteur was settled in 2000 (Luna E., 2006).

- Birmex, a state enterprise of Mexico, initially invested 40-60 million US dollars to construct a vaccine plant with scale of 20 million doses per year using cell-based technology (Betancourt M. and Palacios E., 2006). Figure 6.2 depicts the capital investment by production scale, and table 6.2 presents average investment cost per dose of vaccine.

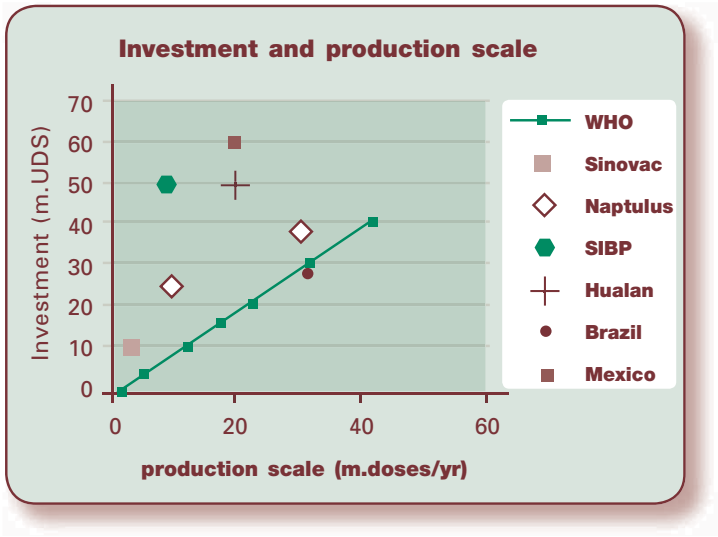

Figure 6.2 Investment cost (million US dollars) and production scale of seasonal influenza vaccine (million doses per year).

Table 6.2 Average capital Investment cost (US dollar per dose) of seasonal vaccine production according to its production scale (million doses per year) in each plant

Production scale (million doses per year)	WHO	Sinovac (China)	Neptunus (China)	SIBP (China)	Hualan (China)	Instituto Butatan (Brazil)	Birmex (Mexico)
1	1						
2	1	5					
5	1						
10	1		2.5	5			
15	1						
20	1				2.5		3
30	1		0.625			0.9	

The lowest capital investment is that of Instituto Butatan of Brazil which is 0.9 US dollars per of vaccine. This figure is close to WHO's estimation, which is 1 US dollar per dose. The lowest cost investment may be due to the agreement was done before the start of widespread epidemics of avian influenza. Neptunus and Hualan have similar unit cost of investment i.e. 2.5 US dollars per dose. Hualan's scale is 20 million doses per year while Neptunus's maximal scale is 10 million doses per year. In addition, it will cost Neptunus an additional investment of 0.625 US dollars per dose to increase the production scale from 10 to 30 million doses per year. Unit cost of investment of Sinovac and SIBP is higher than other manufacturers i.e. 5 US dollars per dose. This may be due Sinovac produces vaccine at small scale and the SIBP had to pay for the renovating the old building of SIBP. Birmex of Mexico invested around 3 US dollars per dose which is lower than what Sinovac and SIBP invested for egg-based technology. The reasons may be that the lower cost for technology transfer since the negotiation with French vaccine manufacturer was done through the French Government. In addition, Mexico has high demand of seasonal influenza vaccine because this vaccine has been added into the national vaccination program since 2004. In 2006, Mexico provided 16 million doses of seasonal influenza vaccine of which valued around 30 million US dollars to their population.

From the information mentioned above, it is suggested that the average capital investment cost should not be higher than 5 US dollars per dose. To build a new vaccine plant with egg-based technology, an appropriate capital investment should be around 2.5 US dollars per dose. The average capital cost per dose depends on production scale. From the above information, 2.5 US dollars per dose is for the production scale of 10 million doses or 20 million doses per year. These sizes of scale can be expanded to be 30 million doses per year with small marginal investment. Though there is no difference in investment cost per dose between cell-based and egg-based technology, some conditions such as government-to-government contact and being a regular large volume vaccine consumer are required for cell-based technology transfer. The information on the relationship between production of pandemic and seasonal vaccine and scale of production in terms of

technical and economic (investment) has been discussed, the next topic to consider is on how to make the best use of influenza vaccine using information regarding the use of seasonal influenza vaccine. Concept of economic evaluation was applied to set priority in term of efficiency of used to utilize this vaccine.

6.4 Efficient use of seasonal influenza vaccine

Objective of analysis

To prioritize population by age group for receiving seasonal influenza vaccine by applying an analysis of economic evaluation.

Age group

The population were classified into 20 age groups which are; less than 6 months, 6-12 months,1-2 years, 2-3 years, 3-5 years, 5-9 years, 10-14 years, 15-19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years, 40-44 years, 45-49 years, 50-54 years, 55-59 years, 60-64 years, 65-69 years, 70-74 years and more than 75 years.

Methodology

We analyzed the net cost which is the cost difference in case which seasonal influenza vaccine was provided and the case without vaccination.

Net cost = cost in case of vaccination - cost in case of no vaccination

Positive net cost means additional expense when seasonal influenza vaccination is provided for that age group. Negative net cost means that there was some cost saving if the vaccine was provided to that age group.

Cost in case of no vaccination is the cost of seasonal influenza illness because of no vaccine protection. This includes medical care cost, transportation cost for treatment and productivity loss from absenteeism of work.

- Cost in case of no vaccination = cost of influenza illness
- Cost of influenza illness = incidence rate of influenza x (medical care cost + transportation cost + productivity loss)

Medical care cost: For out - patient services, medical cost of influenza was composed of ancillary cost per OPD visit and routine service cost per OPD visits. For in - patient services, medical cost of influenza was composed of ancillary cost per admission and routine service cost per admission day times average length of stay.

- Medical cost for Influenza OPD = ancillary cost per OPD visit + routine service cost per OPD visits
- Medical cost for Influenza pneumonia = ancillary cost per admission + (routine service cost per admission day x average length of stay)

Transportation cost: Since there was no national data on transportation cost specific for seasonal influenza patients. Moreover, there was only transportation cost for admitted patients. Therefore two assumptions were applied. First, transportation cost for influenza was not different from that of other diseases. Second, the transportation cost for out-patient services was one forth of that of inpatient cases.

Productivity loss: The productivity loss was calculated from number of day of absenteeism of work and productivity cost per day. Children and elderly patient were assumed to be under the care of one person, the production loss is the productivity loss of the caregiver. For adult patient, the productivity loss is his/her absenteeism of work. For out-patient cases, an absenteeism workday was average number of days affected by the illness. The absenteeism workday for in-patient was the length of stay in hospital and number of recovery day at home, which was assumed as half of length of stay in the hospital. These numbers of day were analyzed by 20 age groups, the lost of an absenteeism of work assumed to be 100, 200, 300, 500 and 1,000 Baht per day.

Cost in case of vaccination was composed of cost of influenza vaccination and left-over cost of influenza.

- Cost in case of vaccination = cost of influenza vaccination + left-over cost of influenza

Cost of influenza vaccination was composed of cost of vaccine, cost of purchasing and delivery of vaccine, and cost of vaccinating process.

- Cost of influenza vaccination = cost of vaccine + cost of purchasing and delivery vaccine + cost of vaccinating process

Left-over cost of influenza was one minus effectiveness of vaccination times cost of influenza

- Left-over cost of influenza = (1-effectiveness)x cost of influenza

The cost estimated was the BE 2549 (2006) value. The medical care cost was adjusted by medical consumer price index while the transportation cost was adjusted by consumer price index related to transportation and communication items (Ministry of Commerce, 2007)

Coverage

In this study, the cost of seasonal influenza flu covered only (i) illness that seek out-patient treatment with influenza like illness (according to WHO definition, the body temperature is higher than 38 °C with cough or sore throat) and (ii) in - patient pneumonia. All cases were confirmed by laboratory tests such as cell culture or PCR test. For Pneumonia, the diagnosis was confirmed by chest x-ray (details of screening can be found in Simmerman et al., 2006). However, this did not cover the influenza patients with other symptoms such as ear infection, eye infection, etc. Moreover, this analysis did not cover cost of death since the epidemiological data from community-based surveillance in Srakaeo and Chaiyaphum province during 2003-2004 did not confirmed death from influenza.

Table 6.3 Data and data sources for analysis

Data	Source of Information
Epidemiological data	
▪ Out-patient influenza per person per year by age groupstudy 2003-2004	Thai-USA Collaboration (TUC) active surveillance
▪ In - patient influenza Pneumonia per person per year by age group	Thai-USA Collaboration (TUC) active surveillance study 2003-2004
▪ Average length of stay of in - patient influenza Pneumonia by age group	Thai-USA collaboration (TUC) active surveillance study 2003-2004
Medical care cost	
▪ Ancillary cost of influenza out-patient and in - patient services by age group Information	in - patient database in 2004 and out - patient database in 2002 from National Health Security Office filtered with related ICD code*
▪ Routine services cost per out-patient visit and per inpatient day	Input/output database: Form 11-5 report, Ministry of Public Health
Transportation cost	
▪ out-patient visit ▪ admission	Health and Welfare Survey of National Statistical Office in 2005, assuming that out - patient traveling cost is 25% of inpatient cost's*
Productivity loss	
▪ working absenteeism for out-patient influenza	Health and Welfare Survey of National Statistical Office 2005
▪ working absenteeism for admitted influenza pneumonia	Thai-USA collaboration (TUC) active surveillance study 2003-2004, with assumption mentioned above
▪ Productivity cost (Baht per day)	Assuming cost ranged from 100, 200, 300, 500 and 1,000 Baht per day
Cost of vaccination	Assuming cost ranged from 100, 150, 200, 250 and 300 Baht per dose**
Administrative and shipment cost	Estimated from EPI program, Department of Disease Control*
Effectiveness of influenza vaccine	- National Institute for Clinical Excellence (United Kingdom)
	- The study among working age found that vaccination reduces sick rate of 26% (Somsak Chaiwat, et al.)* - A stratified, randomized, double blind control trial of 635 elderly (60 years up) found that, with influenza vaccination, the relative risk of ILI was reduced by 56%, (Praditsuwan, et al. 2005)
Medical CPI, and CPI of transportation and communication	Ministry of Commerce (2007)

Note:

* *Veena Bhakdisirivichai (2007)*

** *Sale prices of vaccine outside the country ranged between 3-9 US dollars per dose or 120-360 Baht per dose (exchange rate of 40 Baht per 1 US dollar). In 2006, local selling prices ranged from the minimum price at 167 Baht per dose and maximum price at 412 Baht per dose, with the average price of 287 Baht per dose. If there is a domestic production, it was estimated that vaccine cost (exclude marketing cost) would be around 30% of the sale price. Information on vaccine price purchased by Department of Disease Control was presented in Chapter 2.*

Analysis perspective

This analysis was carried out in two perspectives; societal perspective and health insurance perspective. For societal perspective, the analysis covered all costs while the health insurance perspective concerned only the medical care cost. Transportation cost incurred to patient or family and productivity loss incurred to employer, or patient him/herself were not covered in health insurance viewpoint.

Information for analysis and their sources are indicated in table 6.3

Analysis Results

The results indicated that cost of seasonal influenza illness in case of vaccination and no vaccination and net cost varied by age group. For example, in the scenario that cost of vaccine was 150 Baht per dose, productivity cost was 200 Baht per day and effectiveness of seasonal influenza vaccine was 70 % (Table 6.4), cost of seasonal influenza illness without vaccination for age group of less than or equal to 6 months old were 139 Baht and 164 Baht per person for societal and health insurance perspective, respectively. Cost in the societal perspective was higher than that of health insurance perspective since it covered the productivity loss for both patient and care giver if the patient is children and elderly. The cost in case of vaccination was 325 baht per person in insurance perspective and 333 baht per person in societal perspective. Net cost (cost in case of vaccination minus cost in case of no vaccination) was 186 Baht per person in health insurance perspective, and 168 Baht per person in societal perspective. It meant that providing seasonal influenza vaccine for population who was 6 months old or less, additional resource around 186 Baht per person in social perspective, or 168 Baht per person in health insurance perspective is needed. The net cost in health insurance perspective is higher than social perspective because the potential benefit both from cost saving from avoided work absenteeism was not included in calculation of health insurance perspective.

The net cost indicated whether additional resources are required to provide seasonal influenza vaccine. The negative net cost meant that providing seasonal influenza vaccine would result in some saving. On the contrary, positive net cost and high net cost mean it needs a large amount of additional resource to provide seasonal influenza vaccine. Comparing among different age groups, the vaccine should be provided to the age group with the lowest net cost first and followed by the higher one.

Table 6.4 Cost and net cost of seasonal influenza illness (Baht per case) in health insurance perspective and societal perspective in case of vaccination and no vaccination of different age group in the scenario that cost of vaccine was 150 baht per dose, productivity loss was 200 baht per day with 70% vaccine effectiveness

Age group	vaccination		no vaccination		Net Cost	
	health insurance perspective	societal perspective	health insurance perspective	societal perspective	health insurance perspective	societal perspective
1. < 6 mo	325	333	139	164	186	168
2. 6-12 mo	295	299	39	52	256	247
3. 1-2 yr	294	299	35	52	259	247
4. 2-3 yr	286	288	9	17	277	271
5. 3-5 yr	292	297	29	44	263	252
6. 5-9 yr	288	291	14	26	273	265
7. 10-14 yr	286	290	11	24	276	266
8. 15-19 yr	285	288	6	15	279	273
9. 20-24 yr	285	287	6	13	279	274
10. 25-29 yr	284	285	4	7	280	278
11. 30-34 yr	286	290	10	24	276	266
12. 35-39 yr	285	287	6	11	279	276
13. 40-44 yr	287	292	13	29	274	263
14. 45-49 yr	288	291	15	25	273	266
15. 50-54 yr	289	302	20	62	269	240
16. 55-59 yr	291	302	25	63	265	239
17. 60-64 yr	302	338	61	183	240	155
18. 65-69 yr	303	327	66	147	237	181
19. 70-74 yr	305	341	71	192	233	149
20. > 75 yr	330	370	157	288	173	82

The analysis were carried out in many scenario such as productivity cost ranged from 100-1,000 Baht per day (Figure 6.3 A, Figure 6.3 B and Table 6.5), price of vaccine from 100-300 Baht per dose (Figure 6.4 and Table 6.6) and 30%-90% effectiveness of vaccine on preventing infection (Figure 6.5 and Table 6.7).

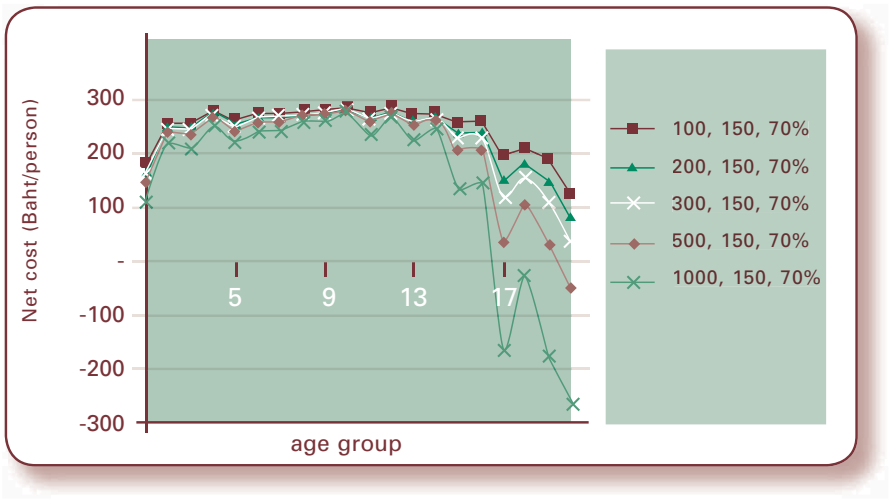

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Figure 6.3 A Net cost with and without seasonal influenza vaccination (Baht per person) of different age groups in **social perspective** of the scenario that cost of vaccine was 150 Baht per dose, productivity loss was 100, 200, 300, 500 or 1,000 Baht per day with 70% vaccine effectiveness.

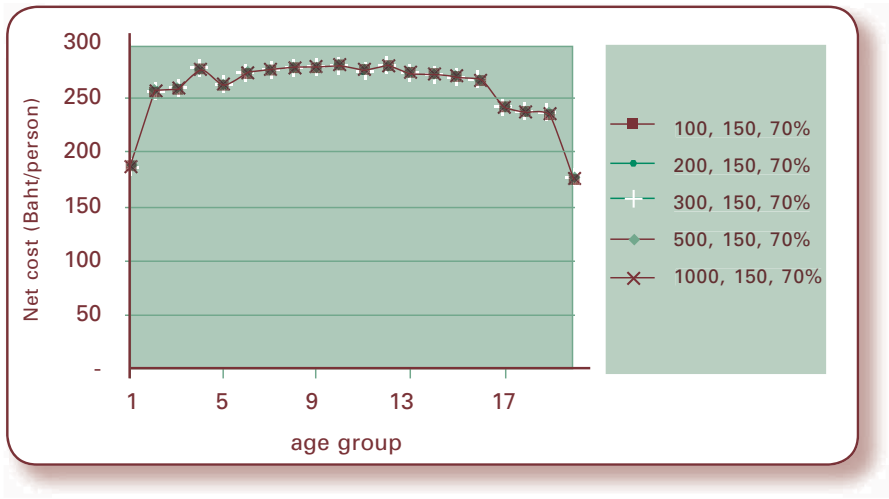

Figure 6.3 B Net cost with and without seasonal influenza vaccination (Baht per person) of different age groups in health **insurance perspective** of the scenario that cost of vaccine was 150 Baht per dose, productivity loss was 100, 200, 300, 500 or 1,000 Baht per day with 70% vaccine effectiveness.

Table 6.5 Net cost for case with and without seasonal influenza vaccination (Baht per case) of different age groups in social perspective and health insurance perspective of the scenario that cost of vaccine was 150 Baht per dose, productivity loss was 100, 200, 300, 500 or 1,000 Baht per day with 70% vaccine effectiveness

Age group	Productivity lost (Baht per day)									
	100		200		300		500		1,000	
	HI	S	HI	S	HI	S	HI	S	HI	S
1. <6 mo	186	176	186	168	186	160	186	145	186	106
2. 6-12 mo	256	251	256	247	256	234	256	235	256	214
3. 1-2 yr	259	252	259	247	259	242	259	231	259	205
4. 2-3 yr	277	274	277	271	277	269	277	264	277	251
5. 3-5 yr	263	257	263	252	263	247	263	238	263	214
6. 5-9 yr	273	269	273	265	273	261	273	254	273	235
7. 10-14 yr	276	271	276	266	276	262	276	254	276	232
8. 15-19 yr	279	276	279	273	279	270	279	265	279	252
9. 20-24 yr	279	276	279	274	279	272	279	268	279	258
10. 25-29 yr	280	279	280	278	280	278	280	276	280	271
11. 30-34 yr	276	271	276	266	276	262	276	253	276	230
12. 35-39 yr	279	277	279	276	279	247	279	270	279	262
13. 40-44 yr	274	268	274	263	274	258	274	247	274	221
14. 45-49 yr	273	269	273	266	273	262	273	256	273	239
15. 50-54 yr	269	253	269	240	269	226	269	199	269	132
16. 55-59 yr	265	252	265	239	265	227	265	203	265	142
17. 60-64 yr	240	195	240	155	240	116	240	37	240	-160
18. 65-69 yr	237	207	237	181	237	155	237	103	237	- 27
19. 70-74 yr	233	188	233	149	233	109	233	30	233	-168
20. >=75 yr	173	125	173	82	173	38	173	-48	173	-265

Note:
HI was health insurance perspective while S was societal perspective

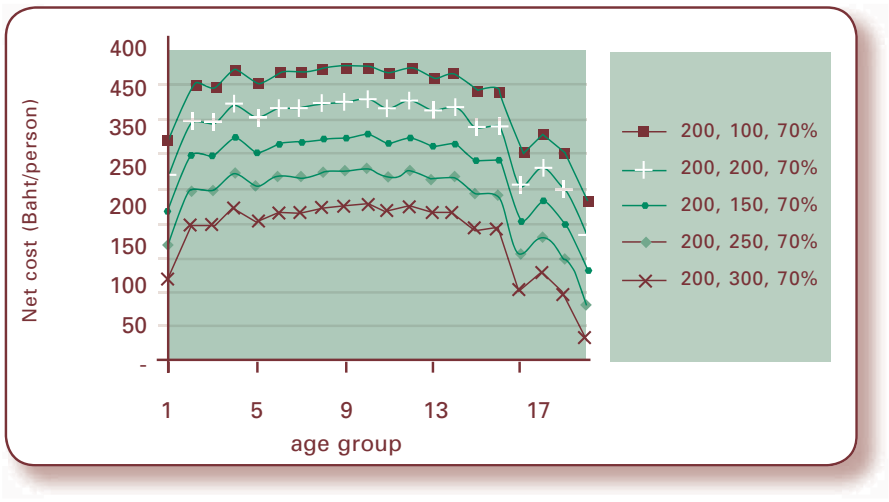

Figure 6.4 Net cost with and without seasonal influenza vaccination (Baht per person) of different age groups in **social perspective** of the scenario that cost of vaccine was 100,150, 200, 250 or 300 Baht per dose, productivity loss was 200 Baht per day with 70% vaccine effectiveness.

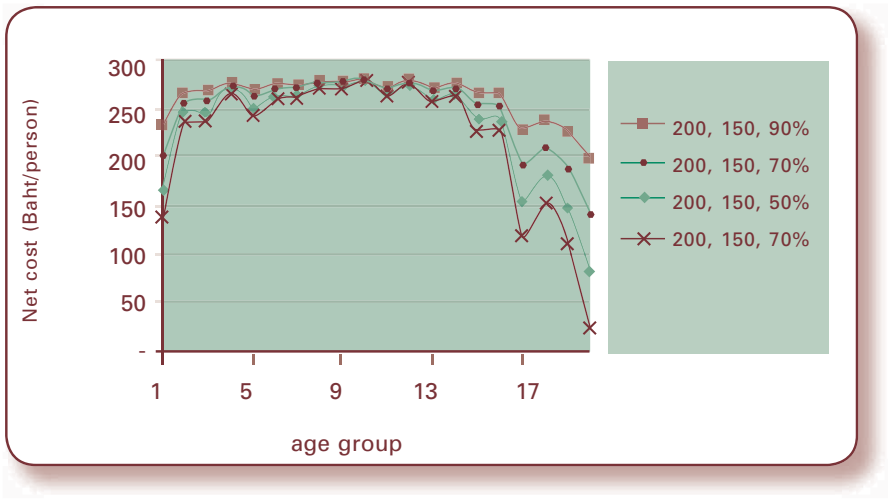

Figure 6.5 Net cost with and without seasonal influenza vaccination (Baht per case) of different age groups in **social perspective** of the scenario that cost of vaccine was 150 Baht per dose, productivity loss was 200 Baht per day with 30%, 50%, 70% or 90% vaccine effectiveness.

Table 6.6 Net cost for case with and without seasonal influenza vaccination (Baht per case) of different age groups in social perspective and health insurance perspective of the scenario that cost of vaccine was 100, 150, 200, 250 or 300 Baht per dose, productivity loss was 200 Baht per day with 70% vaccine effectiveness

Age group	Vaccine cost (Baht per dose)									
	100		150		200		250		300	
	HI	S	HI	S	HI	S	HI	S	HI	S
1. <6 mo	136	118	186	168	236	218	286	268	336	318
2. 6-12 mo	206	197	256	247	306	297	356	347	406	397
3. 1-2 yr	209	197	259	247	309	297	359	347	409	397
4. 2-3 yr	227	221	277	271	327	321	377	371	427	421
5. 3-5 yr	213	202	263	252	313	302	363	352	413	402
6. 5-9 yr	223	215	273	265	323	315	373	365	423	415
7. 10-14 yr	226	216	276	266	326	316	376	366	426	416
8. 15-19 yr	229	223	279	273	329	323	379	373	429	423
9. 20-24 yr	229	224	279	274	329	324	379	374	429	424
10. 25-29 yr	230	228	280	278	330	328	380	378	430	428
11. 30-34 yr	226	216	276	266	326	316	376	366	426	416
12. 35-39 yr	229	226	279	276	329	326	379	376	429	426
13. 40-44 yr	224	213	274	263	324	313	374	363	424	413
14. 45-49 yr	223	216	273	266	323	316	373	366	423	416
15. 50-54 yr	219	190	269	240	319	290	369	340	419	390
16. 55-59 yr	215	189	265	239	315	289	365	339	415	389
17. 60-64 yr	190	105	240	155	290	205	340	255	390	305
18. 65-69 yr	187	131	237	181	287	231	337	281	387	331
19. 70-74 yr	183	99	233	149	283	199	333	249	383	299
20. >75 yr	123	32	173	82	223	132	273	182	323	232

Note: HI was health insurance perspective while S was societal perspective

Table 6.7 Net cost for case with and without seasonal influenza vaccination (Baht per case) of different age groups in social perspective and health insurance perspective of the scenario that cost of vaccine was 150 Baht per dose, productivity loss was 200 Baht per day with 30%, 50%, 70% or 90% vaccine effectiveness

Age group	Effectiveness of vaccine							
	30%		50%		70%		90%	
	HI	S	HI	S	HI	S	HI	S
1. < 6 mo	242	234	214	201	186	168	158	135
2. 6-12 mo	272	268	264	257	256	247	248	237
3. 1-2 yr	273	268	266	257	259	247	252	237
4. 2-3 yr	281	278	279	275	277	271	275	268
5. 3-5 yr	274	270	269	261	263	252	257	243
6. 5-9 yr	279	275	276	270	273	265	270	260
7. 10-14 yr	280	276	278	271	276	266	274	262
8. 15-19 yr	281	279	280	276	279	273	278	270
9. 20-24 yr	281	279	280	277	279	274	278	272
10. 25-29 yr	282	281	281	280	280	278	280	277
11. 30-34 yr	280	276	278	271	276	266	274	262
12. 35-39 yr	282	280	280	278	279	276	278	273
13. 40-44 yr	279	275	277	269	274	263	272	257
14. 45-49 yr	279	276	276	271	273	266	270	261
15. 50-54 yr	277	265	273	252	269	240	265	227
16. 55-59 yr	276	264	271	252	265	239	260	227
17. 60-64 yr	265	228	253	192	240	155	228	119
18. 65-69 yr	263	239	250	210	237	181	224	151
19. 70-74 yr	262	226	248	187	233	149	219	110
20. >75 yr	236	197	205	139	173	82	142	24

Note: HI was health insurance perspective while S was societal perspective

Considering net cost in social perspective, the first 5 age groups that had the lowest net cost (the high priority to get vaccination) were group of 75 years old or older, 70-74 years, 60-64 years, 6 months or less, and 65-69 years accordingly. Five groups with highest net cost (the low priority groups) are group of 25-29 years, 35-39 years, 20-24 years, 15-19 years and 2-3 years, accordingly. The priority was slightly different in various scenarios. Risk factors such as chronic conditions were not included in this analysis.

Discussion:

Value of productivity loss (Baht per day), vaccine cost (baht per dose) and effectiveness of vaccine had different impacts on the net cost (Table 6.8). The higher the effectiveness of vaccine, the lower the net cost. The higher the vaccine cost, the greater the net cost. As mentioned earlier, net cost indicated the extra resources needed for providing seasonal influenza vaccination to each age group.

Table 6.8 Impacts of productivity loss, vaccine cost and effectiveness of vaccine on net cost

	High Value	Low Value
Productivity loss	Deceased Net Cost	Increased Net Cost
Vaccine cost	Increased Net Cost	Deceased Net Cost
Effectiveness of vaccine	Deceased Net Cost	Increased Net Cost

Net cost can also be viewed as the cost of influenza vaccination minus the offset cost. The offset cost was the potential benefit of vaccine in reducing medical care cost, transportation cost, and productivity cost.

Net cost = cost of influenza vaccination - offset cost

Offset cost depended on the effectiveness of influenza vaccine and cost of influenza in which the productivity loss was a part of it. The cost of vaccine directly affects cost of influenza vaccination.

The analysis results were used for sorting priority age groups for seasonal influenza vaccine from the highest priority (most significant) age group to the lowest priority (least significant) in the scenario that the productivity loss was 200 Baht per day, vaccine cost was 150 Baht per doses and 70% effectiveness of vaccine as shown in Table 6.9 and Figure 6.6.

If the seasonal influenza vaccine was to provide to the highest priority group i.e. group 75 year or older which was approximately 1.5 million people (or 2.2% of the Thai population), the cost of vaccination would be 414 million Baht. The potential benefit as the offset cost would be around 294 million Baht or 14.4% of overall offset cost. If we considered the net cost (the difference between cost of vaccination and offset cost), the vaccination for 75 year or older group would require about 119 million Baht or 0.7% of the resources required in the case of vaccination to all age groups.

The vaccination for the 5 most significant groups (75 or more age group, 70-74 years, 60-64 years, < 6 months and 65-69 years group) would cover 7.3 million population or 11.2% of the total population. The vaccination cost would be 2,076 million Baht and the offset cost would be 1,002 million Baht or 48.8% of the total offset cost. Considering both vaccination cost and offset cost, the vaccination of the 5 most significant groups would require 1,075 million Baht or 6.5% of the resource required in the case of vaccination to all age groups.

In the case that the vaccination cost i.e. vaccine cost, cost of vaccine logistics and cost of delivering vaccine was reduced to 150 baht per person, in the scenario that the productivity loss was 200 baht per day and effectiveness of the vaccine was 70%, vaccinating 75 or older age group would result in negative net cost. Or in the other word, the vaccination of this age group would incure more return to the society than the invest cost. If the vaccine was provided to the top five highest priority groups, it would consume extra resource of 98 million Baht for 7.3 million populations with 48.8% of the total offset cost. Therefore, measures to reduce cost of vaccination including vaccine cost, efficient vaccine logistics and distribution system, were very important in determining the resources needed for providing the vaccine and the number of population accessible to the vaccine.

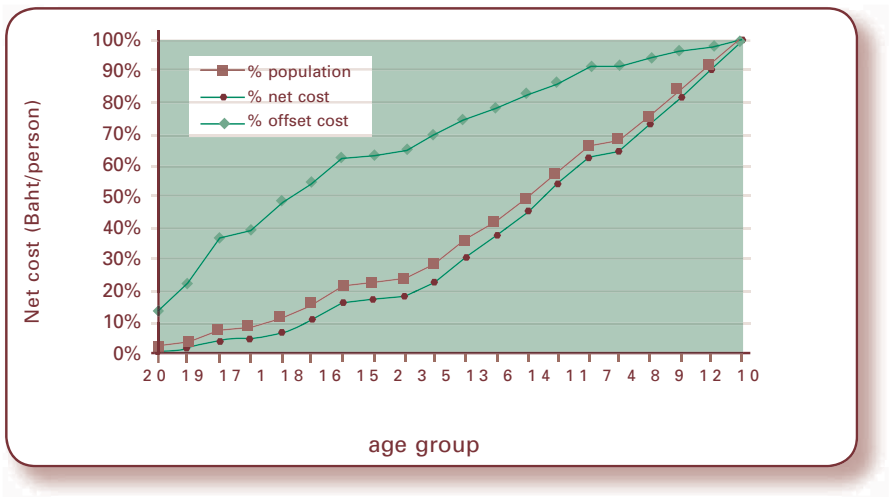

Figure 6.6 Cumulative percentage of net cost, offset cost and population sorted by high to low priority age groups.

Table 6.9 Costs and Net cost (with and without seasonal influenza vaccination) sorted by the priority age group in societal perspective in the scenario that vaccine cost was 150 Baht per dose, productivity loss was 200 Baht per day and 70% vaccine effectiveness

Priority group	Age group	Population by age group (million)	Cumulative population* (million)	Cost of influenza vaccination (Baht per person)	Total cost of vaccination (million Baht)	% cumulative cost of vaccination *	Offset Cost (Baht per person)	Total offset cost (million Baht)	% cumulative offset cost *	Net cost (Baht per person)	Total net cost (million Baht)	% cumulative net cost*
1	=>75 yr	1.461	1.461	283	414	2.2%	201.54	294	14.4%	82	119	0.7%
2	70-74 yr	1.334	2.794	283	378	4.3%	134.50	179	23.1%	149	198	1.9%
3	60-64 yr	2.215	5.009	283	627	7.7%	128.08	284	36.9%	155	344	4.0%
4	< 6 mo	0.508	5.517	283	144	8.5%	115.06	58	39.8%	168	85	4.6%
5	65-69 yr	1.813	7.330	283	514	11.2%	102.58	186	48.8%	181	328	6.5%
6	55-59 yr	2.856	10.186	283	809	15.6%	43.94	125	54.9%	239	683	10.7%
7	50-54 yr	3.789	13.975	283	1,073	21.4%	43.38	164	63.0%	240	909	16.2%
8	6-12 mo	0.508	14.483	283	144	22.2%	36.32	18	63.9%	247	125	17.0%
9	1-2 yr	0.936	15.418	283	265	23.7%	36.15	34	65.5%	247	231	18.4%
10	3-5 yr	2.740	18.158	283	776	27.9%	31.12	85	69.7%	252	691	22.6%
11	40-44 yr	5.257	23.415	283	1,489	35.9%	20.35	107	74.9%	263	1,382	31.1%
12	5-9 yr	3.932	27.348	283	1,114	42.0%	18.27	72	78.4%	265	1,042	37.4%
13	45-49 yr	4.734	32.082	283	1,341	49.2%	17.66	84	82.4%	266	1,257	45.1%
14	30-34 yr	5.464	37.546	283	1,548	57.6%	16.83	92	86.9%	266	1,456	53.9%
15	10-14 yr	5.193	42.739	283	1,471	65.6%	16.80	87	91.2%	266	1,384	62.4%
16	2-3 yr	1.012	43.751	283	287	67.1%	11.93	12	91.8%	271	275	64.0%
17	15-19 yr	5.244	48.995	283	1,485	75.2%	10.24	54	94.4%	273	1,432	72.8%
18	20-24 yr	5.318	54.313	283	1,506	83.3%	8.91	47	96.7%	274	1,459	81.7%
19	35-39 yr	5.517	59.830	283	1,563	91.8%	7.62	42	98.7%	276	1,521	90.9%
20	25-29 yr	5.353	65.183	283	1,516	100.0%	4.81	26	100%	278	1,491	100.0%
Total		65.183			18,464			2,052			16,412	

*Note: * calculation from cumulative amount or percentage from the highest priority group to the determined group.*

Phasing of Extending coverage:

To support the production of the new vaccine plant, it is best to increase consumption of the seasonal influenza vaccine in the country. Currently, Thailand, with the current population of 65 millions, purchased around 200,000-400,000 doses of seasonal influenza vaccine annually. From the analysis in Table 6.1, the target vaccine production for the smallest size vaccine plant to cover all Thai population in 3 months should be 8.6 million doses per year. If the normal operating of the plant was about 50% of the maximum, the plant would routinely produce 4.3 million doses of seasonal vaccine per year to maintain the potentiality of adequate production in emergency situation. A plan to expand the vaccine consumption to the level of 4.3 million doses per year should therefore be implemented. Currently, the Department of Disease Control plans to increase the consumption of seasonal influenza vaccine up to 1 million doses per year. This will start with public health and medical personnel. Besides these groups, information from above analysis would be useful in setting up the priority group for seasonal influenza vaccination. Other risk factors such as chronic conditions should be included in further analysis. The relationship of the expansion of seasonal vaccine consumption and production capacity in normal and pandemic influenza vaccine was presented in Figure 6.7.

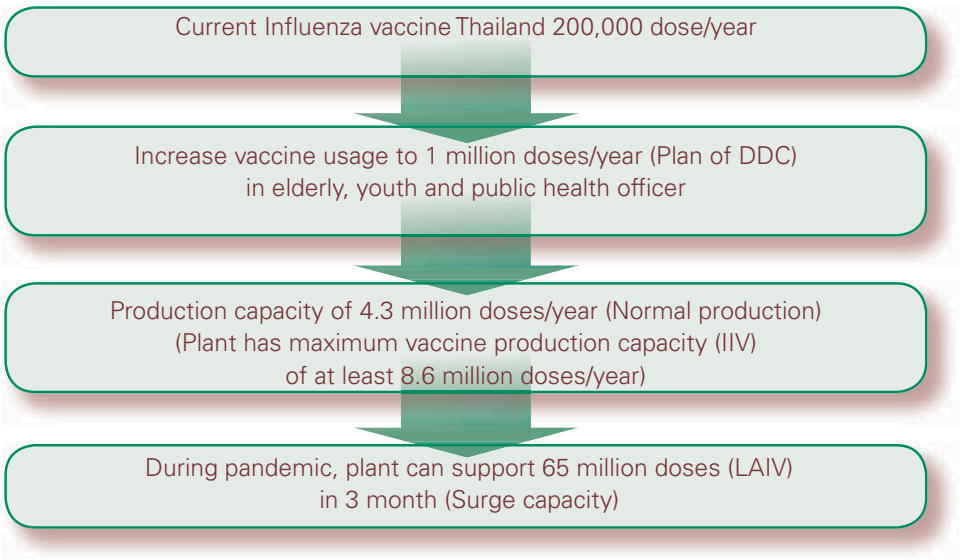

Figure 6.7 Example of the expansion of seasonal influenza vaccination utilization in Thailand.

This analysis will be a useful input for priority setting for launching seasonal influenza vaccine. In the analysis, priority was set according to net cost or resources needed for providing vaccine to specific age groups. However, the number of target population was not determined by the model but by the existing resources available. The more groups to cover, the more resources required. Since the seasonal influenza is an annual vaccine, thus the extra resources are also needed every year. It was estimated that to provide seasonal influenza vaccine to the top 5 most significant age groups would require resources more than the current annual budget for implementing all vaccines under the EPI program. Therefore, policy decision on setting target group for seasonal influenza vaccine is very crucial. Short- and long-term financial implication and returns should be seriously considered.

6.5 Summary

This chapter presented ideas to consider the production capacity of influenza vaccine for both pandemic and seasonal. Establishing of a vaccine plant for influenza should be based on both the national security and efficiency of resources use. The production capacity of pandemic influenza vaccine and seasonal influenza vaccine must be estimated concurrently since they are on the same production unit. To examine the scale of pandemic vaccine production in seasonal influenza vaccine plant, 7 factors were considered i.e. population, target coverage, vaccine wastage, required doses per person, capacity to increase production such as antigen sparing and changing vaccine type, production timeframe, and reserve capacity. With the best available adjuvant, the vaccine plant should have maximum production capacity of 43 million doses per year in order to produce two doses of inactivated vaccine for the whole Thai population within 3 moth period. However, if a single dose of live-attenuated vaccine is to be used for the whole population in similar timeframe, the new plant should have maximum capacity of only 8.6 million doses of inactivated vaccine per year. With current production technology, establishing vaccine plant with lesser maximum capacity may increase risk of insufficient vaccine production during emergency period.

On investment cost analysis of establishing influenza vaccine plant, it indicated that an average investment cost should be around 2.5 US dollars per dose for the scale of 10-20 million doses of egg-based technology. Specific conditions were observed for lower investment cost or accessibility to cell-based technology. With limitation of information, economy of scale of operating cost cannot be analyzed.

On demand side analysis, the economic evaluation concept was applied for setting priority group for seasonal influenza vaccine. It was found that the elderly should receive the vaccine. How far the expansion of the coverage should be is determined by the availability of resources. As the cost of providing vaccine is expected to be higher than returns from vaccination, the more vaccine is provided, the more additional resource is needed. However, if the vaccine is produced at low cost with the improve efficiency of vaccine distributing and delivery system, the additional resources needed to provide the vaccine to the top five priority groups would be marginal. Besides, the cost of establishing the new plant and maintaining the plant with seasonal vaccine production is much less than potential loss from pandemic situation.

There was a number of limitations, especially on the information, in the analysis. Many assumptions were applied to analyze the existing information. Adjustment of the assumptions with up to date data will improve the analysis results closer to the real situation and more useful for making proper policy on influenza vaccine preparedness in the future.

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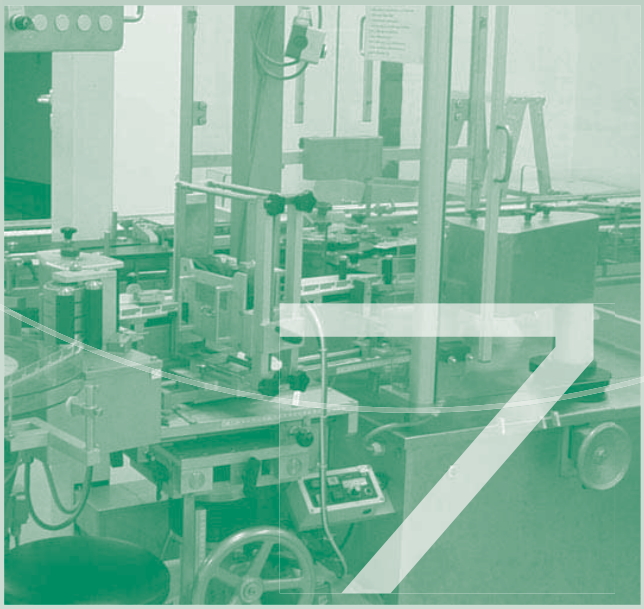
Chapter 7

Production Standard, Law and Regulation for Vaccine Registration During Emergency

- Production in Good Manufacturing Practice (GMP) Standard
- Law and Regulation for Vaccine Fast Track Registration



Chapter 7 Production Standard, Law and Regulation for Vaccine Registration During Emergency

7.1 Production in Good Manufacturing Practice (GMP) standard

7.1.1 Main Principle

Currently, every pharmaceutical manufacturer in Thailand must follow the Good Manufacturing Practice (GMP) that has been issued and is legally enforced (1). This GMP regulation has been developed from the WHO's recommendation (WHO Technical Report Series No. 823, 1992; Good Manufacturing Practice for Pharmaceutical Products) which contents contain the general principles of GMP and regulation for all sterile products.

The WHO later revised this regulation by separating it into two issues as follows:

1. WHO Technical Report Series No. 902, 2002; Good Manufacturing Practices for sterile products
2. WHO Technical Report Series No. 908, 2003; Good Manufacturing Practices for pharmaceutical products: main principles

For vaccine, that is classified as a biological product, the manufacturer has to follow the Good Manufacturing Practice for biological products which was developed from the WHO Technical Report Series No. 822, 1992; Good Manufacturing Practice for Biological Products and which is legally enforced (2).

The Pharmaceutical Inspection Co-operation Scheme or PIC/S, is another association that sets regulations for GMP and its performance is now recognized worldwide. There are 29 membership countries and most of them located on the European continent. The United State of America also expressed desire to be a new member on 16 September 2005. It regularly takes 3 years to inspect the standard GMP of a country that applies for its membership. Thailand, via the Food and Drug Administration (FDA) has also applied for the PIC/S membership since 24 February 2006.

PIC/S guidelines for the Good Manufacturing Practice for Medicinal Products, PE 009-6, 5 April 2007 has its content and scheme relatively similar to the WHO's guideline. The difference is the higher creditability of the PIC/S' membership because the GMP inspection organization of particular member country must pass the requirement of the committees assigned from the other PIC/S members. A country that has adopted the GMP guidelines from the WHO is not obliged to pass the evaluation unless upon request.

For standard influenza vaccine manufacturing, there are two WHO's documents that issue some guidelines. One is the WHO Technical Report Series 638, 1979; Annex 3 Requirements for influenza vaccine (inactivated) and for influenza vaccine (live). Another one is WHO Technical Report Series 927, 2005; Annex 3 Recommendations for the production and control of influenza

vaccines. With regard to vaccine transportation, distribution and preservation, some guidelines can be found in WHO Technical Report Series 937, 2006; Annex 5 Good distribution practices for pharmaceutical products and WHO Technical Report Series 908, 2003; Annex 9 Guide to good storage practices for pharmaceuticals.

7.1.2 Drug Manufacturing License and GMP Certificate

Vaccine manufacturers are legally obligated to acknowledge and adopt the GMP standard into the vaccine production plants. Characteristics and properties of their products must be fully understood before requesting for a modern drug manufacturing license and drug license from the Thai FDA. The details of the procedure are on the web site of the Thai FDA http://www.fda.moph.go.th. Requirements for registration are;

1. Request for a Modern Drug Manufacturing License
2. Request for a Pharmacopoeia registration
3. Request for GMP Certificate by having the remedy for production with the following data/form;
    - 3.1 Process validation in commercial batch size not more than three production lots
    - 3.2 Stability Study
    - 3.3 Applicant form for plant survey to receive a GMP Certificate and related documents to the FDA as follows:
        - Copy of Modern Drug Manufacturing License
        - Plant Master File or Site Master File
        - Quality Manual
        - List of SOPs

7.1.3 GMP Standard of Vaccine Plant

As stated above, Thailand's GMP standard is under revision and about to follow the PIC/S (Guide to Good Manufacturing Practice for Medicinal Products, PE 009-5, 1 August 2006). Thus, vaccine manufacturers must thoroughly study the details of its regulations especially the following principles.

1. Standard of cleanliness level in the manufacturing area

Vaccines are classified in the sterile drug category. According to the GMP standard, the manufacturing process including transportation, relocation, package preparation, mixing packaging, etc. must be carried out in a clean area, especially for the vaccines that cannot be sterilized after packaging. To reduce the chance of contamination, the manufacturing process must be performed as an aseptic process with strict control of the level of dust particles and numbers of microorganisms in the process area.

Cleanliness classification directly affects the product quality. The buildings structure plays an essential part for the cleanliness level as defined. The designer, constructor and related personnel must comprehensively study the clean room principles and understand the production process and properties of the products.

There are several countries that provide their own clean room standards such as US Federal Standard 209E, Britain BS 5295 and Japan JIS B 9920, etc. This causes difficulty for citation and reference. Therefore, an attempt to assemble those standards into a single standard was performed by The International Organization for Standardization. This standard is the Cleanrooms and Associated Controlled Environments Standard (ISO 14644) which is widely accepted in the EU and USA.

GMP guidelines on what activity is operating in which cleanliness level is clearly specified especially in the new GMP Guidelines of PIC/S or of US FDA or the current WHO guidelines. These new guidelines have defined the cleanliness level in operation while the previous GMP guideline from the WHO did not clearly indicate this issue which may have lead to misunderstanding that the examination and measurement could be done at rest.

2. Biosafety

Manufacturing of biological products requires a special specification to control the risk of contamination of pyrogen, microorganisms or other particles into the products. The manufacturing process may involve in use of cell/microbial culture, disease causing microorganisms, toxin extraction, etc. Protection systems for the safety of the operators and environment such as water drainage or dispersal to the surroundings outside the plant must be implemented. Especially, for avian influenza/influenza vaccine production, it was suggested by many organizations that manufacturers should adopt the regulations of Containment Laboratory – Biosafety Level 3 such as;

- The cracks of the ceiling must be sealed to prevent the contamination from above the ceiling.
- The Air Handling Units must be specifically designed for each area depending on the risk from microorganism contamination. It is not allowed for air from the bio-working area to circulate to other areas unless recycling to the same place.
- Positive pressure control should be conducted for the aseptic drug/vaccine manufacturing area (no contaminants allowed). Negative pressure control should be used to contain disease causing organism/microbes.
- The area surrounding the negative pressure control area or bio-safety cabinet should be a sterile positive pressure control area.

More details are in the Laboratory Biosafety Manual, 3rd edition, 2004, WHO or Biosafety in Microbiological and Biomedical Laboratories, 4th edition, 1999, US CDC&NIH, etc.

3. Quality Management

Qualified buildings and manufacturing equipment are not sufficient to ensure that the product will meet the standards and safety required. It is necessary that the manufacturer integrates good quality management into the production process. This ensures that the product quality meets the drug regulation requirement. To achieve this objective, it is a responsibility of chief executive with co-operation of all personnel involved. Quality assurance must be well planed and organized. This includes the good measures in production and quality control, good paper work and effective follow up, sufficient resources and personnel with suitable working areas, equipment and facilities.

The basic principles of quality assurance, highly qualified manufacturing and quality control are related and correlated. The following sections explain the relationship and importance of the production and quality control of pharmaceutical products.

3.1 Quality Assurance

Quality assurance generally covers every aspect that affects the drug/product quality. Quality assurance and good management ensure that the drug/product will meet the specified standards and utilization objectives as in the following examples;

- Drug has been designed and developed according to GMP and Good Laboratory Practice (GLP).
- The manufacturing procedure is clearly defined and controlled with GMP standard.
- Management responsibility is clearly defined.
- Good production management and resource allocation.
- All necessities are properly controlled during production and regularly examined.
- Ready made ingredients must be strictly controlled and examined.
- The drug is not permitted to be distributed if it is not certified by the authorized person that the drug has met the pharmacopoeia registration and other regulations related of the production line.
- Good management to assure the products are well preserved, sold and maintained during their shelf life.
- Self assessment and quality assurance should be carried out regularly

3.2 Good Manufacturing Practice for Medical Products

GMP is part of the quality assurance which ensures that the production line and quality control regularly met the standards, utilization objectives, pharmacopoeia registration or product regulation required.

GMP is related to manufacturing procedure and quality control with basic principles as follows:

- Every step of the production line is clearly defined and systematically reviewed to be certain that the production line meets all requirements consistently.
- Critical processes or altered procedures must be verified.

- Sufficient facilities that meet GMP including;
  - Qualified and well trained personnel
  - Adequate working areas
  - Appropriate equipment and facilities
  - Proper raw materials and containers, and accurate labeling
  - Instructions and recommendations that are verified and certified
  - Appropriate warehousing and transportation
- Clear instructions and recommendations
- Operator that have been efficiently trained
- Having a production log (book) to record that the instructions were followed in every procedure and the quantity and quality of the product has met the requirements. Any significant deviations must be noted and investigated.
- Having production and distribution records for tracking down the product.
- The distribution process must have the least effect on the drug quality.
- Having an effective recall procedure.
- Inspection of complaint after sale, investigation of the cause of the complaint and issuing the measures to manage and prevent the problem in the future.

3.3 Quality Control

Quality control in GMP is associated with product samplings, specifications and tests which are related to the work on documentation and product release procedures. Quality Control conducts necessary related measures to guarantee that there is no raw material release or final product release until the quality is verified.

Specifications and basic requirements of the quality control are;

- Sufficient facilities, well trained personnel and certified measures for product sampling, inspection/testing of raw material, packaging material, in-line product, final product and environmental inspection to achieve the GMP.
- Sampling of raw material, packaging material, in-line product, ready packed product and final product must be conducted by qualified personnel from the Quality Control division.
- Test procedures must be verified.
- A record to prove that sampling, inspection measures and test procedures have followed the regulations is provided. Any deviation must be recorded and investigated for cause.
- The final product has main active ingredient, purity and proper packaging with correct labeling according to the quantity and quality that is mentioned in the pharmacopoeia registration for that product.
- Record the results of the inspections and tests of raw material, packaging material, in-line product, ready-packed product and final product. There must be a comparison between the results obtained from the inspections/tests and their specifications including product evaluation, reviewing, document verification and deviation verification.

- The drug must not be released for sale or distributed before having certification from the authorized person. The product quality must be according to the pharmacopoeia registration.
- Adequate raw material and final product must be retained for future inspection. The stored product must be in the same package as the product for sale except for one in larger package sizes.

3.4 Product Quality Review

Product quality review must be performed monthly or periodically to ensure the quality control of the processes and confirm suitability of the present specification for raw material and final product. The product quality review could indicate the need to improve the quality of product and manufacturing. The review is usually performed yearly and compares the results with the previous review. The review document should be issued annually. The product quality reviews are composed of;

- Reviewing the standard quality of raw material and packaging material especially materials from a new resource.
- Reviewing the important controls in the manufacturing process and the standard quality of the final product.
- Reviewing products that have not met the specification and investigate the cause.
- Reviewing any significant deviations/misspecification and their investigation, problem solving and prevention.
- Reviewing any changes during production line and inspection measures.
- Reviewing any alteration in pharmacopoeia registration that has been submitted/ received/permitted/denied including document that were issued to a third country (export).
- Reviewing the results of the stability inspection and any undesirable indicators.
- Reviewing the returned product, appeal and recall related to product quality including the investigation of that event.
- Reviewing the problems in production line of a previous product or reviewing of fixing equipment or tools.
- For new pharmacopoeia registration product or alteration in pharmacopoeia registration product, reviewing of the product after release into the market must be performed.
- Reviewing conditions of the tools and the facility such as ventilation, water or compressed air, etc.

7.1.4 Lot release

Biological product is different from other drugs where chemical and physical techniques to control production quality and standard. The biological product requires bioprocesses such as cell/microorganism culture including extraction of biological product when there are several factors that could cause deviation in the product property. Besides, the biological analysis techniques are more complicated than physicochemical analysis. The process control during production is significant in biological product manufacturing.

According to the international system, each lot and every package of the biological product must pass the inspection of drug control division of each country before release. Generally, the manufacturers must submit the samples along with the paper work of manufacturing control and quality control to the drug control division to re-inspect before issuing a certificate of lot release.

In Thailand, according to the FDA's rules and regulation (3, 4), manufacturers and importers must receive a certificate of lot release for biological products from Biological Product Division, Department of Medical Sciences before distributing the product.

7.1.5 WHO Pre-qualification

Most vaccines are used with healthy person in order to stimulate their immune system to prevent disease that normally occurs in people such as infants, children, and the elderly who have lower level immunity to defend against the disease. The standards of quality and safety are very important since unqualified vaccine itself may cause the disease.

The WHO realizes the importance of this issue, therefore the Pre-qualification Program was launched to ensure that the vaccine in each country meets standard qualifications and safety. WHO expert teams were formed to evaluate the vaccine control division in each country to be certain that each country has the ability to control their vaccine standards. The evaluation criteria are different depending on each country's status i.e. a country with the ability to produce vaccine or a country that imports vaccine or a country that relies on vaccine contribution from non-profit organizations such as the UNICEF and UN.

Generally, an expert team from the WHO will be an assessor when requested from any country. For the country with the ability to manufacture vaccine, the organizations to be evaluated comprise of the national vaccine analysis office, vaccine registration office, GMP inspection office, vaccine reaction (side effect) monitoring office, lot release system, clinical trial monitoring office, etc. The evaluation is called "six critical control functions" which are;

1. A published set of requirements for licensing
2. Surveillance of vaccine field performance
3. System of lot release
4. Use of laboratory (when needed)
5. Regular inspections for GMP
6. Evaluation of clinical performance

If the vaccine control organization has passed pre-qualification, the vaccine manufacturing plant of that country has credibility for producing vaccine to quality and safety standards. The country that uses donations from non-profit organizations (United Nation Agencies, UNICEF, etc) to purchase vaccine from somewhere else, has to purchase vaccine from the WHO list of qualified manufacturers categorized by vaccine type only.

From the information previously described, not only that the manufacturing plant has to pass the WHO pre-qualification, but it must also be located in the country that has had its vaccine control division passed for the "six critical control functions" and WHO pre-qualification.

Currently, Thailand has not passed WHO pre-qualification. During 27 November 2006 to 1 December 2006, the expert team from WHO came to evaluate the six critical control functions at Thailand's vaccine control division.

7.2 Law and Regulation for Fast Track Registration

The Thai Food and Drug Administration (FDA) is responsible for control, regulation and supervision of all activities involving health products such as food, drugs, medical devices, cosmetics, hazardous substances, narcotics, psychotropic substances and volatile substances, etc. Related laws and regulations have to be implemented for each product differently. Only laws and regulations about drug control will be described in this chapter as follows:

The Drug Act, B.E. 2510 (1967) 5 and Drug Act (3rd revision), B.E. 2522 (1979) have defined the meaning of "Drug" in article 4.

Article 4

(1) Substance that is in the drug list
(2) Substance that aims for diagnosis, relief of pain, therapy or prevention of disease in humans or animals
(3) Substance that is a pharmaceutical chemical finished product or pharmaceutical chemical semi finished product
(4) Substance that aims to affect health, structure or function of humans or animals

The meaning of "Drug" according to Article 4 above includes vaccines which are Biological Products

In addition, the Drug Act, B.E. 2510 (1967) defines more definitions as follows:

"Produce" means make, mix, cook, transform including deform and filling with and without the drug label

"Drug label" means picture, mark, sign, or any sentences shown on the container or drug case

"Drug leaflet" means paper or other material which demonstrates meaning, mark, sign or any sentences with regards to the drug showed on the container or drug case.

"Drug formula" means the formula that defines the ingredients which composes any form of drug. It includes ready made pharmaceutical product that is ready to be utilized by humans or animals.

"Licensee" means the person who has received permission according to the Act. Refers to the juristic person, the person who has received a license, including the manager or representative of the juristic person.

"Licenser" means;

(1) Secretary General of the FDA or representative who received permission to give a license to the manufacturer or importer into the Kingdom of Thailand.

(2) Secretary General of FDA or representative to received permission to give a license to a drug vendor in Bangkok

The FDA as a National Control Authority (NCA) has responsibility to control and maintain surveillance of drug products including vaccines in accordance with the national legislation regulations and other related principles. Vaccines, especially, must be strictly controlled from the research and development, manufacturing process, quality control, transportation and preservation until in the hands of the user. This requires expertise, skill, discipline and caution since vaccine is a biological product that needs extra care. The product quality may deviate more and be more complicated than other pharmaceutical products. To achieve a Assured Quality Vaccine, co-operation among National Regulatory Authorities such as the FDA Drug Control Division, Monitoring and Inspection of Health Production Office and Division of Planning and Technical Coordination, Department of Medical Sciences for Biological Products, Department of Disease Control Bureau of Epidemic and General Communicable Diseases is required.

The WHO pays substantial attention to vaccine control and regulation by establishing the "1 system plus 6 functions". It is an Assessment Tool of National Regulatory Authority used for evaluation of the vaccine control authority. All critical Indicators and critical sub-indicators must be evaluated and passed to ensure an Assured Quality Vaccine.

The WHO outlines the criteria for Assured Quality Vaccine (11) as follows ;

1. National Regulatory Authority (NRA) independent from the vaccine manufacturer
2. NRA fully functional (1 system + 6 regulatory functions)
3. No unresolved reported problems with the vaccine

There is a WHO Pre-condition for every vaccine manufacturers to receive Pre-Qualification in which the national regulatory authorities must be a Fully Functional NRA before they are able to sell their product to UN agencies such as the UNICEF. The Fully Functional NRA must be qualified for all critical indicators and critical sub-indicators and not less than 50% for non-critical indicators. Details of the critical indicators and critical sub-indicators are shown in Table 7.1.

Table 7.1 Details of the Critical Indicators and Critical Sub-Indicators

System/Function	Indicators Critical: Non-Critical	Sub-Indicators Critical: Non-Critical
1. National Regulatory System	4 : 7	13 : 30
2. Marketing Authorization (MA)	6 : 9	13 : 28
and Licensing Activities Function		
3. Post-marketing activities including surveillance of Adverse Events Following Immunization (AEFI) Function	6 : 8	10 : 23
4. NRA Lot Release Function	4 : 4	8 : 18
5. Laboratory Access Function	8 : 12	12 : 28
6. Regulatory Inspections Function	4 : 6	10 : 16
7. Authorization/Approval of Clinical Trials Function	0 : 4	0 : 17

Table 7.2 Responsibility in vaccine control for stimulating immunity according to source of vaccines (12)

NATIONAL REGULATORY FUNCTIONS DEPEND ON VACCINE SOURCE

REGULATORY FUNCTIONS

Regulatory functions	Source of vaccines: UN agency	Procure	Produce
Regulatory systems	✓	✓	✓
Marketing Autorization & Licensing activities	✓	✓	✓
Postmarketing: AEFI	✓	✓	✓
Lot release	Functions Undertaken by WHO on Behalf of UN agencies or producing countries	✓	✓
Laboratory access		✓	✓
Regulatory inspections		Functions Undertaken by the producing country	✓
Authorization & monitoring of CTs			✓

CTs : Clinical trials, UN: United Nations, AEFI: Adverse Events Following Immunization

World Health Organization, HTP/IVB/ATT.LBelgharbi

This chapter emphasizes the Pharmacopoeia that includes the vaccine. According to table 7.1, the WHO system is related to the Marketing Authorizing (MA) and Licensing Activities Function. The Critical Indicator: Indicator is 6:9. The Thai FDA operates according to the WHO's suggestions shown in Table 7.3.

Table 7.3 Marketing Authorization (MA) and Licensing Activities Function

Main Indicators related to above function	Indicator
1. MA system established and operational	CRITICAL
2. Submission of MA applications	CRITICAL
3. Assessment of MA application	CRITICAL
4. Appropriate assessment expertise	CRITICAL
5. Same criteria/standards for evaluation of MA applications for products regardless of the source	
6. GMP assessment in MA process	CRITICAL
7. Requirements for evaluations to be submitted and assessed	CRITICAL
8. Clear and comprehensive approved information on authorized products	
9. List of authorized products and companies	

Requirements for Vaccine Registration

1. **Application for registration of drug sample**
   - For manufacture of drug samples, using ผ.ย.8 form with related documents and
   - For import of drug samples, using น.ย.8 form with related documents
2. **Application for approval of drug,** using ท.ย.1 form with

2.1 Quality Documents/Dossiers

2.2 Safety or Non-Clinical Documents/Dossiers

2.3 Efficacy or Clinical Documents/Dossiers

Guidelines for drug approval that are internationally recognized are from organizations such as the National Regulatory Authority (NRA) and/or the Industrialized Private Sector of developed countries such as the United States, EU and Japan. To reduce repeated experiments when different guidelines for Pre-Clinical/Non Clinical Trials and Clinical Trials are followed, an International Conference on Harmonization of Technical Documents for Registration of Pharmaceutical Products (ICH) was set up. This could cut down on waste of human resources and assets. Moreover, the patients may have opportunity to rapidly access to the high quality drug. A guideline from the ICH for drug registration is called **ICH CTD: Common Technical Documents/Dossiers** (13) used to ensure quality, safety and effectiveness of the drug.

ASEAN countries which comprise of 10 members; Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam sent their representatives to attend the ASEAN Consultative Committee on Safety and Quality – Pharmaceutical Products Working Group **(ACCSQ-PPWG)**. The ASEAN members agreed to obligatory following co-operate guideline for ASEAN drug registration known as the **ASEAN Common Technical Document: ACTD** (14). The working group uses the ICH CTD as a guideline. Besides ACTD, ASEAN countries also set up four ASEAN Common Technical Requirements (ACTR) which are 1) ASEAN BA/BE Guidelines, 2) ASEAN Stability Guideline, 3) ASEAN Process Validation Guideline and 4) ASEAN Analytical Validation Guideline to be suited to ASEAN countries' context.

Thailand has declared to the ACCSQ-PPWG meeting that ASEAN drug registration by the FDA will be fully implemented from 31 December 2007. The permitted manufacturers and importers of modern drugs must submit documents and proof according to ACTD. However, it has been agreed by ASEAN members that the ICH CTD guidelines can also be used for registration of New Chemical Entities and Biological Products instead of ACTD. The documents to submit for ACTD and ICH CTD are shown in Table 7.5. Comparing the content of the documents and proof for ACTD and ICH CTD (Appendix 4), the CTD Core Dossier/Data has closely followed the ICH CTD since ASEAN uses ICH CTD as a model except for the numbering, that is different.

Influenza and Avian Influenza vaccine is categorized as biological products. The Biologic License Application (BLA) must be submitted with following documents:

1) Quality Documents/Dossiers
2) Safety or Non-Clinical Documents/Dossiers and
3) Efficacy or Clinical Documents/Dossiers

The Thai FDA has enforced New Drugs and New Generic Drugs registration since 3 August 2004 (15) with the procedure for accelerated or priority review. This is a Fast Track registration for special cases such as Avian Influenza because it is classified as an urgent matter of national public health, public health problem or dangerous drugs. Some documents such as Clinical Research Phase II can be relieved by using 100-300 working days for consideration.

Table 7.4 shows the overview of the National Regulatory Agency Pathways of many countries such as Australia, Canada, EU, Japan, USA and Thailand.

Table 7.4 Overview of National Regulatory Agency Pathways (1)

National Regulatory Agency	Australia TGA	Canada Health Canada	European Union
Regulatory Authority	Therapeutic Goods Act,1989 and Therapeutic Goods Regulations,1990, Trade Practices Act, 1974, Quarantine Act of 1908	Food and Drugs Act and Regulations, Public Safety Act	Directive 2001/83/EC, Article 8-Marketing and Authorization Application, Regulation (EEC) 726/2004-Submission to the EMEA through centralized procedure
Submission Type	Category 3 Application	New Drug Submission (NDS): including an On Site Evaluation	Centralized Procedure (CP) Mutual Recognition Procedure (MRP)
Timelines	Category 3 Application: 45 days after receipt of application	NDS: 300 days License Amendments: 90 days	C P:210 days+ EC 30 days MRP:210 days (initial national authorization) + 90 days (mutual recognition)

Table 7.4 Overview of National Regulatory Agency Pathways (1) (continued)

National Regulatory Agency	Australia TGA	Canada Health Canada	European Union
Annual Influenza Vaccine Licensure	Full submission required, including quality, pre-clinical and clinical data (in accordance with general CPMP guidance for new vaccines)	Filing of an amendment to the existing license, in which manufacturers would submit for review only their revised labeling material for the new yearly strain	A special fast track type II variation procedure is applicable for annual variation of human influenza vaccines
Proposed Pandemic Regulatory Pathway	TGA accepts EMEA guidelines on pandemic vaccine licensing	Submission of an NDS and not an amendment to an existing annual influenza license	Submission and approval of the pre-pandemic core dossier during the inter-pandemic period for evaluation by fast track authorization. Once a pandemic is declared a variation to the core pandemic dossier for fast track approval will be submitted

Table 7.4 Overview of National Regulatory Agency Pathways (1) (continued)

National Regulatory Agency	Australia TGA	Canada Health Canada	European Union
Pre-Pandemic Vaccine	Licensure is based on approval of a core dossier for a pre-pandemic vaccine with quality, safety and efficacy data provided and authorized during inter-pandemic period	Mock Vaccine development and licensure: -quality data- clinical trial applications (CTAs)	Pre-pandemic-CTA for pandemic trial protocols (some mock data) http://www.emea.eu.int/pdfs/human/vwp/471703en.pdf http://www.emea.eu.int/pdfs/human/vwp/498603en.pdf
Pre-Pandemic Uses	Same as Europe	HC must be able to validate productions process, test production capacity and establish minimum standards and requirements for safety and efficacy	The core dossier is not to be used out of the pandemic context. For vaccines containing avian strains with pandemic potential such as H5N1, CHMP has adopted a draft explanatory note, identifying dossier requirements. Such avian influenza vaccines for human used must be based entirely on the circulating influenza strain against which protection is claimed

Table 7.4 Overview of National Regulatory Agency Pathways (1) (continued)

National Regulatory Agency	Australia TGA	Canada Health Canada	European Union
Quality and Manufacturing Requirements	Data obtained in inter-pandemic period. Same for all uses.	*Production and testing of vaccine seed lot, manufacturing process and validation *Specifications *Adjuvant, excipients, container and preservative information *Batch analysis *Reference standards *Stability information *Product specific facility information	*Viral safety information *Vaccine reference virus development and testing *Vaccine seed lots production process, etc. *Formulation *Vaccine standardization *Adjuvant *Stability data and protocol
Clinical Data Requirements	Data obtained in inter-pandemic period. Different depending on use; A.Stockpiling for use at beginning of the pandemic B.Use for people at high risk C.Use as prime and boost for population at large-Human immunogenicity and safety studies	*Challenge studies in animals *Local tolerance studies *Clinical (immunogenicity) studies on healthy adults *Targeted studies on the vulnerable *Protocols for post-market studies, including any necessary informed consent documents	*Immunogenicity and safety *Non-clinical safety *Novel adjuvant *Challenge experiments *Human clinical data *Formulation *All criteria for annual influenza vaccines *Post-authorization commitments

Table 7.4 Overview of National Regulatory Agency Pathways (1) (continued)

National Regulatory Agency	Australia TGA	Canada Health Canada	European Union
Emergency Use Additional Requirements	-	*Expedited review *Notice of compliance with conditions *Special access program (SAP) *Interim order *Clinical trials	In case a pandemic occurs before a core dossier is approved: Emergency authorization to be used, relying on very close interaction between the manufacturer and the EMEA using a rolling review process of data packages before the submission of a formal application
Accelerated Approval/Emergency Use Provisions	Pandemic declared-core pandemic dossier using the actual pandemic strain and submit quality/technical data in parallel with product as a pandemic variation to TGA for rapid approval and release	Licensure of a pandemic vaccine will follow the filing of an NDS containing composite information on the pre-pandemic vaccine supplemented with additional information on the actual pandemic vaccine	Emergency authorization: *Accelerated review process (max. 150 days) *Conditional marketing authorizations in case of public health crisis

Table 7.4 Overview of National Regulatory Agency Pathways (2) (continued)

National Regulatory Agency	Japan	United States FDA	Thailand TFDA
Regulatory Authority	Pharmaceutical Affairs Law (PAL) (Law 145,1 960 revised 2005) Infectious Disease Law (revised name 1998)	Section 351 of Public Health Service Act. Food, Drug and Cosmetic Act	Drug Act B.E. 2510
Submission Type	New Drug Application	Biologic License Application (BLA)	Biologic License Application (BLA)
Timelines	17.7 months (2001 data): 45 days after receipt of application	BLA standard review-10 months, BLA priority review-6 months, CMC supplement-4 months	BLA standard review-210-280 working days, BLA priority review-100-130 working days
Annual Influenza Vaccine Licensure	-	Submission of a prior approval manufacturing supplement to an existing BLA is required for strain changes (chosen yearly, based on circulating wild-type strains)	Submission of a prior approval manufacturing supplement to an existing BLA is required for strain changes (chosen yearly, based on circulating wild-type strains)
Proposed Pandemic Regulatory Pathway	Expected 2006-Phase I/II & III, submission 2007-Approval of the H5N1 vaccine currently under development	Supplement to existing BLA, or Accelerated approval of a new BLA	Accelerated approval of a new BLA

Table 7.4 Overview of National Regulatory Agency Pathways (2) (continued)

National Regulatory Agency	Japan	United States FDA	Thailand TFDA
Pre-Pandemic Vaccine	H5N1 vaccine development -National project under collaboration of MHLW,NIID and 4 manufacturers: *License for alum-adjuvanted formaline-inactivated whole virus vaccine (prototype) *Clade 2 vaccine (mockup strategy)	FDA views pandemic strain as a "strain change" to annual influenza vaccine for licensed manufacturers, therefore only a supplement to an existing BLA is required	-
Pre-Pandemic Uses	-	-	-
Quality and Manufacturing Requirements	Control tests for pandemic vaccines on bulk materials: *protein content *sterility *toxicity *inactivation *pH *HA content *thimerosol, aluminum and formaldehyde contents	With adequate controls and characterization, FDA permits use of recombinant or cell based technologies in strain production. Either a reassortment or wild type virus	*Production and testing of vaccine seed lot, manufacturing process and validation *Vaccine reference virus development and testing *Formulation *Vaccine standardization *Specifications *Adjuvant, excipients, container and preservative information *Batch analysis *Reference standards *Product specific facility information *Viral safety information *Stability data and protocol

Table 7.4 Overview of National Regulatory Agency Pathways (2) (continued)

National Regulatory Agency	Japan	United States FDA	Thailand TFDA
Clinical Data Requirements	*Common protocol agreed by PMDA for each manufacturer *Phase I studies in healthy male adults *Phase II and III studies in healthy adults *safety *effectiveness *comparative analysis	**Supplement to BLA:** Limited clinical trials and adequate safety data and **New BLA:** Clinical trials data, post-marketing study protocols and safety data	*Immunogenicity and safety *Non-clinical safety *Novel adjuvant *Challenge experiments *Human clinical data *Formulation *All criteria for annual influenza vaccines *Post-authorization commitments
Accelerated Approval/Emergency Use Provisions	Submisssion license and approval through fast track evaluation process	*Accelerated approval of New BLA for serious or life-threatening illnesses *Emergency use authorization (EUA) *Investigational New Drug (IND) Use	*Accelerated or priority review process (max. 130 days) *Conditional marketing authorizations in case of public health crisis
Emergency Use Additional Requirements	-	*Accelerated approval of New BLA for serious or life-threatening illnesses *Emergency use authorization (EUA) *Investigational New Drug (IND) Use	*Accelerated approval of New BLA for serious or life-threatening illnesses *Emergency use authorization (EUA)

Note: During an emergency period such as epidemic of avian influenza or influenza, the Ministry, Bureau, and Department, The Thai Red Cross Society and The Government Pharmaceutical Organization can produce or import vaccine and drug which does not require to be registered in the drug list, according to Drug Act B.E. 2510 (1967), section 72, paragraph 2.

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Chapter 8: Policy Recommendations on "Thailand vaccine Preparedness for Pandemic

- Conclusion of Preparedness Strategy on vaccine for Pandemic Influenza in Thailand
- Roles of four preparedness strategies on vaccine for influenza pandemic
- Progress of relevant contexts
- Other recommendations

Chapter 8: Policy Recommendations on "Thailand Strategy vaccine Preparedness for Pandemic Influenza"

8.1 Preparedness Strategy on vaccine for Pandemic Influenza in Thailand

This report is aimed at providing preparedness strategy on vaccine for influenza pandemic in Thailand. After the brainstorming discussions with experts, experienced people involved in vaccine manufacturing and international experts four preparedness strategies on vaccine to cope with influenza pandemic in Thailand are recommended.

Strategy I: Strategy for purchasing and stockpiling influenza vaccines

The vaccines which would be purchased and stockpiled are pre-pandemic influenza vaccines. The strategy should be implemented immediately within 3-6 months due to the unknown timing of the pandemic. Since the restriction of global productivity of pandemic influenza vaccine during the pandemic occurrence, this strategy is then applicable to situations prior to the pandemic. To lower the risk of mismatch between the vaccine virus strain and the pandemic causing strain, more than one vaccine strains should be purchased and stockpiled. The vaccine with cross immunogenicity is recommended. Levels of vaccine stockpile should be ample for at-risk groups e.g. health workers and pandemic responders directly controlling the transmission.

Technical and administrative considerations for this strategy are also given. The technical consideration is associated with the mismatch risk of vaccine virus strains and the pandemic causing strain as said. The administrative consideration is about communication with fiscal agencies which should be aware that stockpiled vaccines may not be really used but are necessary in aspect of investing for public insurance, controlling and delaying the global pandemic. The estimated budget would be ranged between 174–1,160 million Baht for stockpiling finished influenza vaccines of 60,000–400,000 doses for 5 years. More budgets are needed if the vaccine is aimed for all Thais.

Strategy II: Strategy for filling bulk influenza vaccines

This stretegy is for stockpiling of bulk vaccines. The bulk vaccines would later be filled into bottles/vials at appropriate size for vaccination. Advantages of stockpiling the bulk vaccines are for example bulk vaccine lifetime is longer than that of finished vaccines and 10-20 % of the budget could be saved in relation to using the whole budget for purchasing the finished vaccines. Furthermore, Thailand has a number of vaccine and pharmaceutical manufacturers that are able to fill influenza vaccines. This strategy maximizes the use of existing infrastructures. Usually, bulk vaccine importation and filling are an initial step of manufacturing technology transfer.

However, a limitation of this strategy is similar to Strategy I, which is the risk of mismatch between the stockpiled vaccine strain and pandemic causing strain. Technical and administrative considerations are similar to that of Strategy I. The advantage of this strategy is the lower budget requested in relation to the estimated budget for Strategy I. About 16 % or 28–186 million Baht could be saved for 5 years. Nevertheless, Strategy II is, similar to Strategy I, only suitable for a short term plan when no other alternative is available.

Strategy III: Strategy for modifying animal vaccine plants to produce human vaccines in emergency situation

This strategy is aimed at modifying the avian vaccine plant of the Bureau of Veterinary Biologics (BVBs), Animal Health Department, Ministry of Agriculture and Cooperatives to be the contingent plant upon emergency situation for producing pandemic influenza vaccines. Compared with new plant investment, this strategy consumes less time and expenditure. This plant has been designed and structured according to the German standard as the modular system which is convenience for plant modifications. If the plant is aimed for producing 7.2 million doses per week of live-attenuated influenza vaccines (LAIV), it will take about 1-2 years and 100 million Baht for modifying the plant.

In addition, the officials of the Bureau of Veterinary Biologics (BVBs),have the expertise on egg-based technology for avian vaccine production. This egg-based technology is currently used for producing influenza vaccines. Upon request, in emergency situation, the plant could support its human resources and improve its animal vaccine manufacturing standard to meet human vaccine manufacturing standard. However, a drawback could be public and the administrators' acceptance of the quality of the vaccine produced from the animal vaccine plant. The key success factors of this strategy are; the internal cooperation between Ministry of Agriculture and Cooperatives and Ministry of Public Health to control and regulate this vaccine manufacturing standards and public relations to ensure public understanding and acceptance of the vaccines produced. It should be noted that this plant is not aimed at long term influenza vaccines production. The manufacturing would start only in emergency situation. The main agencies which could initiate and actively implement this strategy are Ministry of Public Health, Ministry of Agriculture and Cooperatives and Ministry of Science and Technology.

Strategy IV: Strategy for establishing the human vaccine plant

This strategy is aimed at building a new plant for manufacturing both seasonal influenza and pandemic influenza vaccines. The egg-based technology would be used since it has high potential for vaccine production. However, there is a risk of a shortage of clean chicken eggs for vaccine production if there is epidemic in chickens. Prior to the pandemic, the plant could produce seasonal influenza inactivated vaccines and the plant should be able to switch to produce live attenuated vaccines to meet high demand of vaccine levels in the pandemic situation. More research on live attenuated vaccines is also needed because of limited information on the use of this vaccine on particular aged groups. The plant must have the maximum productivity of inactivated vaccines at leust 8.6 million doses per year in order to have capacity when switched to produce live attenuated vaccines to be sufficient to all Thais within 3 months. Much

higher capacity, 21–43 million doses per year, is required when only the inactivated vaccine is to produce in the pandemic situation. The budget required for building the plant depends upon available infrastructures. The investment budget would be substantial, if the infrastructure system e.g. water, electricity, waste water treatment is not available. To establish the plant manufacturing at the capacity 10 million doses/year of inactivated seasonal influenza vaccines using egg-based technology, the budget would be about 1,800 million Baht. The construction time would be over 5 years.

The critical success factors of this strategy are management of raw materials used for vaccine manufacturing, research and development, human resource development and preparedness for technology transfer. Moreover, public agencies and statutory health insurers must advocate and support the use of seasonal influenza vaccines produced by this plant to help it reach its economy of scale of production and produce vaccines continuously. This strategy is regarded as a permanent strategy for national security to face with influenza pandemic. Establishing influenza vaccine plant also has the spillover effects which help develop other vaccine manufacturing in Thailand. Presently, the Government Pharmaceutical Organization (GPO) has undertaken the strategy implementation.

8.2 Roles of four preparedness strategies for pandemic influenza

The ultimate goal of influenza vaccine preparedness is to prevent and control influenza pandemic. The vaccine strains derived from infection strains would be prepared as many and quickly as possible since the timing of the pandemic is not known. The stockpiled level would be sufficient to all or at least to high risk people e.g. health care personnel and pandemic responders. The four recommended strategies play different roles of vaccine preparedness with respect to the time i.e. short, medium and long term.

Short term

Within 1-2 years, the appropriate strategies are Strategy I and II. They would be considered as the main strategy and the other would be the subordinate. These two strategies are practical to implement for the time being though they are unable to lessen the risk of the strain mismatch between the vaccine strain and the pandemic causing strain.

Medium term

Within 3-5 years, Strategy III would be the main strategy while either Strategy I or II would become the backup strategies. The decision to take up Strategy III must be made earlier. At the same time, Strategy I and II should be implemented in parallel. Strategy III would be continuously implemented till the new plant under Strategy IV could start manufacturing vaccines which would take about 5 years.

Long term

Starting from the 6th year, the vaccine plant under Strategy IV would be the main strategy while others are backup strategies. The decision on the plant establishment must be done before the 5th year. Roles and relationships of the four strategies are shown in Table 8.1.

Table 8.1 Roles of strategies for influenza vaccine preparedness for influenza pandemic

Strategy	Short term (1st-2nd yr)	Medium term (3rd-5th yr)	Long term (6th yr and longer)
1. finished vaccine stockpiling	Main strategy	Backup strategy	Backup strategy
2. bulk vaccine purchasing and filling	Backup strategy	Backup strategy	Backup strategy
3. modifications of an existing avian vaccine plant	Preparation	Main strategy	Backup strategy
4. establishment of a new vaccine plant	Preparation	Preparation	Main strategy

All four strategies should be altogether implemented at each time frame for influenza pandemic preparedness since it is a National security. For sustainable development, the establishment of a new vaccine plant strategy which serves longer term should be emphasized while second strategies or backup strategies could be adjusted to appropriately respond to the current situations.

Table 8.2 shows the estimated budget needed for implementing the 4 strategies for 5 years. The vaccine stockpiling under Strategy I and II for 60,000 doses per year and the plant modifications, which required about 100 million Baht, would be immediately implemented. In sequent years, about 10 million Baht per year is needed for exercising the manufacturing processes of influenza vaccines to maintain the manufacturing capacity. The vaccine plant establishment to produce 10 million doses per year needs 1,800 million Baht or 360 million Baht per year on average (real expenditure per year is not equal, and return on investment after the plant able to produce vaccines is not considered). Therefore, total budget for 4 strategies implementation for 5 years would be about 2,125 million Baht. After the 5th year, the budget would be lessened as to maintain the implementation of the strategies.

Table 8.2 Estimated budget for implementing influenza vaccine preparedness strategies for 5 years

Strategy	Year				
	1st	2nd	3rd	4th	5th
I & II	35	35	35	25	15
III	100	10	10	10	10
IV	360	360	360	360	360
Total	**495**	**405**	**405**	**395**	**385**

Although the vaccine plant is completely constructed and ready for producing influenza vaccines, Strategy III, the modifications of the plant of Stock Live Development Department remains worth for implementation. This can be shown in Table 8.3.

If the avian vaccine plant (BVB's plant) is modified to install hatching egg incubators to hatch infected eggs at 120,000 eggs per week by working 2 cycles to serve in emergency situation, the plant would be able to produce 7.2 million doses of live attenuated influenza vaccines (LAIV) per week since one infected egg able to produce 30 doses of LAIV.

For the inactivated influenza vaccine (IIV), however, one infected egg could only produces 3 doses of vaccines. If the new plant is set to produce inactivated seasonal influenza vaccines (IIV) at normal productivity of 2 million doses within 6 months, this plant must have the incubators to accommodate 83,333 eggs. Therefore, this new plant would be capable of producing 0.5 million doses of IIV per week or 5 million doses of LAIV per week.

Five scenarios are set up for exercising the influenza vaccine preparedness using strategy 3 and 4 as follows:

Scenario 1: the BVB modified plant producing LAIV
Scenario 2: A new vaccine plant producing LAIV
Scenario 3: The new plant producing LAIV until enough for most people, then cleaned and changed to produce IIV to provide those unable to take LAIV
Scenario 4: the BVB modified plant producing LAIV while new plant producing IIV for those unable to take LAIV
Scenario 5: both the BVB modified plant and the new plant producing LAIV until enough for most people, then cleaned so as to switch to produce IIV for those unable to take LAIV

Table 8.3 shows the estimated doses for vaccine production based on these 5 scenarios from 5th–6th to 23rd–24th week. The process of obtaining and preparing vaccine working seed virus would be in the first four weeks. Sources of acquiring this virus would be from either WHO, NIBSC or national scientists. Table 8.3 also shows produced vaccine level at the end of each week respective to five scenarios. For example, at the end of 6th week, the total amount of produced LAIV would be about 14.4 million doses.

Scenario 1 is set in the situation that the BVB modified plant is the only plant available to produce the vaccine while the new plant has not yet started its production. To produce vaccines (LAIV) enough for all people at one dose per person, the plant needs 9 weeks for the whole production or 13 weeks after an announcement of the outbreak. This scenario cannot be true unless modification to the plant is carried out before the outbreak. This scenario yields high risk because it relies on only a vaccine plant. If there is any technical problem of production

to the plant, it will hamper accomplishment of the target vaccine level. In addition, IIV would be unavailable if the plant only produces LAIV. It is therefore suggested that the plant should prepare for producing both LAIV and IIV.

Scenario 2 to 5 would take place only when the new plant is completely constructed and ready for production. Time needed for construction would be at least 5 years. If the decision for building the plant is made in 2007, the plant could produce vaccines in 2011. Both Scenario 2 and 3 use the new plant for producing all vaccines while Scenario 4 and 5 use both plants.

Scenario 2 is set for only using the new plant to produce LAIV. To provide vaccination to all at one dose per person, the plant would need 12 weeks after starting the production or 16 weeks after the pandemic announcement. Limitations of this scenario similar to that of Scenario 2 are the risk of relying on one plant for vaccine production and possibility that some people may not suitable for using LAIV.

Scenario 3 pictures that the new plant would produce LAIV sufficiently covering most people and be able to clean and change for manufacturing IIV to serve those allergic to LAIV later. Scenario 3 is set for resolving the problem of a number of people who are allergic of LAIV after enough LAIV is manufactured.

Scenario 4 is determined by having the BVB modified plant to produce LAIV while the newly constructed plant produces IIV to serve people allergic to LAIV. Those unable to use LAIV could be vaccinated by IIV since the first week of vaccine production. The IIV productivity level would be about 500,000 doses per week ready for vaccination by 8^{th} week of vaccine production or 12^{th} week after pandemic announcement. The estimated production levels would be 57 million doses of LAIV and 4 million doses of IIV to serve particular at-risk groups.

Scenario 5 would have both the BVB modified plant and the new plant produce LAIV at the same time to have sufficient level of vaccine to cover most people. Both plants would then be cleaned and changed to produce IIV to serve those not compatible with LAIV. This scenario is set for quickening the vaccine production to reach needed level as fast as possible. Six weeks after the starting of the LAIV production or 10 weeks after pandemic announcement would be needed for providing vaccination to most people at one dose per person. Later, the IIV production would be carried out.

It is demonstrated that there are several advantages of using both plants. The target vaccine level could be rapidly reached the coverage of most people for 6-8 weeks after vaccine production or 10-12 weeks after pandemic announcement. There is also a possibility to produce the vaccine to serve particular at-risk groups in prevention of allergic reactions leading to injuries or deaths. Moreover, if one plant discontinues the production because of technical problems, the other remains producing.

Table 8.3: Production estimation of pandemic influenza vaccine during pandemic occurrence (million doses)

Week after Pandemic starts at beginning of 1st week	2	4	6	8	10	12	14	16	18	20	22	24
Seed virus available from NIBSC	X	X										
Seed virus → working seed	X	X										
Scenario I												
BVB plant produces LAIV[1]			14.4	28.8	43.2	57.6	72					
Scenario 2												
New plant produces LAIV[2]			10	20	30	40	50	60	70	80	90	100
Scenario 3												
New plant produces LAIV[2] then clean&validate			10	20	30	40	50	60	na	na	na	na
New plant produces IIV[3]			na	na	na	na	na	na	clean&validate		1	2
Scenario 4												
BVB plant produces LAIV[1]			14.4	28.8	43.2	57.6	72					
New plant produces IIV[3]			1	2	3	4	5	6	7	8	9	10
Scenario 5												
BVB plant produces LAIV[1]			14.4	28.8	43.2	57.6	72					
New plant produces LAIV[2]			10	20	na	na	na	na	na	na	na	na
New plant produces IIV[3]			na	na	clean&validate		1	2	3	4	5	6

Note :

BVB plant: LAIV[1] calculated from incubator 120,000 egg [x]2 cycles/week [x]30 doses/egg= 7.2 million dose/week

New plant:

- *LAIV[2] calculated from capacity of trivalent 2 m.dose/ 6 months production time → capacity 83,333 egg/cycle-week → In emergency to produce LAIV 2 cycles/week [x]30 doses/egg = 5 million dose/week*
- *IIV[3] calculated from 83,333 egg/cycle [x]2 cycles/week [x]3 doses/egg = 500,000 doses/week*

For scenarios which have switching it is assumed that 4 week period is required for cleaning and validating.

8.3 Progress of relevant contexts

As the influenza pandemic can occur any time, it concerns every country and organization involved especially WHO, a leading international organization directly responsible for public health. WHO has proposed a global action plan aimed at increasing supply of influenza vaccines in order to reduce the gap between demand and supply in the pandemic situation. The global plan is composed of three strategies which are to increase the use of seasonal influenza vaccines, to increase the capacity of influenza vaccine production and to support the research and development of influenza vaccines. The four strategies proposed for Thailand are in accordance with the global plan which recommended to WHO's country members. WHO has also implemented various activities to support its country members on both technical and financial part.

The influenza vaccine preparedness in Thailand has made considerable progress while this report has been developed. Two significant catalysts of this progress are that the returning epidemic of avian flu in poultry and human in late 2006 to early 2007 and Thailand's proposal to WHO was awarded the financial support for preparing the national production of influenza vaccines within 1 year after financial installment. These two factors have made 3 significant impacts;

1. Rising attention in executives of Ministry of Public Health leading to critical decision on assigning the GPO as the main agency responsible for influenza vaccine manufacturing,

2. A decision of selecting China as the source of transferring influenza vaccine production technology to Thailand, which shows clear commitment of building the vaccine production plant in Thailand,

3. Increase understanding of influenza vaccine production technology especially LAIV because a number of meetings among both national and international experts have greatly contributed this understanding and the development of this report.

With both internal and external factors concerning Thailand's current situation, it is clear that Thailand is developing the vaccine production plant corresponding Strategy IV stated in this report. However, there are other strategies which could be supplementary to Strategy IV to facilitate Thailand's preparedness plan more effectively and efficiently.

8.4 Other recommendations

8.4.1 Success factors

Although there is the decision of establishing the vaccine production plant for Thailand, the vaccine production would need efficient management in order to get good quality of vaccine produced and effective coordination between organizations involved such as Ministry of Science and Technology, academic institutions which have virology experts capable of developing seed virus appropriate for vaccine production, Ministry of Agriculture and Cooperatives and private organizations to produce cleand chicken eggs which is a crucial component of vaccine manufacturing, etc.

8.4.2 Other preparations

A quality control system for vaccine manufacturing should be prepared as well as studies on vaccine safety and effectiveness by performing pre-clinical and clinical trials. This report gives the details of vaccine production standard and vaccine registration. The produced vaccine or stockpiled vaccine should be registered as soon as possible. The vaccine quality and effectiveness evaluation is important to ensure public confidence on the vaccine. Although there are rapidly increasing demand for vaccine levels in the pandemic situation, the vaccine quality must be a first concern.

To ensure that the vaccine timely reach all people, prior to the pandemic, Ministry of Public Health must develop the vaccine deployment plan comprising the list of priority groups for pandemic influenza vaccine, multi-agency coordination plan, rehearsal implementation of vaccine distribution throughout the nation and pubic relation plan, etc.

Before the influenza pandemic, the newly constructed plant could produce seasonal influenza vaccine in which more public demand should be induced. Ministry of Public Health should take roles to promote the use of seasonal influenza vaccine e.g. recommendation of vaccination according to the priority list, coordinate with key health insurance agencies e.g. National Health Security Office, Social Security Office and the Controller General's Department, Ministry of Finance to include seasonal influenza vaccine into their benefit packages.

The critical point of preparing the pandemic influenza vaccine in order to mitigate the pandemic impact is to quickly identify the pandemic causing strain and use it to develop seed virus for vaccine production. The preparedness of epidemic surveillance became a key success factor of preparing the vaccine production. The surveillance needs cooperation from various levels. It is also a key measure of providing the epidemic warning and preventing the spread of infection.

8.4.3 Regional security for national security

The past epidemics of avian flu have made significant concern over transnational epidemics. The implementation of disease surveillance and control by one country surrounded by others doing nothing on such measures is not effective. Therefore, the level estimation of needed may include levels needed by neighboring countries where there is no capability of producing vaccines. If Thailand can help neighboring countries either control or delay the influenza epidemics, Thailand can take consequent both directly and indirectly benefits.

Annex

Annex

Annex 1

1 A. Influenza vaccine production by Baculovirus Expression Insect Cell System

Vaccine produced from this system is made from recombinant influenza virus protein such as hemagglutinin or neuraminidase by insertion of these genes into a baculovirus genome. The genetically engineered baculovirus containing the influenza gene is then infected into insect cells, which are natural hosts for the baculovirus. The infected insect cells produce recombinant influenza virus protein according to the type of gene inserted.

Recombinant protein production by Baculovirus Expression Insect Cell System

Two main components in the system are:

Host cell

Insect cell lines isolated from insect organ such as ovary are used as the baculovirus host. The cells can be grown continuously in a synthetic medium containing serum or without serum (serum free medium as suspension cell and/or attached cell. The optimal temperature for culturing is 27°C

Baculovirus

Baculovirus is an insect specific virus. These viruses are species specific and do not replicate in plants or vertebrates. *Autogarapha californica* MNPV (AcMNPV) is mostly used baculovirus for producing recombinant protein since there is substantial information on its complete genome and more than 30 species of insect cell are their natural host.

Baculovirus has a strong promoter, polyhedrin, which can control insect cells to synthesize up to 50% of the total insect protein. A high level of gene expression is expected for the gene expressed under the control of the polyhedrin promoter.

Influenza vaccine production by Baculovirus Expresssion Insect Cell System

In 1999, Smith et al. from Protein Sciences Corporation (Meriden, CT) applied for an influenza vaccine patent in which the Baculovirus Expression Insect Cell System was employed to produce two recombinant influenza virus proteins, hemagglutinin and neuraminidase. The recombinant proteins are used as vaccine (trade name is FluBlok) for which its efficacy was tested in healthy adults and elderly. A 100% efficacy for virus infection (tested by cell culture method) was obtained by using a 45 µg dose for each HA antigen of a trivalent vaccine in phase I clinical trials and phase II/III. In 2005, and the vaccine was approved by FDA with condition of "accelerated approval" and expect to sell by 2006 or not later than an epidemic of influenza in 2007/2008 [1] .

The researchers also applied this technology to produce H5N1 influenza vaccine, which is predicted to cause pandemic, and tested in chicken. By using high dose, it prevented disease since none of the chickens were sick or died. In addition, the chickens did not produce shed virus by this pandemic vaccine. Not only the baculovirus expression system can be used to produce vaccine in the form of recombinant protein, but Galarza et. al.[2] also applied this system to produce "Influenza virus like particle" or VLPS by using four influenza virus genes; HA, NA, M1 and M2. All four genes were expressed and produced in insect cells and assembled to VLP. The VLP was tested in rats and it could prevent infection from H3N2. Novavax, Inc. is now developing this vaccine production process.

Advantages of using the Baculovirus Expression Insect Cell System

1. No allergic reactions to chicken egg protein since the recombinant vaccine is produced from insect cell culture
2. Both baculovirus and insect cell are safe for humans
3. The production process is much easier than production of the whole virus particle since it is a subunit vaccine so safety does not need to be considered during the production, and there is no need to use BSL3. It also has high potential to expand to an industrial scale.
4. The same production line can be used to produce recombinant vaccine from the influenza seasonalflu strain and pandemic strain.
5. There is no genetic heterogeneity.
6. Vaccine inactivation process is not needed. Contamination by chemicals used for virus inactivationis not a concern.

Limitations of the Baculovirus Expression Insect Cell System

1. Culture medium for insect cell culture is costly.
2. Insect cells have a post translation modification that is different from mammal so that the recombinant vaccine needs to be strictly tested. However, the past results of recombinant influenza vaccine in clinical trials were satisfactory. This means that the recombinant vaccine from thissystem is reliable; the post translation modification process has no effect on immune stimulation for this disease.

Potential of Baculovirus Expression Insect Cell System in influenza vaccine production

There are two reports on the recombinant HA protein production for vaccine for influenza virus as follows:

1. Wang K. et al.[3], at Protein Sciences who own this production patent, produced and purified recombinant HA protein (99% purity) from insect cell culture in an amount of 6.4 mg HA protein/litre in a 15 liter fermenter. 1,500 doses of vaccine (135 mg recombinant HA /dose) can be produced in a 500 liter fermenter. From the published report, the production efficiency will be further increased.
2. New N. et al.[4] also published work on the production of recombinant HA protein H5N1 from insect cells. The production yielded 68 mg/liter from an insect cell culture but this was the amount of recombinant protein which had not yet been purified.

Summary There is a high possibility to produce influenza vaccine on a large scale by using the Baculovirus Expression Insect Cell System. This technology provides safety for the production process and the vaccine causes no harm to humans since it uses viral proteins as antigens instead of whole virus particles.

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1 B. Purification of influenza recombinant proteins from the Baculovirus Expression Insect Cell System

Recovery and purification of the products produced are most critical in biotechnology and biopharmaceutical industries since not only purities of the products are of significant concern but also their biological functions are equally important. Further, the Thai or US Food and Drug Administration (FDA) mandates manufacturers of recombinant proteins intended for human use to demonstrate virus clearance of their purification train since raw materials involved such as mammalian cells, fetal bovine serum and engineered vectors pose risks for virus contamination in the final products (FDA (1993, 1997), ICH (2001)). Since for industrial production of therapeutic recombinant proteins productivity is of highest priority, therefore, maximization of product produced as a function of time must be closely monitored. For instance, with the baculovirus expression system, the progress of viral infection could be monitored by performing hemadsorption (hemagglutination) of chicken red blood cells due to the presence of sialic acid residues (Barrett and Inglis (1991)). Nevertheless, Wang et al. (2006) studied the possibility of producing HA of A/New Caledonia/20/99 (H1N1) influenza using *Autographa* California Nuclear *Polyhedrolysis* Virus (AcMNPV) and found that harvesting of the products at 57 – 65 hours post infection led to highest protein yield while Smith et al. (1999) found that to attain maximal HA productivity of influenza A/Beijing/353/89 using *Spodopter frugiperda* cell line, harvest should be performed at 72 hours post infection.

Owing to the fact that HA and NA produced are embedded on the plasma membrane of the host cells, insect cells were therefore first harvested by centrifugation. Subsequently, solubilization of HA and NA subunits from surface glycoprotein must be achieved by extracting with buffer containing detergents such as Triton X-100 (Gerentes et al. (1996)) or Tergitol NP-9 (Wang et al. (2006)) for a specified time period. Subsequently, the mixture was ultracentrifuged at 150,000g for 30 minutes at 4°C. The pellet was discarded while the presence of target proteins in the supernatant was verified by polyacrylamide gel electrophoresis (PAGE). Prior to the further purification step, the supernatant was dialyzed against phosphate saline buffer (PBA) to recover isotonicity. In order to recover HA particles, Gerentes et al. (1996) loaded the mixture onto HiTrapTM NH-S activated Sepharose columns (Pharmacia) previously bound with a specific type of monoclonal antibodies (MAb) depending on the strains of viruses used, at the flow rate of 2 ml/minute. In the case where the target protein was HA, the HiTrapTM NH-S activated Sepharose column was then equilibrated with 6L2H10 monoclonal antibody (IgA isotype, H3 subtype specific) designated as IaH-chromatography. While contaminant proteins including NA passed through the column, HA proteins were bound to the MAb resulting an anti-HA MAb/HA complex that could be recovered by eluting the column with citrate-phosphate buffer with pH ranging from 3.4 to 7.0. It was found that HA with active biological function could be efficiently eluted at pH 6. The authors further found that 99 and 75% of purity and recovery could be attained, respectively.

After extracting the cell pellet with Buffer A (20 mM sodium phosphate, 1.0 mM EDTA, 0.01% Tergitol-NP9, 5% glycerol, pH 5.8) supplemented with 1% Tergitol NP-9 for 30 minutes at 4°C and centrifuged at 10,000g for 25 minutes, Wang et al. (2006) found that a cation and anionic exchange column could also be employed to recover HA proteins. The insoluble pellet was discarded while supernatant was loaded onto a UNOsphere-Q (anion exchange) column and then a SP-Sepharose Fast Flow (cation exchange) column consecutively. Impurities bearing negative charges were trapped by the Q column while HA monomer whose pI is approximately 6.3 was bound tightly to the SP column. Consequently, HA

captured in the SP column could be eluted with Buffer B (20 mM sodium phosphate, 0.03% Tergitol-NP9, 5% glycerol, pH 7.02) and Buffer C (20 mM sodium phosphate, 150 mM NaCl, 0.03% Tergitol-NP9, 5% glycerol, pH 7.02). To further purify, the eluted Buffer B fraction was then loaded onto the hydroxypatite type I (HX-I) previously equilibrated with Buffer B at the flow rate of 2 ml/min. HA protein was eluted with Buffer D (40 mM sodium phosphate, 0.05% Tween-20, 5% glycerol, pH 7.0), E (100 mM sodium phosphate, 0.05% Tween-20, 5% glycerol, pH 7.0) and F (500 mM sodium phosphate, 0.05% Tween-20, 5% glycerol, pH 7.0), respectively. The fraction containing HA monomers (Buffer D) was then subjected to ultrafiltration to remove impurities and at the same time concentrate using regenerated cellulose membrane with 100 molecular weight cut-off (MWCO) in Buffer G (10 mM sodium phosphate, 150 mM NaCl, 0.01% Tween-20, pH 7.2). Wang et al. (2006) found that more than 95% purity and approximately 57% overall yield could be accomplished within 6 hours.

Smith et al. (1999) have proposed the following method to recover the HA protein produced using the baculovirus expression system. The infected Sf9 cells were harvested by centrifugation at 3200g for 15 minutes, then washed with serum free TNMFH media and centrifuged at 10,000g for 30 minutes. The supernatant was discarded whereas pellet was resuspended and disrupted in ice cold buffer (30 mM Tris-HC pH 8.4, 25 mM LiCl, 1% Tween 20, 1 mg/ml leupeptin) with homogenizer. The homogenate was then centrifuged at 9,200g for 30 minutes. Supernatant was discarded and the insoluble pellet was subjected to further homogenization to extract the HA protein from the plasma membrane, for 2 minutes in buffer (30 mM Tris, 10 mM ethanolamine, pH11, 25 mM LiCl, 2% Tween-20), and incubated for 60 on ice. At the end of incubation, the pH of the mixture was adjusted to 8.4 and insoluble materials were removed by centrifugation at 9,200g for 30 minutes. The supernatant was then applied to a Pharmacia DEAE Sepharose Fast Flow column with the outlet connected to the inlet of a Pharmacia Lentil Lectin Sepharose 4B column. The columns were then washed with buffer (30 mM Tris-HCl pH 8.4, 25 mM LiCl, 0.5% Tween 20) until the OD280 of the effluent of the lentil lectin column returned to baseline. Most of the impurities were bound to DEAE while the glycosylated HA protein passed through and finally bound the Lentil Lectin affinity matrix. Both columns were disconnected and the lentil lectin column was again washed with buffer (30 mM Tris-HCl pH 8.4, 25 mM LiCl, 0.4% sodium deoxycholate). HA particles were subsequently eluted from the column with buffer (30 mM Tris-HCl pH 8.4, 25 mM LiCl, 0.4% sodium deoxycholate) containing 0.3 M ∞-D-methyl mannoside. To remove other impurities including buffer components, the eluate was dialyzed against pH 7.5 PBS leading to HA protein with at least 95 % purity.

Even though both HA and NA are components of the glycoprotein on the surface of the influenza virions, after administration, only the HA subunit has been illustrated to possess immunogenicity. However a number of studies have demonstrated that incorporation of the NA subunit into the vaccines could significantly enhance prophylactic properties (Kilbourne et al. (1995), Johannson (1999), Johannson et al. (1998)). Laver (1978) developed a procedure to purify NA molecules using pronase digestion together with gradient centrifugation while Gallagher et al. (1984) found that solubilization with octylglucoside followed by DEAE chromatography could also be as effective. Gerentes et al. (1996) found that the NA subunit could be recovered by loading the mixture previously treated as described above to a HiTrapTM NH-S activated Sepharose column that was then equilibrated with 6T7E3 monoclonal antibody (IgG1 isotype, N2 subtype specific) which is designated as IaN-chromatography. In a similar fashion as that of IaH-chromatography, NA proteins were bound to the MAb resulting in the anti-NA MAb/NA complex whereas impurities including

HA passed through the column. NA proteins could be recovered by eluting the column with citrate-phosphate buffer with pH ranging from 3.4 to 7.0. It was found that NA could be efficiently eluted at pH less than 5. The authors found that approximately 99% purity could easily be accomplished, however only 25% recovery could also be attained due to the fact that the NA proteins recovered were partially degraded when exposed to low pH during elution. It was anticipated that sensitivity of NA proteins to the acidic pH may be derived from the fact that there are an unusually large number of charged residues in close proximity to the active site of NA molecules (Colman et al. (1983)). Additionally, the NA molecules eluted at low pH were irreversibly modified and could not be recovered during dialysis against neutral pH buffer.

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Annex 2

Standard of Specific pathogen free egg (SPF egg) and Clean egg

2.1 General principle of microbiological monitoring for SPF chicken (Chinese national standard)

1. Salmonella Pullorum
2. Avian Influenza Virus(Type A)
3. Infectious Bronchitis Virus
4. Infectious Bursal Disease Virus
5. Infectious Laryngotracheitis Disease Virus
6. Newcastle Disease Virus
7. Fowl Pox Virus
8. Marek's Disease Virus
9. Haemophilus paragallinarum
10. *Pasteurella multocida*
11. Avian Adenovirus Group II
12. *Mycoplasma gallisepticum*
13. *Mycoplasma synoviae*
14. Avian Encephalomyelitis Virus
15. Lymphoid Leukosis Virus
16. Reticuloendotheliosis Virus
17. Avian Reovirus
18. Avian Adenovirus Group I
19. Chicken Infectious Anaemia Virus

2.2 Standard of Specific pathogen free egg (SPF egg) from LohmannTierzucht Company, Germany

1. Avain adenoviruses
2. Avian encephalomyelitis
3. Avian infectious bronchitis virus
4. Avian infectious laryngotracheitis virus
5. Avian leucosis viruses
6. Avian nephritis virus
7. Avian reoviruses
8. Avian reticuloendotheliosis virus
9. Haemagglutinating avian adenovirus
10. Infectious bursal disease virus
11. Influenza A virus
12. Marek's disease virus
13. Newcastle disease virus
14. Turkey rhinotracheitis virus
15. *Mycoplasma gallisepticum*
16. *Mycoplasma synoviae*
17. *Salmonella pullorum*

Annex 3

Comparison between ACTD and ICH CTD (document for medical registration)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
Number of Modules / Parts:	5 Modules	4 Parts
Module / Part 1:	Module 1: Specific Information for Each Region (Non CTD)	Part 1: Table of Contents Administrative Data and Product Information Section A: Introduction Section B: Table of Contents 1. Application Form 2. Letter of Authorization (Where applicable) 3. Certificates 4. Labelling 5. Product Information
Module / Part 2:	Module 2: Summaries -Quality -Safety -Efficacy 2.2 Introduction 2.3 Quality overall summary 2.4 Non-clinical Overview 2.5 Clinical Overview 2.6 Non-clinical Written and Tabulated Summaries 2.7 Clinical summary	Part 2: Quality Section A: Quality Overall Summary *S: Drug Substance* S1: General Information Nomenclature Structural Formula General Properties S2: Manufacture S 2.1 Manufacturer(s) S 2.2 Description of Manufacturing Process and Process Controls S 2.3 Control Materials S 2.4 Control of Critical Steps and Intermediates S 2.5 Process Validation and/or Evaluation S 2.6 Manufacturing Development S3: Characterization S 3.1 Elucidation of Structure and other Characteristics S 3.2 Impurities S4: Control of Drug Substance S 4.1 Specification S 4.2 Analytical Procedures S 4.3 Validation of Analytical Procedures

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
		S 4.4 Batch Analyses S 4.5 Justification of Specification S5: Reference Standards or Materials S6: Container Closure System S7: Stability Stability Summary and Conclusion Post-approval Stability Protocol and Stability Commitment Stability Data ***P: Drug Product*** P1: Description and Composition P2: Pharmaceutical Development P2.1 Information on Development Studies P2.2 Components of the Drug Product P2.3 Finished Product P2.4 Manufacturing Process Development P2.5 Container Closure System P2.6 Microbiological Attributes P2.7 Compatibility P3: Manufacture P3.1 Batch Formula P3.2 Manufacturing Process and Process Control P3.3 Control of Critical Steps and Intermediates 3.4 Process Validation and/or Evaluation P4: Control of Excipients P4.1 Specification P4.2 Analytical Procedures P4.3 Validation of Analytical Procedures P4.4 Justification of Specification P4.5 Excipient of Human or Animal Origin P4.6 Novel Excipients P5: Control of Finished Product P 5.1 Specification P 5.2 Analytical Procedures

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
		P 5.3 Validation of Analytical Procedures P 5.4 Batch Analyses P 5.5 Characterization of Impurities P 5.6 Justification of Specification P6: Reference Standards or Materials P7: Container Closure System P8: Stability -Stability Summary and Conclusion -Post-approval Stability protocol and Stability Commitment P9: Product Interchangeability Equivalence Evidence **Section B: Table of Contents** **Section C: Body of Data** ***S: Drug Substance*** S1: General Information S1.1 Nomenclature S1.2 Structural formula S1.3 General Properties S2: Manufacture S2.1 Manufacturer(s) S2.2 Description of Manufacturing Process and Process Controls S2.3 Control Materials S2.4 Control of Critical Steps and Intermediates S2.5 Process Validation and/or Evaluation S2.6 Manufacturing Development S3: Characterization S3.1 Elucidation of Structure and other Characteristics S3.2 Impurities S4: Control of Drug Substance S4.1 Specification S4.2 Analytical Procedures S4.3 Validation of Analytical Procedures

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
		S4.4 Batch Analyses S4.5 Justification of Specification S5: Reference Standards or Materials S6: Container Closure System S7: Stability Stability Summary and Conclusion Post-approval Stability Protocol and Stability Commitment Stability Data *P: Drug Product* P1: Description and Composition P2: Pharmaceutical Development P2.1 Information on Development Studies P2.2 Components of the Drug Product P2.3 Finished Product P2.4 Manufacturing Process Development P2.5 Container Closure System P2.6 Microbiological Attributes P 2.7 Compatibility P3: Manufacture P3.1 Batch Formula P3.2 Manufacturing Process and Process Control P3.3 Control of Critical Steps and Intermediates P3.4 Process Validation and/or Evaluation P4: Control of Excipients P4.1 Specification P4.2 Analytical Procedures P 4.3 Validation of Analytical Procedures P 4.4 Justification of Specification P 4.5 Excipient of Human or Animal Origin P 4.6 Novel Excipients P5: Control of Finished Product P 5.1 Specification P 5.2 Analytical Procedures P 5.3 Validation of Analytical Procedures

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
		P 5.4 Batch Analyses P 5.5 Characterization of Impurities P 5.6 Justification of Specification P6: Reference Standards or Materials P7: Container Closure System P8: Stability -Stability Summary and Conclusion -Post-approval Stability protocol and Stability Commitment P9: Product Interchangeability Equivalence Evidence **Section D: Key Literature References**
Module / Part 3:	**Module 3: Quality Documents** 3.2 Body of Data ***3.2.S Drug Substance*** 3.2.S.1 General Information 3.2.S.2 Manufacture 3.2.S.3 Characterization 3.2.S.4 Control of Drug Substance 3.2.S.4.1 Specification 3.2.S.4.2 Analytical Procedures 3.2.S.4.3 Validation of Analytical Procedures 3.2.S.4.4 Batch Analyses 3.2.S.4.5 Justification of Specification 3.2.S.5 Reference Standards or Materials 3.2.S.6 Container Closure System 3.2.S.7 Stability ***3.2.P Drug Product*** 3.2.P.1 Description and Composition of the Drug Product	**Part 3: Non-Clinical Document** **Section A: Table of Contents** **Section B: Non-clinical Overview** 1. General Aspects 2. Content and Structural Format **Non-Clinical Overview** 1. Overview of the Non-Clinical Testing Strategy 2. Pharmacology 3. Pharmacokinetics 4. Toxicology 5. Integrated Overview and Conclusions 6. List of Literature Citations **Section C: Non-Clinical Written and Tabulated Summaries** 1. Non-Clinical Written Summaries 1.1 Introduction 1.2 General Presentation Issues 2. Content of Non-Clinical Written and Tabulated Summaries

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
	3.2.P.2 Pharmaceutical Development 3.2.P.3 Manufacture 3.2.P.4 Control of Excipients 3.2.P.4 Control of Excipients 3.2.P.5 Control of Drug Product 3.2.P.5.1 Specification(s) 3.2.P.5.2 Analytical Procedures 3.2.P.5.3 Validation of Analytical Procedures 3.2.P.5.4 Batch Analyses 3.2.P.5.5 Characterization of Impurities 3.2.P.5.6 Justification of Specification 3.2.P.6 Reference Standards or Materials 3.2.P.7 Container Closure System 3.2.P.8 Stability 3.2.A Appendices 3.2.A.1 Facilities and Equipments 3.2.A.2 Adventitious Agents Safety Evaluation 3.2.A.3 Excipients 3.2.R Regional Information 3.3 Literature References	2.1 Pharmacology 2.1.1 Written Summary – Brief Summary 2.1.1.1 Primary Pharmacodynamics 2.1.1.2 Secondary Pharmacodynamics 2.1.1.3 Safety Pharmacology 2.1.1.4 Pharmacodynamic Drug Interactions – Discussion and Conclusions – Tables and Figures 2.1.2 Pharmacology Tabulated Summary 2.2 Pharmacokinetics 2.2.1 Written Summary - Brief Summary - Method of Analysis 2.2.1.1 Absorption 2.2.1.2 Distribution 2.2.1.3 Metabolism(inter-species comparison) 2.2.1.4 Excretion 2.2.1.5 Pharmacokinetic Drug Interaction 2.2.1.6 Other Pharmacokinetic Studies - Discussion and Conclusions - Tables and Figures 2.2.2PharmacokineticsTabulated Summary 2.3 Toxicology 2.3.1 Written Summary -Brief Summary -Toxicology Program 2.3.1.1 Single-Dose Toxicity 2.3.1.2 Repeated-Dose Toxicity 2.3.1.3 Genotoxicity 2.3.1.4 Carcinogenicity 2.3.1.5 Reproductive and Developmental Toxicity 2.3.1.5.1 Fertility and Early Embryonic Development Toxicity 2.3.1.6 Local Tolerance

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
		2.3.1.7 Other Toxicity Studies (if available) -Discussion and Conclusions -Tables and Figures 2.3.2 Toxicology Tabulated Summary 3. Non-Clinical Tabulated Summaries **Section D: Non-Clinical Study Reports** 1. Table of Contents 2. Pharmacology 2.1 Written Study Reports 2.1.1 Primary Pharmacodynamics 2.1.2 Secondary Pharmacodynamics 2.1.3 Safety Pharmacology 2.1.4 Pharmacodynamic Drug Interactions 3. Pharmacokinetics 3.1 Written Study Reports 3.1.1 Analytical Methods and Validation Reports 3.1.2 Absorption 3.1.3 Distribution 3.1.4 Metabolism 3.1.5 Excretion 3.1.6 Pharmacokinetics Drug Interaction 3.1.7 Other Pharmacokinetic Studies 4. Toxicology 4.1 Written Study Reports 4.1.1 Single-Dose Toxicity 4.1.2 Repeated-Dose Toxicity 4.1.3 Genotoxicity 4.1.3.1 In-vitro Reports 4.1.3.2 In-vivo reports 4.1.4 Carcinogenicity 4.1.4.1 Long Term Studies 4.1.4.2 short or Medium Term Studies 4.1.4.3 Other Studies 4.1.5 Reproductive and Developmental Toxicity 4.1.5.1 Fertility and Early

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
		Embryonic Development 4.1.5.2 embryo-Fetal development 4.1.5.3 Prenatal and Post natal Development 4.1.5.4 Studies in which the Offspring are Dosed and/or Further Evaluated 4.1.6 Local Tolerance 4.1.7 Other Toxicity Studies (if available) 4.1.7.1 Antigenicity 4.1.7.2 Immunotoxicity 4.1.7.3 Mechanistic Studies 4.1.7.4 Dependence 4.1.7.5 Metabolites 4.1.7.6 Impurities 4.1.7.7 Other **Section E: list of Key Literature References** - Appendix A: Non-Clinical Tabulated Summaries
Module / Part 4:	**Module 4:Nonclinical Documents** 4.2 Study Reports 4.2.1 Pharmacology 4.2.1.1 Primary Pharmacodynamics 4.2.1.2 Secondary Pharmacodynamics 4.2.1.3 Safety Pharmacology 4.2.1.4 Pharmacodynamic Drug Interactions 4.2.2 Pharmacokinetics 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available) 4.2.2.2 Absorption 4.2.2.3 Distribution	**Part 4: Clinical Document** **Section A: Table of Contents** **Section B: Clinical Overview** 1. Product Development Rationale 2. Overview of Biopharmaceutiics 3. Overview of Clinical Pharmacology 4. Overview of Efficacy 5. Overview of Safety 6. Benefits and Risks Conclusions Section C: Clinical Summary 1. Summary of Biopharmaceutic Studies and Associated Analytical Methods 1.1 Background and Overview 1.2 Summary of Results of Individual Studies 1.3 Comparison and Analyses of Results Across Studies

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
	4.2.2.4 Metabolism 4.2.2.5 Excretion 4.2.2.6 Pharmacokinetic Drug Interactions (non-clinical) 4.2.2.7 Other Pharmacokinetic Studies 4.2.3 Toxicology 4.2.3.1 Single-Dose Toxicity (in order by species, by route) 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration, including supportive toxicokinetics evaluations) 4.2.3.3 Genotoxicity 4.2.3.3.1 In vitro 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations) 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations) 4.2.3.4.1 Long-term studies (in order by species, including range-finding studies that cannot be appropriately included under repeat-dose toxicity or pharmacokinetics) 4.2.3.4.2 Short-or medium-term studies (including range-finding studies that cannot be appropriately included under repeat-dose toxicity or pharmacokinetics) 4.2.3.4.3 Other studies 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following	- Appendix 1 2. Summary of Clinical Pharmacology Studies 2.1 Background and Overview 2.2 Summary of Results of Individual Studies 2.3 Comparison and Analyses of Results Across Studies 2.4 Special Studies - Appendix 2 3. Summary of Clinical Efficacy 3.1 Background and Overview 3.2 Summary of Results of Individual Studies 3.3 Comparison and Analyses of Results Across Studies 3.4 Analysis of Clinical Information Relevant to Dosing Recommendations 3.5 Persistence of Efficacy and/or Tolerance Effects - Appendix 3 4. Summary of Clinical Safety 4.1 Exposure to Drug 4.2 Adverse Events 4.3 Clinical Laboratory Evaluations 4.4 Vital Signs, Physical Findings and Other Observations Related to Safety 4.5 Safety in Special Groups and Situations 4.6 Post-marketing Data - Appendix 4 5. Synopses of Individual Studies **Section D: Tabular Listing of All Clinical Studies** **Section E: Clinical Study Reports (if applicable)** 1. Reports of Biopharmaceutic Studies 1.1 BA Study Reports 1.2 Comparative BA or BE Study Reports

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
	subheadings should be modified accordingly) 4.2.3.5.1 Fertility and early embryonic development 4.2.3.5.2 Embryo-fetal development 4.2.3.5.3 Prenatal and postnatal development, including maternal function 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated 4.2.3.6 Local Tolerance 4.2.3.7 Other Toxicity Studies (if available) 4.2.3.7.1 Antigenicity 4.2.3.7.2 Immunotoxicity 4.2.3.7.3 Mechanistic studies (if not included elsewhere) 4.2.3.7.4 Dependence 4.2.3.7.5 Metabolites 4.2.3.7.6 Impurities 4.2.3.7.7 Other 4.3 Literature References	1.3 In-vitro, in-vivo Correlation Study Reports 1.4 Reports of Bioanalytical and Analytical Methods for Human Studies 2. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials 2.1 Plasma Protein Binding Reports 2.2 Reports of Hepatic Metabolism and Drug Interaction Studies Human Biomaterials 2.3 Reports of Studies Using Other Human Biomaterials 3. Reports of Human Pharmacokinetic (PK) Studies 3.1 Healthy Subjects PK and Initial Tolerability Study Reports 3.2 Patient PK and Initial Tolerability Study Reports 3.3 Population PK Study Reports 4. Reports of Human Pharmacodynamic (PD) Studies 4.1 Healthy Subject PD and PK/PD Study Reports 4.2 Patient PD and PK/PD Study Reports 5. Reports of Efficacy and Safety Studies 5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication 5.2 Study Reports of Uncontrolled Clinical Studies 5.3 Reports of Analyses of Data from More than One Study, including any Formal Integrated Analyses, Meta-analyses, and Bridging Analyses 5.4 Other Clinical Study Reports 6. Reports of Post-marketing Experience 7. Case report Forms and Individual Patient Listing **Section F: List of Key Literature References**

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
	Module/Part: 5 **Module 5:Clinical Documents** 5.3 Clinical Study Reports 5.3.1 Reports of Biopharmaceutic Studies 5.3.1.1 Bioavailability (BA) Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.1.3 In vitro – In vivo Correlation Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies "Study Report 1" "Study Report 2" "Study Report 3" 5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials 5.3.2.1 Plasma Protein Binding Study Reports "Study Report 1" "Study Report 2"	-

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
	"Study Report 3" 5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies "Study Report 1" "Study Report 2" "Study Report 3" 5.3.2.3 Reports of Studies Using Other Human Biomaterials "Study Report 1" "Study Report 2" "Study Report 3" 5.3.3 Reports of Human Pharmacokinetic (PK) Studies 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.3.2 Patient PK and Initial Tolerability Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.3.3 Intrinsic Factor PK Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.3.4 Extrinsic Factor PK Study Reports "Study Report 1" "Study Report 2"	

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
	"Study Report 3" 5.3.3.5 Population PK Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.4 Reports of Human Pharmacodynamic (PD) Studies 5.3.4.1 Healthy Subject PD and PK/PD Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.4.2 Patient PD and PK/PD Study Reports "Study Report 1" "Study Report 2" "Study Report 3" 5.3.5 Reports of Efficacy and Safety Studies 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication "Study Report 1" "Study Report 2" "Study Report 3" 5.3.5.2 Study Reports of Uncontrolled Clinical Studies "Study Report 1" "Study Report 2" "Study Report 3" 5.3.5.3 Reports of Analyses of Data from More than One Study "Study Report 1" "Study Report 2"	

Comparison between ACTD and ICH CTD (document for medical registration) (continued)

Common Technical Documents/Dossiers (CTD)	ICH Tripartise	ASEAN 10 Member Countries
	"Study Report 3" 5.3.5.4 Other Study Reports "Study Report 1" Study Report 2" "Study Report 3" 5.3.6 Reports of Post-marketing Experience 5.3.7 Case Report Forms and Individual Patient Listings "Study Report 1" "Study Report 2" "Study Report 3" 5.4 Literature References	

Annex 4

List of influenza vaccine plant (World Health organization)

Country	Producer	Web site
1. Australia	CSL	http://www.csl.com.au
2. Austria Czech Republic	Baxter– Immuno AG	http://www.baxtervaccines.com
3. Belgium	GSK	http://www.gsk.com
4. Brazil	Butantan	http://www.butantan.gov.br
5. Canada	GSK- ID Biomedical	http://www.gsk.com
6. China	Zhejiang Tianyuan - BioPharmaceutical Co. Ltd	http://www.ty-pharm.com
7. China	Sinovac Kexing Biological Product Co., Ltd	http://www.sinovac.com
8. China	Beijing Institute of Biological Products (BIBP)	http://www.ccibp.com
9. China	Shanghai Institute of Biological Products (SIBP)	http://www.siobp.com
10. China	Changchun Institute of Biological Products (CCIBP)	http://www.ccibp.com
11. China	Changchun Changsheng Life Sciences Ltd	e-mail : cssy@public.cc.j1.cn
12. China	Lanzhou Institute of Biological Products (LIBP)	http://www.vacmic.com
13. China	Shenzhen-Sanofi Pasteur (Filler)	http://sanofipasteur.com
14. China	Changzhou Yanshen Biotechnology Co., Ltd	Not available
15. China	Liaoning Tiancheng Bio-pharmacy Institute Co. Ltd	Not available
16. France	Sanofi Pasteur	http://www.sanofipasteur.com
17. Germany	Chiron	http://www.chiron-behring.de
18. Hungary	Omninvest Ltd.	http://www.omninvest.hu
19. Italy	Chiron	http://www.chiron-behring.de
20. Japan	Denka Seiken Co, Ltd	http://www.denka-seiken.co.jp
21. Japan	Chemo-Sero-Therapeutic Research Institute	http://www.kaketsuken.or.jp
22. Japan	Kitasato Institute	http://www.kitasato.or.jp
23. Japan	Biken	http://www.biken.osaka-u.ac.jp
24. Korea	Dong Shin Pharmaceuticals	http://www.dong-shin.com
25 Korea	Korea Vaccine Co. Ltd	http://www.kovax-v.co.kr
26. Korea	Korea Green Cross	http://www.kuraish.com http://www.rheinbiotech.com http://www.bernabiotech-asia.com
27. Netherlands	Solvay Healthcare	http://www.solvaypharmaceuticals.nl
28. Romania	Cantacuzino Institute	http://www.cantacuzino.ro
29. Russia	Immunopreparat Research productive association, Ufa, Products Immunologicals and Drugs. Irkutsk, RIVS, Saint Petersburg	http://www.microgen.ru

List of influenza vaccine plant (World Health organization) (continued)

Country	Producer	Web site
30. Serbia	Torlak Institute	http://www.torlakinstitut.com
31. Switzerland	Berna Biotech	http://www.bernabiotech.com
32. UK	Chiron	http://www.chiron-behring.de
33. USA	Medimmune-Avirion	http://www.aviron.com
34. USA	Sanofi Pasteur	http://www.sanofipasteur.com
35. USA	Wyeth Lederle	http://www.wyeth.com

Current Vaccine Production Capacity in Thailand

1. Animal Vaccine Plant								GAP ANALYSIS
Production scale	Production unit	Product name	Equipments used in industrial scale production	Technology Platform	Production scale/year	GMP certified	Production period	Possibility for Adaptation (additional resources needed for pandemic vaccine)
Industrial scale production	BVB Animal vaccine plant (Japanese factory)	Foot and Mouth Disease vaccine (FMD) vaccine	1. two 5,000 L fermenters (supplement of a 1,000 L and a 2,000 L fermenter are expected in 2008) 2. two sets of Ultrafiltration with 100,000 Dalton with 350-400 L/h (2 additional sets are expected in 2008) 3. two continuous centrifuges (6,000 rpm, 480 L/h) (2 additional sets are expected in 2008) 4. Four high speed centrifuge (two of 1Lx 6 and two of 0.4 Lx 6) (two additional of 0.4 Lx 6 sets are expected in 2008)	A filling machine 4,000 vials/h	17 million doses/year (virus type=O, A and Asia one)		1 year	1. BSL 3 2. Cells 3. medium and medium change equipment 4. Seed virus 5. Purification equipments 6. WFI

Current Vaccine Production Capacity in Thailand (continued)

1. Animal Vaccine Plant								GAP ANALYSIS
Production scale	Production unit	Product name	Equipments used in industrial scale production	Technology Platform	Production scale/year	GMP certified	Production period	Possibility for Adaptation (additional resources needed for pandemic vaccine)
Industrial scale production	BVB Animal vaccine plant (French factory)	Foot and Mouth Disease vaccine (FMD) vaccine	1. three 3,200 L fermenters and a 1,400 L fermenter 2. two sets of Ultrafiltration with 100,000 Dalton with 350-400 L/h 3. two continuous centrifuges (6,000 rpm, 480 L/h) 4. two high speed centrifuge (1Lx 6) 5. Ultracentrifuge for centrifugation with sucrose gradient	A filling machine 3,000 vials/h	20 million doses trivalent vaccine/year (virus type=O, A and Asia one)	No	1 year	1. BSL 3 2. Cells 3. medium and medium change equipment 4. Seed virus 5. Purification equipments 6. WFI
		New Castle vaccine		Egg-Based large scale production	200-250 million doses/year			

Current Vaccine Production Capacity in Thailand (continued)

2. Human Vaccine Plant								GAP ANALYSIS
Production scale	Production unit	Product name	Equipments used in industrial scale production	Technology Platform	Production scale/year	GMP certified	Production period	Possibility for Adaptation (additional resources needed for pandemic vaccine)
Industrial scale production	Thai Red Cross	BCG vaccine	1. Distillation unit for WFI 2. Sterilizers 3. Incubator 4. Lyophilizer 5. Cold storage	1. Seed development and production under BSL2 2. Filling 3. Freeze drying 4. Packaging	5 million doses/year	GMP certified by Thai FDA	2 months	
		Rabies vaccine				GMP certified		
	Merieux Biologicals Co.Ltd	Rabies Vaccine and NMR vaccine		Local formulation	20 million doses/year			
		HBV vaccine		Bulk filling platform				
		OPV vaccine		Packaging platform				

Current Vaccine Production Capacity in Thailand (continued)

2. Human Vaccine Plant								GAP ANALYSIS
Production scale	Production unit	Product name	Equipments used in industrial scale production	Technology Platform	Production scale/year	GMP certified	Production period	Possibility for Adaptation (additional resources needed for pandemic vaccine)
Industrial scale production	GPO	Vaccine from mice brain		Vaccine production				
Pilot scale production	Department of Medical Sciences			Building of vaccine plant within 5 years	100,000-200,000 doses/year			
	Thai Red Cross	Recombinant vaccine		1.finished plant complies GMP (BSL 2) 2. two cold rooms for quarantine and release	Depends on capacity of machine	No		Compact line for washing, sterile, filling and capping of vials
Lab scale	Department of Medical Sciences	Finished product		Production				

Current Vaccine Production Capacity in Thailand (continued)

1. Animal Vaccine Plant								GAP ANALYSIS
Production scale	Production unit	Product name	Equipments used in industrial scale production	Technology Platform	Production scale/year	GMP certified	Production period	Possibility for Adaptation (additional resources needed for pandemic vaccine)
Lab scale	GPO	JE vaccine (tissue culture derived vaccine)	1.Carbondioxide incubator 2. Deep freezer 3. Chromatography	Research and Development				
	KMUTT	Human growth hormone (therapeutic protein)	fermenter (at Thai Red Cross)			Plan to use GMP facility at GPO		
		Purified influenza vaccine	Bioreactor					

Annex 6

SPF egg production plan at BVB

House 1				House 2				House 3				House 4				Use
week	per day	quantity	use	week	per day	quantity	use	week	per day	quantity	use	week	per day	quantity	use	per Day
0				0												
1				1												
2				2												
3				3												
4				4												
5				5												
6				6												
7				7												
8				8												
9				9												
10				10												
11				11												
12				12												
13				13												
14				14												
15				15												
16				16												
17				17												
18				18												
19				19												
20				20												
21				21												
22				22												
23	1040	7280	5096	23	1040	7280	5096									10192
24	1200	8400	5880	24	1200	8400	5880									11760
25	1248	8736	6115	25	1248	8736	6115									12230
26	1280	8960	6272	26	1280	8960	6272									12544
27	1296	9072	6350	27	1296	9072	6350									12701
28	1296	9072	6350	28	1296	9072	6350									12701
29	1296	9072	6350	29	1296	9072	6350									12701
30	1296	9072	6350	30	1296	9072	6350									12701
31	1296	9072	6350	31	1296	9072	6350									12701
32	1296	9072	6350	32	1296	9072	6350									12701
33	1280	8960	6272	33	1280	8960	6272									12544
34	1280	8960	6272	34	1280	8960	6272									12544
35	1264	8848	6194	35	1264	8848	6194									12387

SPF egg production plan at BVB (continued)

House 1				House 2				House 3				House 4				Use
week	per day	quantity	use	week	per day	quantity	use	week	per day	quantity	use	week	per day	quantity	use	per Day
36	1248	8736	6115	36	1248	8736	6115									12230
37	1248	8736	6115	37	1248	8736	6115									12230
38	1232	8624	6037	38	1232	8624	6037	0				0				12074
39	1216	8512	5958	39	1216	8512	5958	1				1				11917
40	1200	8400	5880	40	1200	8400	5880	2				2				11760
41	1184	8288	5802	41	1184	8288	5802	3				3				11603
42	1184	8288	5802	42	1184	8288	5802	4				4				11603
43	1168	8176	5723	43	1168	8176	5723	5				5				11446
44	1152	8064	5645	44	1152	8064	5645	6				6				11290
45	1136	7952	5566	45	1136	7952	5566	7				7				11133
46	1120	7840	5488	46	1120	7840	5488	8				8				10976
47	1104	7728	5410	47	1104	7728	5410	9				9				10819
48	1088	7616	5331	48	1088	7616	5331	10				10				10662
49	1072	7504	5253	49	1072	7504	5253	11				11				10506
50	1056	7392	5174	50	1056	7392	5174	12				12				10349
51	1040	7280	5096	51	1040	7280	5096	13				13				10192
52	1024	7168	5018	52	1024	7168	5018	14				14				10035
53	1008	7056	4939	53	1008	7056	4939	15				15				9878
54	992	6944	4861	54	992	6944	4861	16				16				9722
55	976	6832	4782	55	976	6832	4782	17				17				9565
56	960	6720	4704	56	960	6720	4704	18				18				9408
57	928	6496	4547	57	928	6496	4547	19				19				9094
58	912	6384	4469	58	912	6384	4469	20				20				8938
59	896	6272	4390	59	896	6272	4390	21				21				8781
60	880	6160	4312	60	880	6160	4312	22				22				8624
								23	1040	7280	5096	23	1040	7280	5096	10192
								24	1200	8400	5880	24	1200	8400	5880	11760
								25	1248	8736	6115	25	1248	8736	6115	12230
								26	1280	8960	6272	26	1280	8960	6272	12544
								27	1296	9072	6350	27	1296	9072	6350	12701
								28	1296	9072	6350	28	1296	9072	6350	12701
								29	1296	9072	6350	29	1296	9072	6350	12701
								30	1296	9072	6350	30	1296	9072	6350	12701
								31	1296	9072	6350	31	1296	9072	6350	12701
								32	1296	9072	6350	32	1296	9072	6350	12701
								33	1280	8960	6272	33	1280	8960	6272	12544
								34	1280	8960	6272	34	1280	8960	6272	12544
								35	1264	8848	6194	35	1264	8848	6194	12387

SPF egg production plan at BVB (continued)

House 1				House 2				House 3				House 4				Use
week	per day	quantity	use	week	per day	quantity	use	week	per day	quantity	use	week	per day	quantity	use	per Day
								36	1248	8736	6115	36	1248	8736	6115	12230
								37	1248	8736	6115	37	1248	8736	6115	12230
								38	1232	8624	6037	38	1232	8624	6037	12074
1				1				39	1216	8512	5958	39	1216	8512	5958	11917
2				2				40	1200	8400	5880	40	1200	8400	5880	11760
3				3				41	1184	8288	5802	41	1184	8288	5802	11603
4				4				42	1184	8288	5802	42	1184	8288	5802	11603
5				5				43	1168	8176	5723	43	1168	8176	5723	11446
6				6				44	1152	8064	5645	44	1152	8064	5645	11290
7				7				45	1136	7952	5566	45	1136	7952	5566	11133
8				8				46	1120	7840	5488	46	1120	7840	5488	10976
9				9				47	1104	7728	5410	47	1104	7728	5410	10819
10				10				48	1088	7616	5331	48	1088	7616	5331	10662
11				11				49	1072	7504	5253	49	1072	7504	5253	10506
12				12				50	1056	7392	5174	50	1056	7392	5174	10349
13				13				51	1040	7280	5096	51	1040	7280	5096	10192
14				14				52	1024	7168	5018	52	1024	7168	5018	10035
15				15				53	1008	7056	4939	53	1008	7056	4939	9878
16				16				54	992	6944	4861	54	992	6944	4861	9722
17				17				55	976	6832	4782	55	976	6832	4782	9565
18				18				56	960	6720	4704	56	960	6720	4704	9408
19				19				57	928	6496	4547	57	928	6496	4547	9094
20				20				58	912	6384	4469	58	912	6384	4469	8938
21				21				59	896	6272	4390	59	896	6272	4390	8781
22				22				60	880	6160	4312	60	880	6160	4312	8624
23	1040	7280	5096	23	1040	7280	5096									10192
24	1200	8400	5880	24	1200	8400	5880									11760
25	1248	8736	6115	25	1248	8736	6115									12230
26	1280	8960	6272	26	1280	8960	6272									12544
27	1296	9072	6350	27	1296	9072	6350									12701
28	1296	9072	6350	28	1296	9072	6350									12701
29	1296	9072	6350	29	1296	9072	6350									12701

Annex 7

Report on China influenza Vaccine Plant Visits
5-10 November, 2006

1. List of China Vaccine Plants

Vaccine plants/units	address	Justification to visit
1. Shenzhen Neptunus Interlong Bio-tech Holdings Co., Ltd.	Haiwang Yingtelong Base, Eastern Changxing Industrial Zone, Gongming Changzhen village, Songbai highway, BioAn District, Shenzhen	The only factory that can immediately supply bulk influenza vaccine.
2. Shanghai Institute of Biological Products (SIBP)	1262 Yan An Road (W), Shanghai	A part of SIBP network that use egg-based technology
3. The China National Biotec Corporation (CNBC Head Quarter)	Jingrun Building No. 28 A Fuchengmen Street, Xicheng Distric, Biejing	CNBC Head Quarter with 7 vaccine plants in the network with an influenza vaccine plant at Shanghai
4. Sinovac Biotech Co., Ltd.	No.39 Shanghdai Xi Rd., Haidan District, Beijing	Production plant for seasonal/ H5N1 vaccine using both cell-based and egg-based technology with the possibility of technology transfer for Thailand
5. Hualan Biological Engineering Inc.	Jia No.1, Hualan Ave., Xinxiang, Henan	The newest flu vaccine plant which is the biggest plant in China (20 million doses/year production

2. List of participants

Name	Affiliation	Topics/technologies evaluated
Assoc. Prof. Prasit Palittapongarnpim	BIOTEC	Chairperson
Dr. Somsak Chunharas	National Health Foundation	Project consultant
Dr. Jongkol Lerttiendamrong (Principal Investigator)	IHPP	Possibility for Thai-China cooperation and financing
Ms. Thipayawan Thanapaisan Prof. Sumana Khomwilai	BIOTEC Thai Red Cross	Strategies for building vaccine plants and analysis of egg-based and cell-based technology bulk vaccine production, logistic management of importing bulk vaccine to Thailand and evaluate vaccine plant
Dr. Somchai Chuewatcharin	Mahidol University	Bioprocess Engineering and technologies used in the vaccine plants
Asst. Prof. Dr. Kanokwan Poompusta	KMUTT	Cell-based technology and down stream process
Pharmacist Prapon Angtragoon	Thai FDA	GMP/WHO prequalification
Pharmacist Pornpit Silkavute	Health Systems Research Institute	Data/knowledge synthesis, compilation and site visit report.
Asst. Prof. Dr. Anan Tongta	KMUTT	Bioprocess Engineering

3. Summary of vaccine plants visit

(1) Shenzen Neptunus Interlong Bio-Technique Company Limited (SNI)

Influenza Vaccine

The first plant to produce Influenza subunit vaccine using egg-base technology

subunit vaccine = 4 eggs/dose

split vaccine = 2 eggs/dose

Production capacity: 1 million doses by using 40 million eggs for subunit vaccine and 20 million eggs for split vaccine

Virus Strain: from Prof. Malik, Hong Kong which is Northern Strain (Southern strain is also available if requested)

Vaccine quality

Split vaccine: protein content ·300 mg and DNA content (EU standard)

Subunit vaccine: protein content ·100 mg and DNA content (EU standard)

Pilot Plant

New plant will be equipped with automatic Equipments from USA and Europe e.g. machine for egg injection from Embrex, USA, machine for harvest virus from TKA, Italy. The plant passed Chinese GMP and in the process of approval by EU in 2008.

Plant visit

New vaccine plant has not yet operated but main equipments have been installed. The system is in BSL3 (100% exhaust). It is expected be operate in 2007.

Vaccine Production Process

10 days old eggs is incubated at 34°C with 60% RH in incubating units (15 units with 80,000 eggs/unit capacities, made in Japan) until ready then sent to cold room 2-8°C overnight. The eggs are then injected with virus and harvested with automatic machine. The harvested virus is then inactivated with formaldehyde, centrifuged, ultrafiltration (Pall, USA) and splitted before purified with Chromatography (gel filtration, GE). The split virus is filter sterilization before filling (2 and capping. The whole processes have been under the supervision of Chiron and Sanofi Pasteur.

Avian Influenza Vaccine

Avian influenza vaccine production using egg-based technology is in the R&D stage. The cell-based technology using MDCK cell is also being studied.

Technology transfer: Unlikely.

(2) Shanghai Institute of Biological Product (SIBP)

Influenza Vaccine: Using egg-based technology from BIKEN, Japan for split influenza vaccine

Vaccine Plant

The plant was constructed by Holland DHV Engineering Firm according to EU GMP. Its main machine consists of virus harvest machine, ultrafiltration, ultracentrifugation (zonal centrifugation for sucrose gradient), filling machine (Bosch), etc.

Production Capacity: 8-10 million doses/year using clean egg of Highland white chicken from contracted farms (50,000-70,000 eggs/batch)
Virus Strain: from NIBSC

Avian Influenza Vaccine: using cell-based technology (MDCK cells)
Technology transfer: Possible.

(3) Hualan Biological Engineering Inc.

Influenza Vaccine:

Egg-based technology is used for production of split influenza virus vaccine. The plant signed a contract with Chinese government to supply vaccine during Olympic in 2008.

Seasonal flu = 3 eggs/dose
Avian flu = 1 egg/dose

The eggs are from Highland white chicken produced in the mountainous area to avoid the diseases.
Virus Strain: from CDC, USA
Vaccine plant

At the time of visiting, the plant is under construction and considered the biggest influenza vaccine plant in China. It is built by the company from Holland following WHO GMP. There are 5 buildings; 1) vaccine production, 2) QA and QC, 3) filling, 4) storage, and 5) animal house. The main machines are harvesting machine, ultrafiltration, ultracentrifugation (zonal centrifugation for sucrose gradient), 3 lines of filling machine (Bosch), etc.
Production Capacity: 20 million doses/year(seasonal flu)
Avian Influenza Vaccine

Egg based technology is used for vaccine production. The vaccine has been tested preclinical animal trial and approved for performing clinical trial by Chinese FDA in cooperation with Baxter.
Technology transfer: Unlikely to supply bulk vaccine of both seasonal and avian flu.

(4) Sinovac

Influenza Vaccine: Split influenza vaccine from egg-based technology using clean egg from contracted farms.
Virus Strain: from NIBSC
Production Capacity: 2 million does/6 months of seasonal flu with surge capacity of 4 million doses/year
Avian Influenza Vaccine:

Whole inactivated virus vaccine is produced by egg-based technology. The vaccine has been tested for phase I clinical trial. Phase II is waiting for the approval. pilot scale production. is also performed for cell-based technology.
Technology transfer: Possible.

Table 1 Summary on Chinese vaccine plants visited from 5th - 10th November, 2006

Vaccine Plant	Vaccine types	investment	Production capacity	GMP certified	Price of finished product	Technology transfer
1. Shenzhen Neptunus Interlong Bio-tech Holdings Co., Ltd. - Private company - Stock market in Honkong	Seasonal flu vaccine	- 200 million Yuan (9 mY on land, 130 mY on equipments, 20 mY on operation costs - 60,000 m^2 - 100 mY more could be invested to expand the capacity to 30 million doses/yr - Use both SPF eggs (20Y/egg) And clean egg (1Y/egg) - Staffs (production-100, engineer-30, pilot plant-50)	- currently at 1 million doses/yr - expected to be expanded to 10 million doses/yr (200,000 doses/batch, 60-100 batch/yr, 2 months/batch) - filling capacity 80,000 doses/yr	- EU GMP in 2008 - technology set up by Chiron and Sanofi Pasteur	40-50 Y/dose	No policy on technology transfer
2. Shanghai Institute of Biological Products (SIBP) - state owned - 6 years construction	Seasonal flu vaccine	- 400 mY for construction (50mUSD) - maintenance cost without production -6-8 mY/, operation cost 20 mY - 21,280 m^2 (5,400 m^2 for clean room) - use 50,000-70,000 egg/batch	Existing capacity 8-10 million doses/yr which is Maximum capacity in current situation	Apply for EU GMP	50-80 Y/dose (the most expensive price)	- transferred technology from BIKEN, Japan - bulk vaccine export is possible - AI split vaccine is being studied at lab scale

Table 1 Summary on Chinese vaccine plants visited from 5th - 10th November, 2006 (continued)

Vaccine Plant	Vaccine types	investment	Production capacity	GMP certified	Price of finished product	Technology transfer
3. The China National Biotec Corporation (CNBC Head Quarter)	Seasonal flu split vaccine	- 400 mY (150 mY for equipments) - Plant will be finished in 2007 (5 buildings in for; production, QA/QC, filling, storage, animal house) - another 40,000 m^2 area for produce 320,000 egg/day	The newest and the biggest plant with production capacity of 20 million doses/year	WHO GMP		- Technology transferred from Holland - bulk vaccine export - strength is in plasma products - informal collaboration with Baxter - cell based technology is in lab scale
4. Sinovac Biotech Co., Ltd.	- seasonal flu vaccine - H5N1 vaccine (in clinical trial)	- 5-7 USD for equipments - production area is in BSL2 (3,000 m^2)	- 2 million doses/6 months with full capacity of 4 million doses/yr - in the process to expand to 20 million doses/yr with many limitations	Chinese GMP		- technology transfer to Thai is possible 400 million (Baht for 2 million doses/yr) but finished product selling is preferred
5. Hualan Biological Engineering Inc. - Head quarter of 7 vaccine plants network with a flu vaccine plant in Shanghai						

Table 2 Summary on Chinese vaccine plants visited from 5th - 10th November, 2006

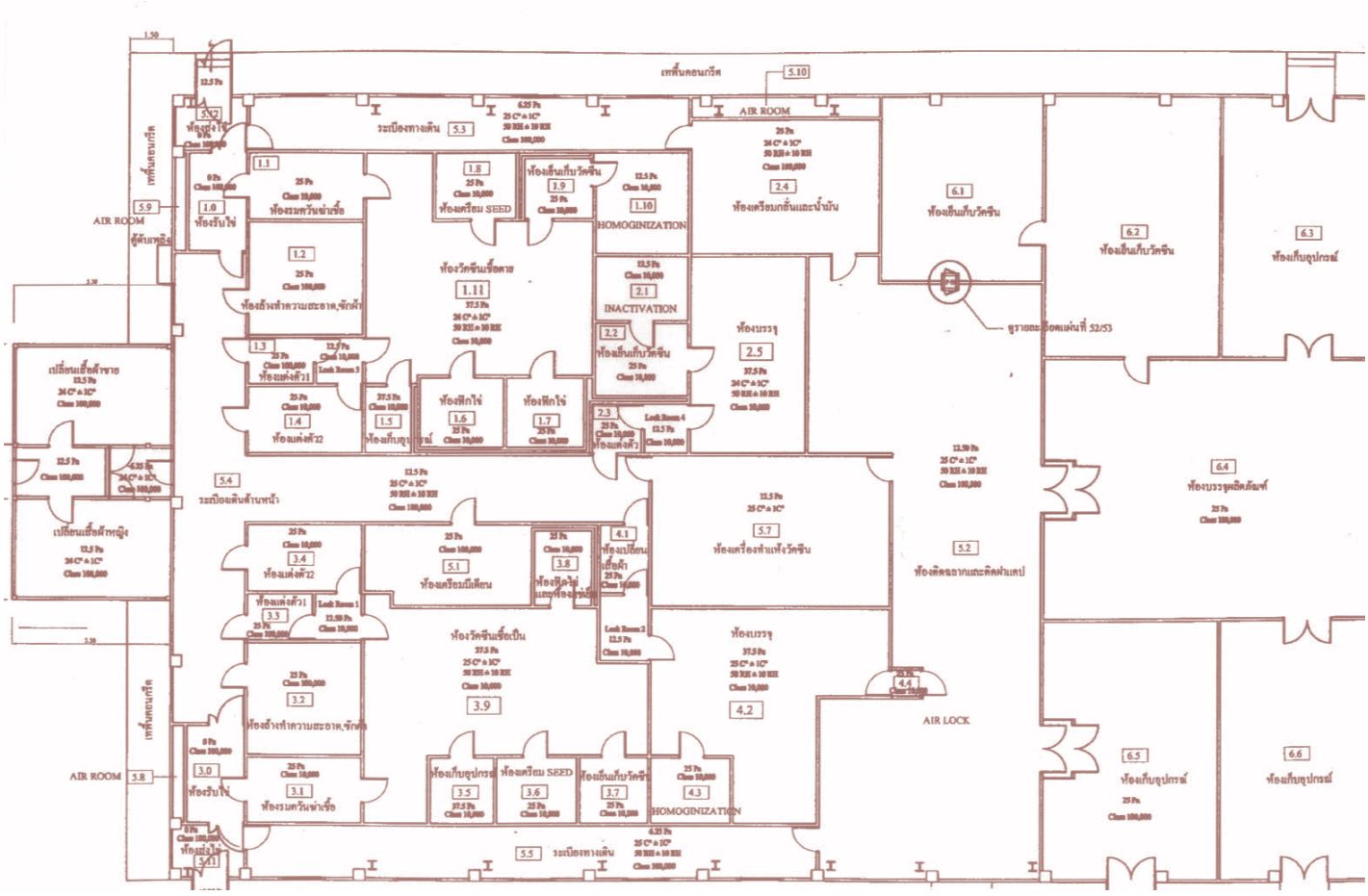
	clinical trial	GMP	lots release	capacity (seasonal)	Batch capacity	network	Cell based	R+D
1. Shenzhen Neptunus Interlong Bio- Tech Holdings Co., Ltd.(1999 est)		New WHO GMP, expected EU GMP in 2008	In preparation , will fininish in 2-3 months	Now 1 m, 3-5 m. in 2007 10 m in 2008	80,000 -200,000 / batch, 2 months	private	MDCK cell reseach based	No information
2. Shanghai Institute of Biological Products (SIBP),		Old version, less concern in containment	Already done	Now: 8-10 m	200,000 vial/batch, 45 days (4 eggs/dose)	National network	MDCK cell reseach based	R&D center
3 . Hualan Biological Engineering Inc.(1992),	Clinical trial in children group	New WHO GMP	In preparation phase	20 m in 2007		Close link with military	MDCK cell reseach based	No information
4. Sinovac Biotech Co., Ltd	Most advance (6 mo advance)	Old version	Applied in July 06	Now 2 m.,		Close link with CDC	MDCK cell reseach based	In Tanshan (old plant)
5. The China National Biotec corporation (CNBC) (Headquarter)		N/A	Already done	Now: 2 m (BTBP)		National network	Finnished vero cell product with JE vaccine,	R&D Center

Annex 8

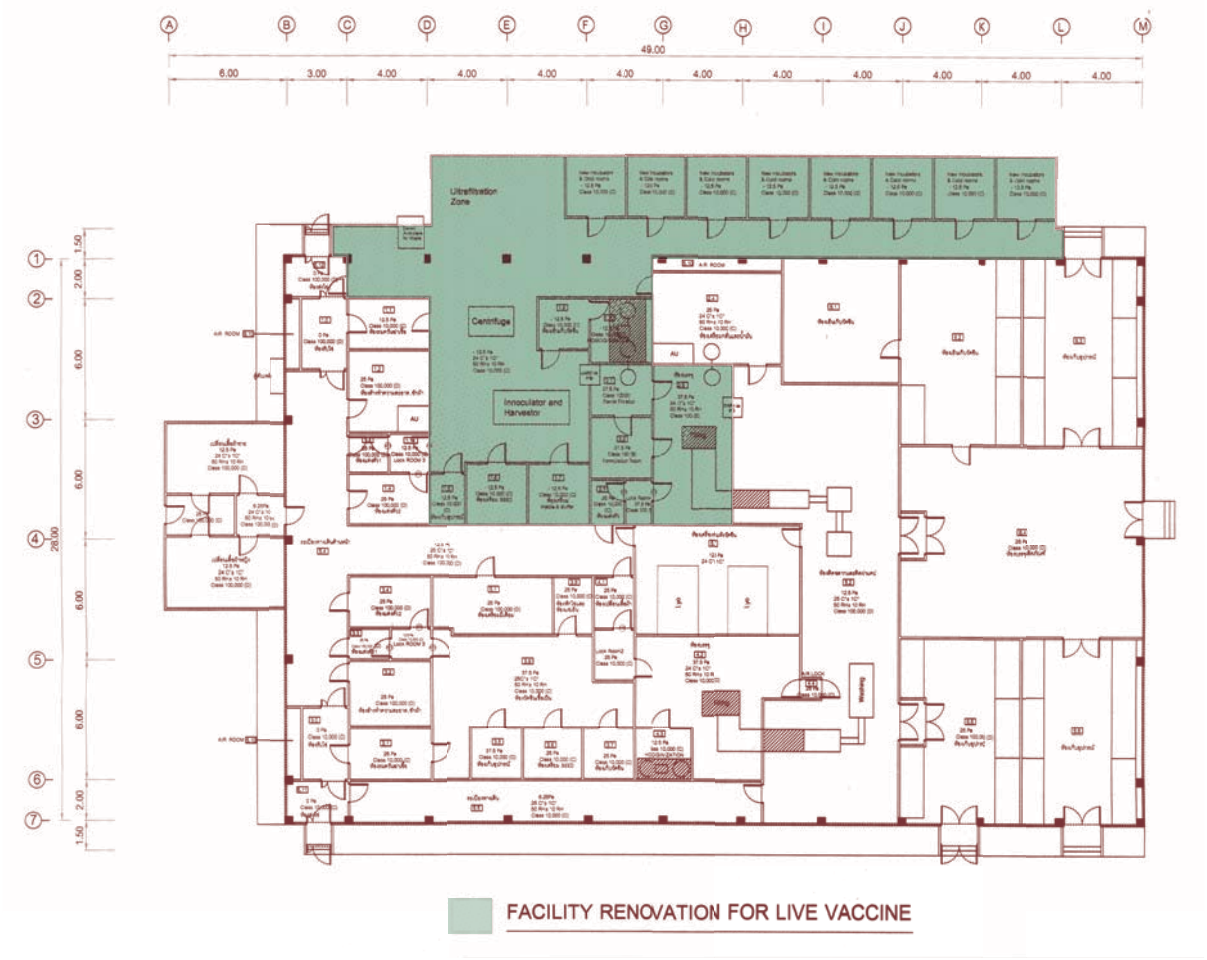
Plan for GMP training

WHO Basic Training on Good Manufacturing Practices (GMP)

1. Introduction to the training course [1-2 hours]
2. Quality management [4 hours]
3. Sanitation and hygiene [3 hours]
4. Qualification and Validation [3 hours]
5. Complaints and recalls [4 hours]
6. Contract production and analysis [3 hours]
7. Self-inspection and Quality Audits [3 hours]
8. Personnel [5 hours]
9. Premises [4 hours]
10. Equipment [5 hours]
11. Materials [3 hours]
12. Documentation (1) (2) [5 hours]
13. Good Practices in Production and Quality Control [7 hours]
14. Sterile production [6 hours]



รูปที่ 4.1 แบบแปลนโรงงานผลิตวัคซีนสัตว์ปีกในปัจจุบันก่อนมีการปรับปรุง



รูปที่ 4.2 แบบแปลนโรงงานผลิตวัคซีนสัตว์ปีกที่ปรับปรุงเพื่อการผลิตวัคซีนเชื้อเป็นอ่อนฤทธิ์ (Live Attenuated Influenza Vaccine, LAIV)