The 29th STAG Board Meeting

Topic 2: Health Care

Discussion 2: Self-production of Pharmaceuticals to Ensure National Health Security

Department of Health, the Executive Yuan

Nov. 02, 2009

- **Domestic Vaccine Production Plan**
- **Blood Derivative Development Plan**

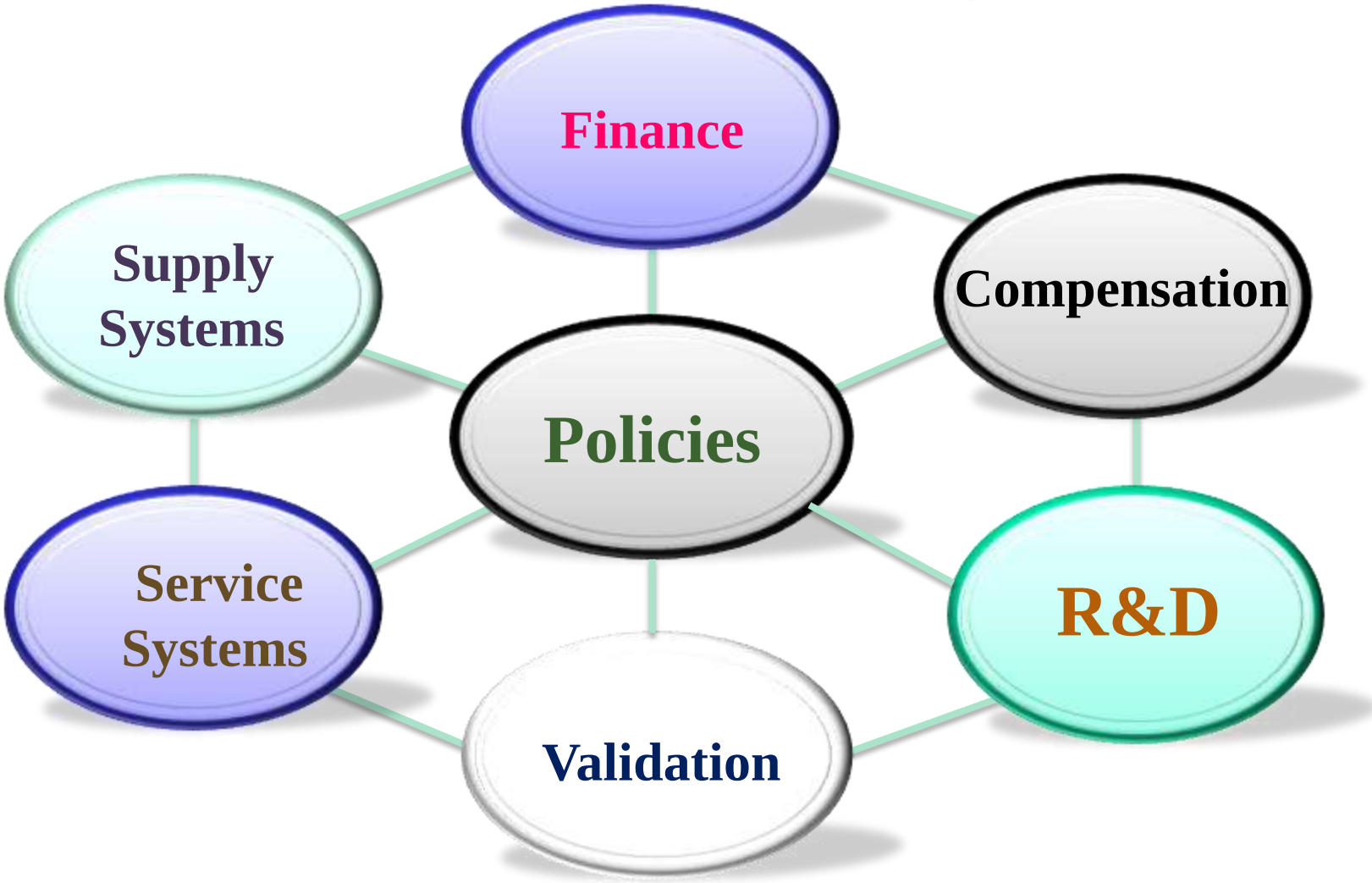
Domestic Vaccine Production Plan Outline

- **Introduction**
- **Current status**
  - Supply & Demand status of Taiwan's vaccine industry
  - Challenges in future promotion
- **Development Strategy**
  - Blueprint and Timetable
  - Action Plan
- **Conclusion**
  - Brief conclusion
  - Issue discussion

Introduction

- Due to the rapid progress in biotechnology in recent years, vaccines become the most efficient precaution against infectious diseases.
- Now, the vaccine industry is thriving. Thus, to ensure the safety of the nation and the population against infectious diseases, the government encourages private enterprises to invest in domestic vaccine production to meet the emergent needs of vaccine.

Elements of Vaccination System



Domestic Vaccine Industry in Different Countries

Low protection (Open system mostly)	Medium protection (Local priority)	High protection (Closed system)
USA	Korea	Japan
EU		

History of Vaccine Supply in Taiwan

- **before 1971**
  - **Flourishing era of Taiwan's vaccine production**
    All vaccine were produced locally.
- **1972-2002**
  - Techniques of vaccine production were improved. New vaccines were rarely developed
  - Life Guard pharmaceutical company
- **2003-2009**
  - Vaccine Research and Development Center of NHRI was established
  - Adimmue produce the H1N1 vaccine
  - Development of molecular vaccines by Academia Sinica

History of Vaccine Supply in Taiwan --- Before 1971

- **Flourishing era of Taiwan's vaccine production**
  - Typhoid fever and Paratyphoid fever vaccine, Diphtheria and pertussis vaccine, Cholera vaccine, Tetanus vaccine, BCG vaccine, Plague vaccine, Smallpox vaccine, Rabies vaccine, and Japanese Encephalitis vaccine.
- **Adimmune**
  - Established in 1965, funded and guided by the Government.
  - Input of Japanese Encephalitis vaccine was banned in 1978.

History of Vaccine Supply in Taiwan --- 1972~2002

- **Techniques of vaccine production were improved, but new vaccines were rarely developed.**
- **Life Guard pharmaceutical company**
  - The first high-tech vaccine manufacturer in Taiwan, which produced plasma-derived hepatitis B vaccine using technology transferred from Sanofi-Pasteur, France.
  - Established in 1984 and disbanded in 1995.

History of Vaccine Supply in Taiwan --- 2003~2009

- **Vaccine Research and Development Center of NHRI was established in 2003**
  - Entrovirus-71 vaccine, Japanese Encephalitis vaccine, Group B Neisseria meningitides recombinant subunit vaccine, Respiratory syncytial virus (RSV) vaccine, H5N1 vaccine.
- **BOO project for self-production of influenza vaccine in 2005**
  - Without our own vaccine plants, we will possibly fail to purchase enough vaccine to meet the needs of our nation facing the imminent threat of the influenza spreading all over the world. Therefore, there is a need for us to build our own vaccine plant and to produce vaccines domestically.

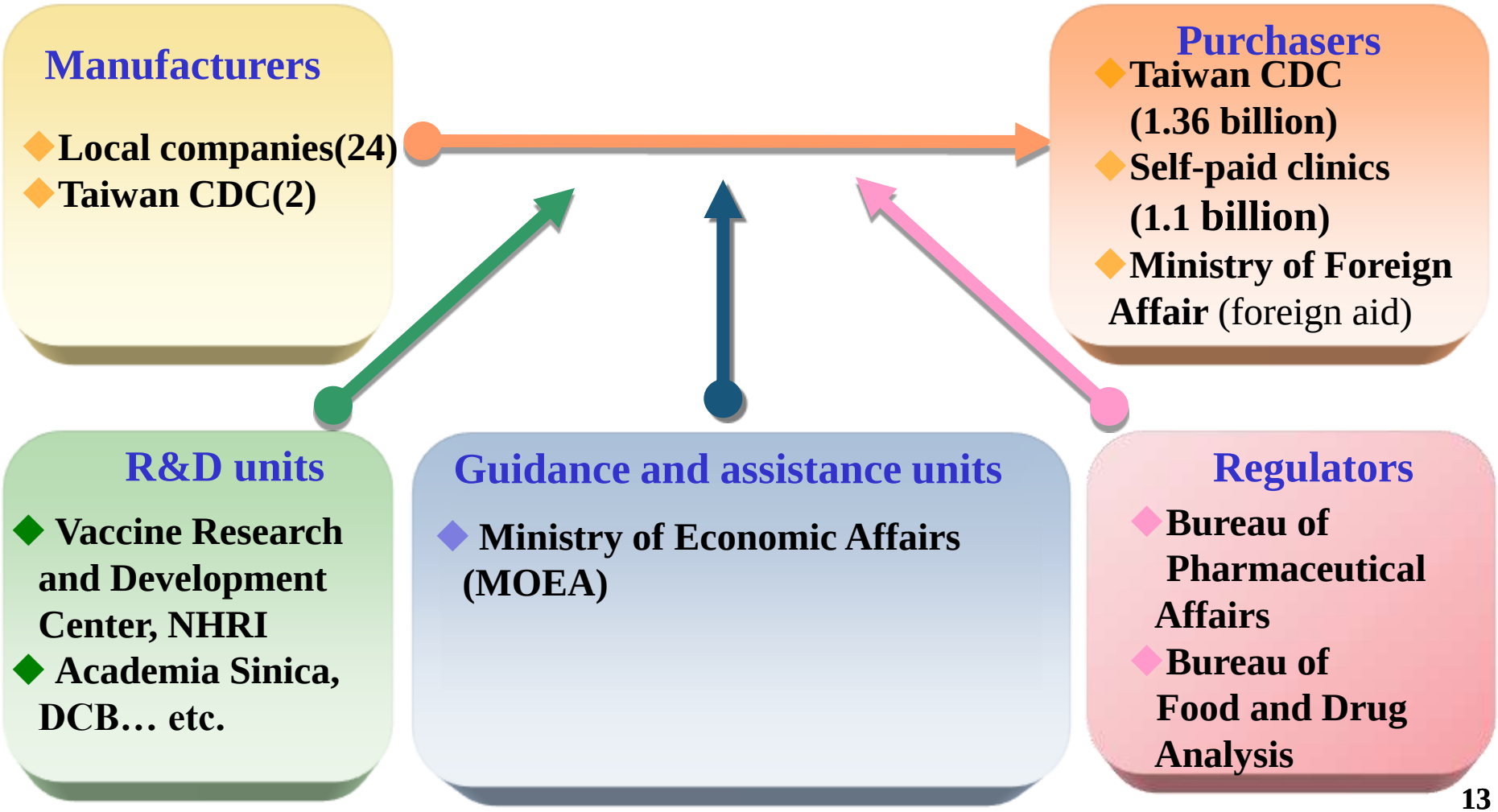
History of Vaccine Supply in Taiwan --- 2003~2009

- **R&D of Molecular Vaccine by Academia Sinica$_{-1}$**
  - Led by Dr. Chi-Huey Wong, the President of Academia Sinica, and Dr. Che Alex Ma and Dr. Chung-Yi Wu from the Genomics Research Center.
  - The research has not only been published on PNAS (Proceedings of The National Academy of Sciences), but also patented by the US. Moreover, we transferred this vaccine technology to OPKO Health in Miami.

History of Vaccine Supply in Taiwan --- 2003~2009

- **R&D of Molecular Vaccine by Academia Sinica-2**
  - The revenue of technology transfer is around 2 to 3 hundred million NTD, and we are entitled to acquire proportional royalty.
  - OPKO Health has to set up a subsidiary company in Taiwan for vaccine development.
  - Academia Sinica, which owns the intellectual property rights and know-how, is entitled to acquire proportional royalty.
  - Human clinical trials for the vaccine produced by using this technology are expected to be conducted in the next 5 years and the vaccines can be introduced to the market within 10 years.
  - This technology can be applied in the production of various vaccines against different human viruses .

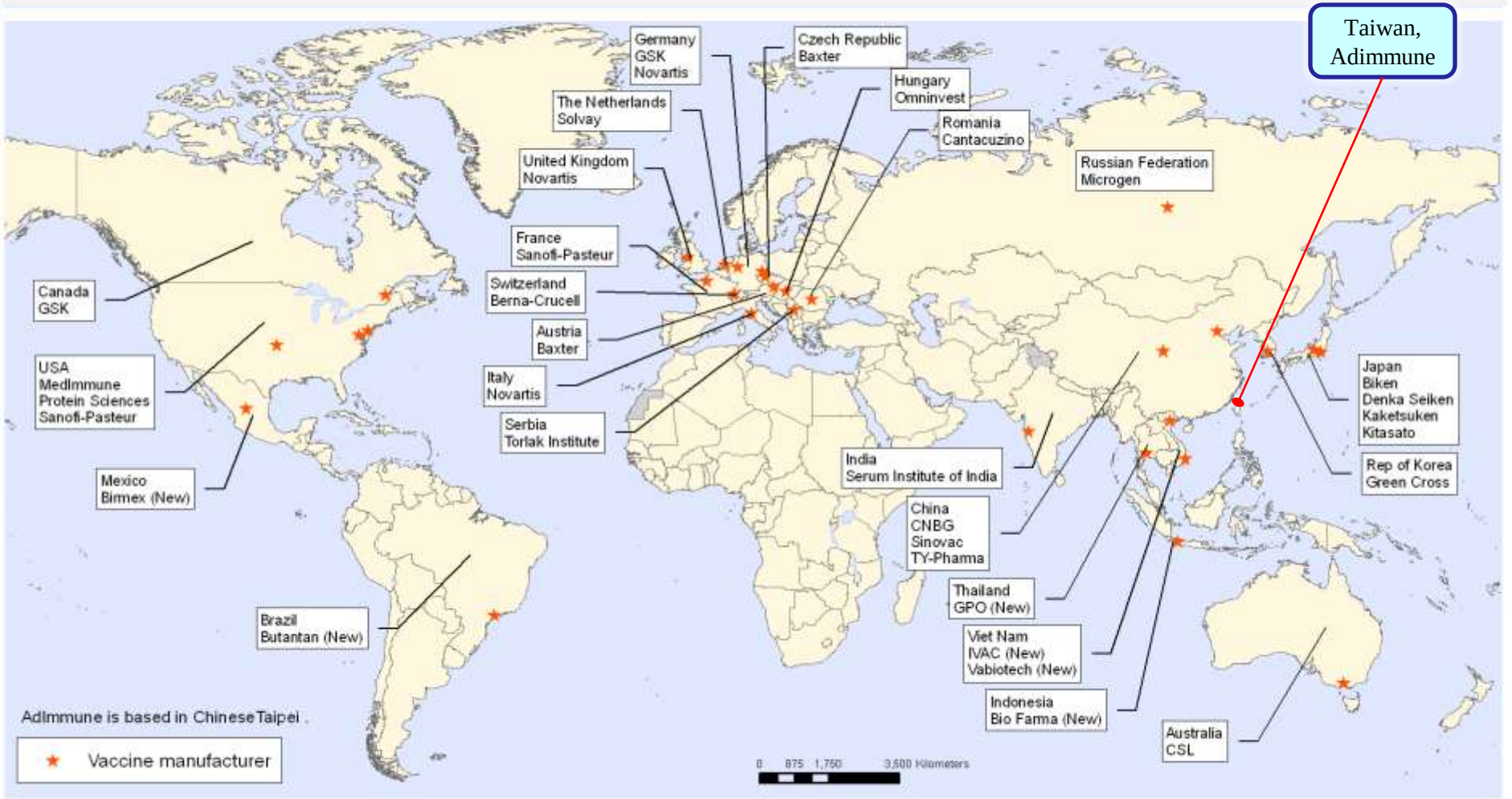
Demand and Supply of Vaccine Industry in Taiwan



Global Status of Influenza Vaccine (Seasonal, Pre-pendemic, Pemdenic)

- **WHO Global Action Plan: Main Strategies to increase influenza vaccine production**
  - Increase use of seasonal influenza vaccine
  - Increase overall production capacity for pandemic vaccines
  - Fund and negotiation for building new plants, technology transfer and consultation

Mapping of Potential Influenza A (H1N1) Vaccine Manufactures



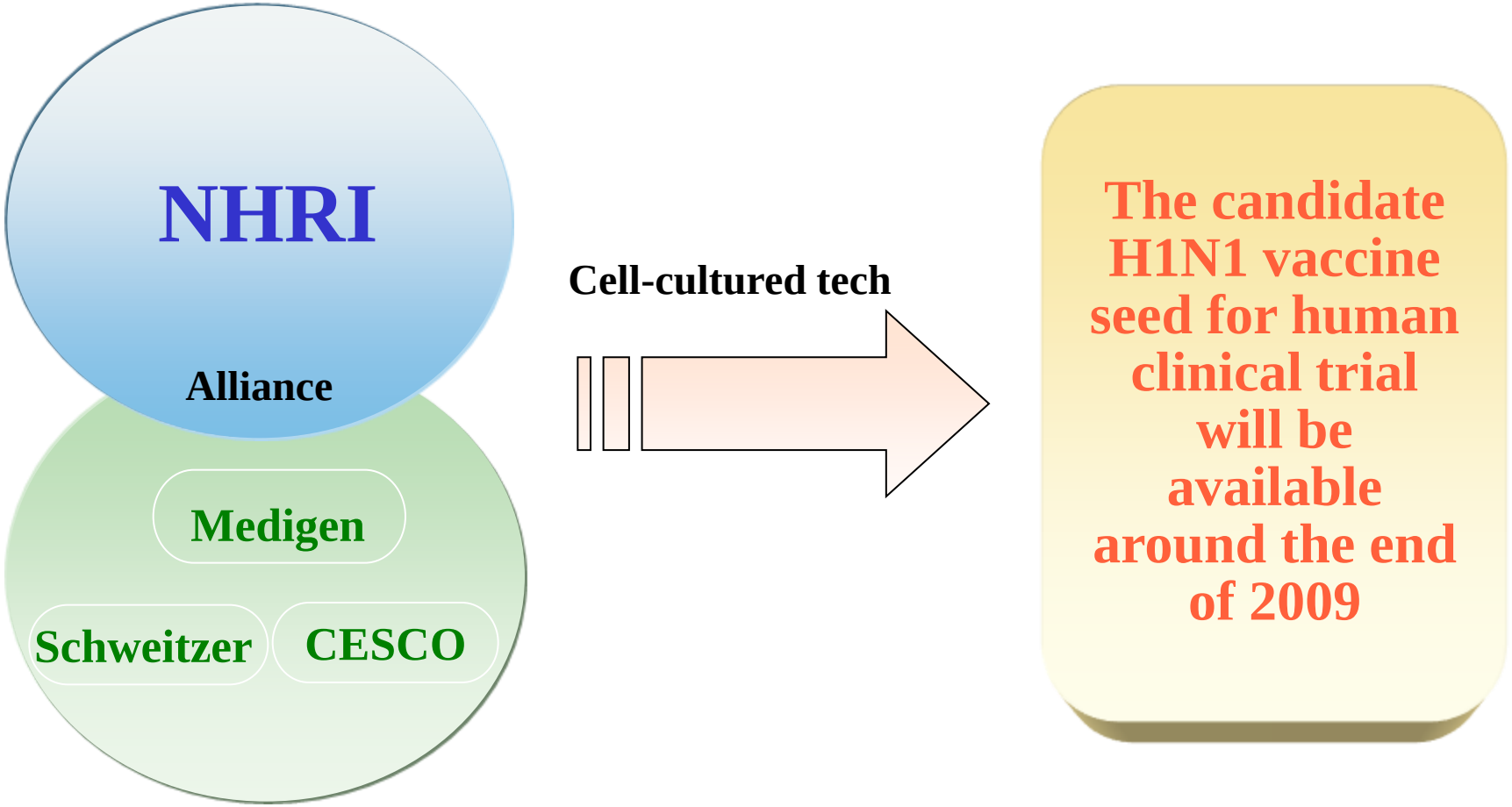
World Health Organization

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

NHRI Development for H1N1 & H5N1 Vaccine

- **H1N1 Vaccine**
  - H1N1 virus seed bank is ready.
  - 60 liters of H1N1 vaccine bulks from 2 batches of roller bottle tissue culture are ready.
- **H5N1 Vaccine**
  - Vaccine for clinical trials were ready in the middle of May, 2009.
  - Bureau of Pharmaceutical Affairs approved human clinical practice on August 20, 2009.
  - Clinical trials started from the beginning of October, 2009.

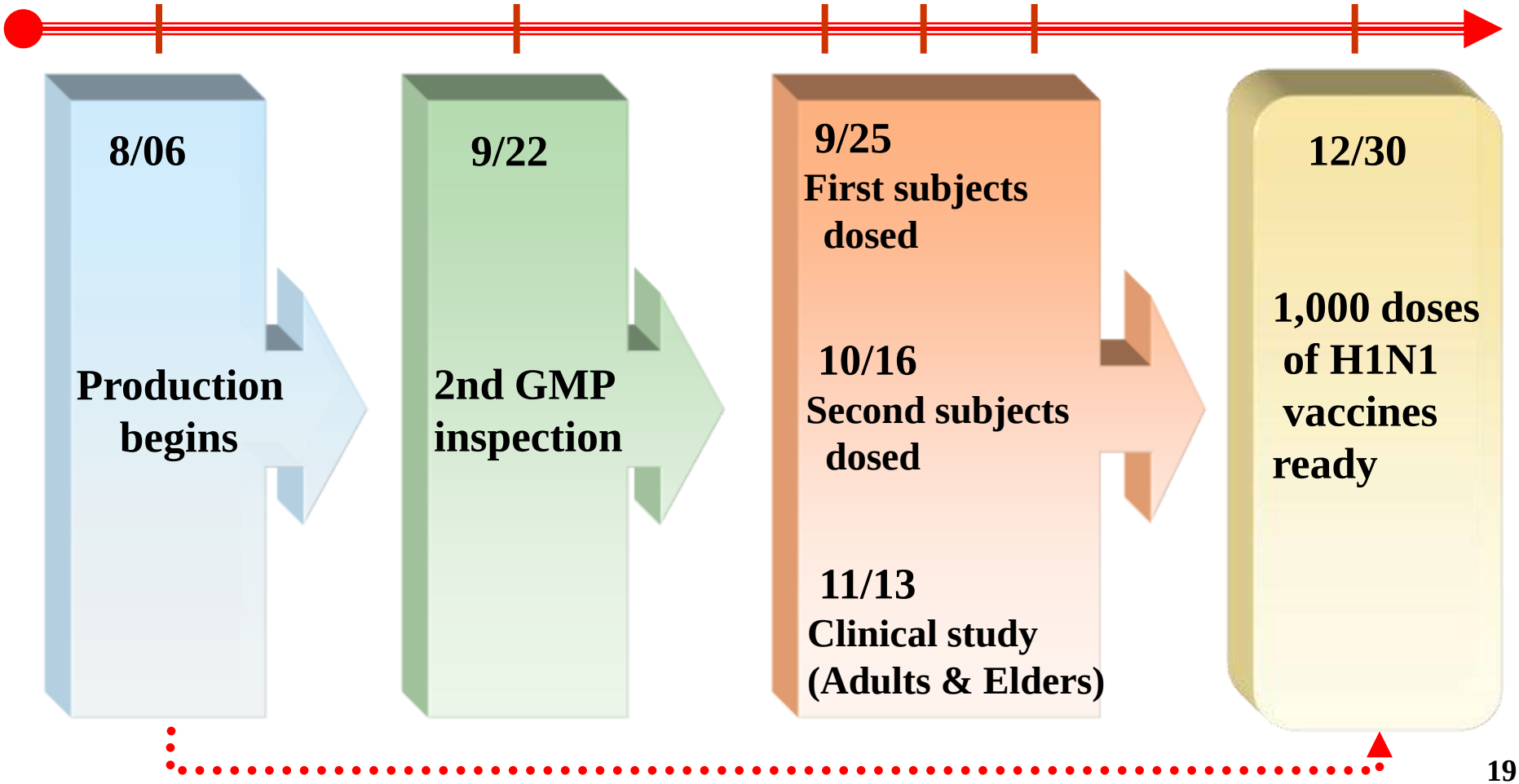
Technology Transfer of H1N1 Vaccine from NHRI



H1N1 Vaccine Production by Adimmune

- **Turning Point: BOO Project**
  - Adimmune turned to Kitasako in Japan and Crucell in the Netherlands for introducing new vaccine production technology.
  - The two ex-Ministers of Department of Health devoted themselves to the management and organization of this company. One was the ex-presidents of Adimmune, and the other one is the current president.
  - With the ongoing circulation of 2009 pandemic influenza A (H1N1) virus, the demand for vaccine has increased tremendously, and now it's the right time for Taiwan to invest in this industry for large-scale vaccine production.

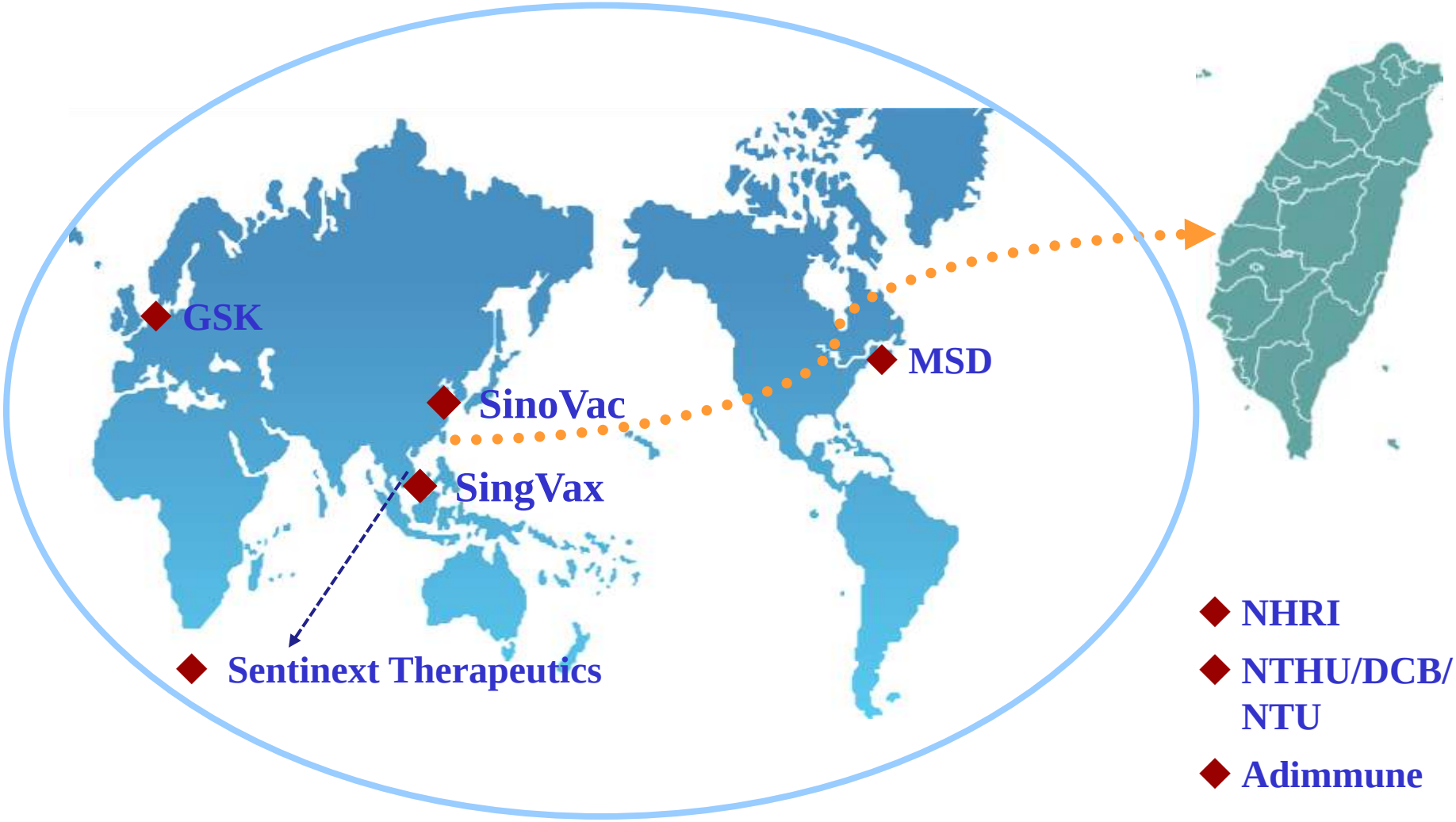
H1N1 Vaccine Production Timeline of Adimmune



Vaccine Adverse Event Reporting System & Evaluation of Influenza Vaccine

- **Monitoring vaccination**
  - Three surveillance systems are used to record notification of adverse effects of vaccination nationwide, Health Insurance database and report of GBS case each week to ensure the health and safety of the public.
- **Evaluation of vaccine protective effects**
  - Analysis of the protective effect of Seasonal Influenza and Influenza A H1N1 vaccines will be used as a reference for the vaccine policy decision during the next influenza season.

Global Development for Entrovirus-71 Vaccine



EV-71 Vaccine R&D

- **Overseas status**
  - SingVax in Singapore is working on the development of the vaccine and the Phase I clinical trial will be conducted in 2010.
  - MSD is in the progress of EV-71 vaccine development.
  - GSK is actively evaluating the Asian market for business of Entrovirus vaccine.
  - China focuses on developing the inactivated Entrovirus-71 vaccine.

EV-71 Vaccine R&D

- **Local Status**
  - EV-71 vaccine developed by NHRI is under the pre-clinic trials.
  - NTHU research team is preparing for the mass production by VLP and negotiating with cooperative manufacturers for the technology transfer.
  - Adimmune owns the key-tech: Method of Effective Antigen Analysis.

Challenges in Future Promotion of Domestic Vaccine Production

Strengths

- Lower labor & land costs
- Sound health insurance & comprehensive database of regional epidemic prevention capabilities
- Superior quality of clinical trials compared to Asian countries nearby
- Respect for intellectual property rights
- Abundant high-quality talents

Weaknesses

- Small local vaccine market
- Insufficient R&D sources
- Inexperienced in developing vaccines and establishing the plants
- No vaccine plants with international accreditation
- Lack of talents and management experiences to internationalize our vaccine industry

Asian Clinical Trial Market

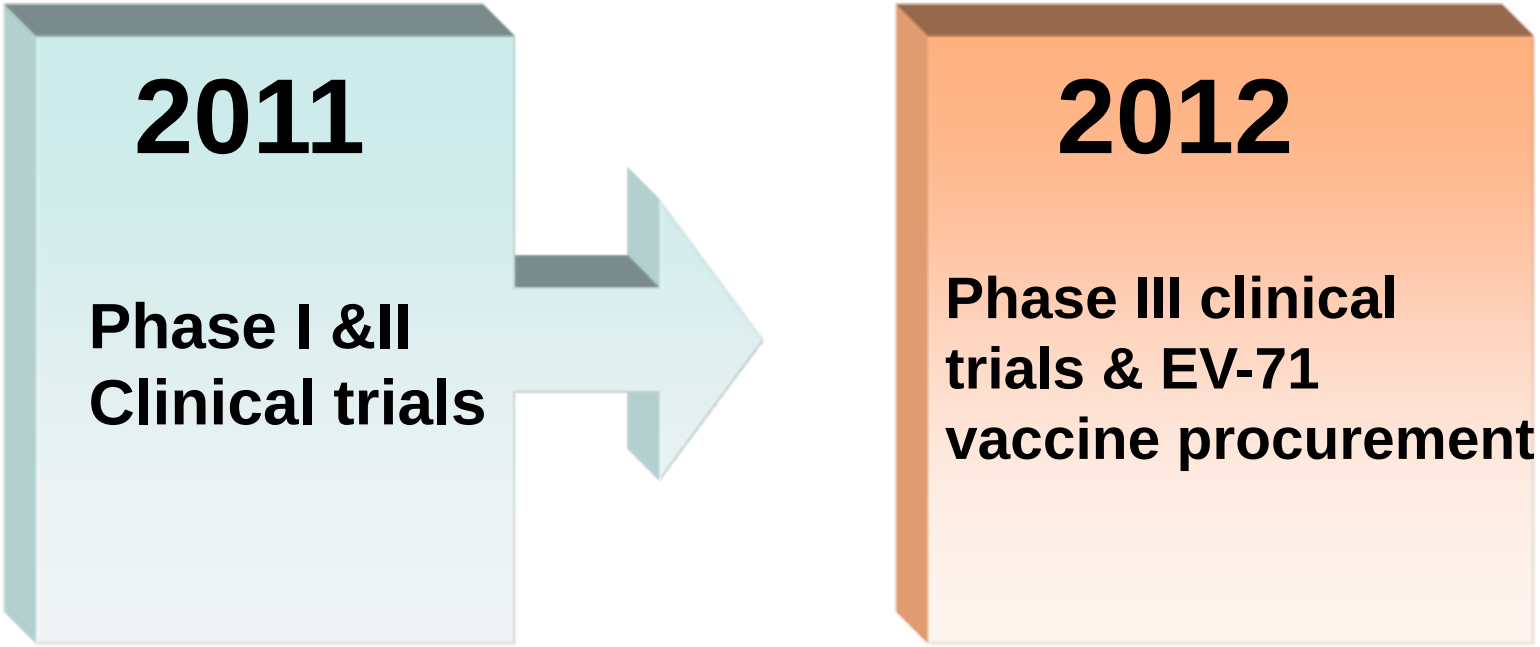
- Singapore: Equipped with advanced medical technology but lacks big population.
- Korea: Slow in opening clinical trial market.
- Japan: Special inspection rules are obstacles to its transnational clinical trials.
- Taiwan: The best choice for clinical trials in Asia with its high-qulaity medical treatment, high quality and recruitment rates in clinic trials.

Execution status of transnational vaccine clinical trials in Taiwan

- Rotavirus vaccine (GSK&MSD)
- Cervical cancer vaccine (GSK&MSD)
- Pneumococcal polysaccharide vaccine (Wyeth)
- Group B Neisseria meningitides(Novartis)
- According to statistics on ClinicalTrials.gov, Taiwan is recruited for 34 transnational vaccine clinical trials.

Development Strategy -- Blueprint and Timetable

- Vaccines focused on regional epidemics – introducing EV-71 vaccine to the market



Development Strategy -- Action Plan

- **Taiwan CDC is strongly accelerating the promotion for Enterovirus vaccine development and will soon take a further application of the“Advanced Market Commitment” (AMC) strategy, drawing up a promotion program to ensure the EV-71 vaccine procurement.**

Conclusion

- To date, the health-related department still makes merely limited effects on industrial strategies. Thus, we hope to integrate resources from all related departments of the government into expanding the capacity for strategy execution and accomplish the goal of protecting the nation and population against infectious diseases and prospering Taiwan's vaccine industry.

- The introduction of EV-71 vaccine to the market is not only a challenge, but also a turning point in local vaccine production .

Issue Discussion

- **How can the government expand Taiwan's R&D capacity and enhance biological products in process of vaccine industry production?**
  - How should the Government combine resources from all related departments and organizations to enhance the R&D capacity?
  - How will the Government take actions to contribute to the harmonization of medical acts and regulations?
  - What biotech market information will the Government provide in the future?
  - What commercial service we can provide to nurture and expand the high-quality vaccine industry of Taiwan?

Blood Product Development Plan

Outline

- **Introduction**
- **Current status**
  - Review of promotion efforts and specific accomplishments
  - Challenges in future promotion
- **Development Strategy**
  - Blueprint and Timetable
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- **Conclusion**
  - Brief conclusion
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Introduction

- **To actively develop domestic blood derivative industry and to promote R&D of blood derivative safety technology.**

Current Status Analysis-

Review of promotion efforts and specific accomplishments

- A four-year Blood Product Development Plan was announced on April 12, 2007 to safeguard the safety and quality of blood derivatives and to ensure blood derivatives supply-demand balance.
- Development of domestic blood derivative industry and promotion of product safety technology R&D were encouraged.
- Taiwan Blood Services Foundation contracted with Australia-based CSL in 2007 to manufacture pharmaceuticals derived from plasma and blood components. Since 2008, four products have been continually produced in production lines.

Domestic Blood Products and Imports 2001-2008

Product	Year	2001	2002	2003	2004	2005	2006	2007	2008
Albumin	Total Production (Certified and Inspected)（kg）	6,583	8,130	9,313	1,1989	11,918	9,333	8,919	9,700
	Domestic Production (kg)	0	0	0	0	0	0	0	430
	Percentage in Total Production (%)	0	0	0	0	0	0	0	4.43
	Imported Products (kg)	6,583	8,130	9,313	11,989	11,918	9,333	8,919	9,270
	Percentage in Total Production (%)	100	100	100	100	100	100	100	95.57
	Consumption figures according to the National Health Insurance (kg)	4,286	4,747	6,026	6,805	6,482	5,812	4,172	3,231

Domestic Blood Products and Imports 2001-2008

Product	Year	2001	2002	2003	2004	2005	2006	2007	2008
IVIG	Total Production (Certified and Inspected) （kg）	158	130	210	63.3	132.9	85.8	125.9	62.41
Intravenous immune globulin	Domestic Production (kg)	0	0	0	0	0	0	0	59.23
	Percentage in Total Production (%)	0	0	0	0	0	0	0	94.9
	Imported Products (kg)	158	130	210	63.3	132.9	85.8	125.9	3.18
	Percentage in Total Production (%)	100	100	100	100	100	100	100	5.1
	Consumption figures according to the National Health Insurance (kg)	84	74.8	71.6	74.5	75.5	67.8	67.7	71

Domestic Blood Products and Imports 2001-2008

Product	Year	2001	2002	2003	2004	2005	2006	2007	2008
FVIII	Total Production (Certified and Inspected)（MIU）	20.1	12.6	8.3	9.9	5.2	2.5	3.98	6.06
High-purity Factor VIII	Domestic Production	0	0	0	0	0	0	0	2.58
	Percentage in Total Production (%)	0	0	0	0	0	0	0	42.57
	Imported Products	20.1	12.6	8.3	9.9	5.2	2.5	3.98	3.48
	Percentage in Total Production (%)	100	100	100	100	100	100	100	57.43
	Consumption figures according to the National Health Insurance (MIU)	13.3	13.2	10.4	8.5	6.2	4.1	3.8	3.8

Domestic Blood Products and Imports 2001-2008

Production	Year	2001	2002	2003	2004	2005	2006	2007	2008
FIX	Total Production (Certified and Inspected)（MIU）	6.3	4.9	5.6	7.2	1.7	3.6	1.9	5.66
High-purity Factor IX	**Domestic Production**	0	0	0	0	0	0	0	2.28
	Percentage in Total Production (%)	0	0	0	0	0	0	0	40.28
	Imported Products	6.3	4.9	5.6	7.2	1.7	3.6	1.9	3.38
	Percentage in Total Production (%)	100	100	100	100	100	100	100	59.72
	Consumption figures according to the National Health Insurance(MIU)	6.4	6	5.1	3.9	2.7	3.1	3.2	2.26

Current Status Analysis -- Challenges of future development

- It is estimated that the annual production of plasma and blood components is 12,000 liters. It does not have the economies of scale nor the productivity to lower production costs or to facilitate domestic productions of blood products.
- The domestic market for blood products is relatively small. Also, the international sales markets have been long dominated by major pharmaceutical companies. It would not be easy for domestic companies to achieve competitive advantage.

Current Status Analysis -- Challenges of future development

Blood Product Productions in the World:

- Countries with domestic production lines:

  U.S., Germany, Australia, Spain, Sweden, Austria, Finland, Switzerland, France, Italy, South Africa, South Korea, Japan, China, etc.

- Countries contracted with pharmaceutical companies for production:

  Brazil, Canada, Greece, New Zealand, Hong Kong, Singapore, Indonesia, Iran, Luxemburg, Malaysia, Morocco, Norway, Poland, etc.

Development Strategy -- Blueprint and Timetable

- Blood transfusion safety and operational quality improvement plan is expected to be completed in 2009.
- Pilot program for domestic blood product production is expected to be completed in 2010.
- A domestic blood product production plan to promote private sector's participation (Build-Own-Operate, BOO) , is expected to come to terms in 2011.
- Initiation of domestic blood product production plan, in the form of BOO, is expected in 2012.

Development Strategy -- Action Plan

- Integration of imported blood products to be managed by a single agency.
- Reimbursement for domestic blood products by the National Health Insurance can be expedited. On the other hand, imported blood, biological, and genetic synthesis products will be self-paid.
- The government purchases and acquires a certain amount of domestic blood products.

Conclusion

- Currently, there is no shortage of blood products supply for medical use. However, the country has been heavily reliant on imported products for years. In addition to the risk of product contamination overseas, in the event of crisis situations (such as war, outbreak), we will have difficulties maintaining timely supply of imported products and will be facing other unexpected restrictions. In order to enhance the safety and quality of blood products and to ensure a stable supply, promotion of a “domestic production of sufficient blood products" policy should be deemed as a long-term objective and should be encouraged.

Issue Discussion

- Manufacture of blood products, namely albumin, IVIG, high-purity FVIII, high-purity FIX, and the affiliated core technologies are closely related to medical and biotechnological R&D and highly associated with patentable inventions. Please discuss what complementary measures should be implemented to help improve the introduction of R&D capabilities and patented technologies.

Thank you for your attention and participation!

Image of Taiwan Centers for Disease Control in 2012

Issue Discussion:

1. International and Cross-Strait Medical Service Program:

- How should the government position itself in the process of promoting medical services to the International and cross-strait medical services?
- In seeking a new role, how does the health authority find the balance point in ensuring public health and fostering the health care industry?
- How to open up the International and cross-strait medical services for our medical industry?

2. Self-production of Pharmaceuticals to Ensure National Health Security:

- How can the government expand Taiwan's R&D capacity and enhance biological products in process of vaccine industry production?
  - How should the Government combine resources from all related departments and organizations to enhance the R&D capacity?
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