Report of the Sixth Meeting with International Partners on Prospects for Influenza Vaccine Technology Transfer to Developing Country Vaccine Manufacturers

Dubai, United Arab Emirates, 18-19 March 2013
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CONTENTS

Abbreviations and Acronyms .................................................................................................................. 4
SESSION 1. INTRODUCTION AND UPDATES ..................................................................................... 7
  1.1 What will it take to reach the GAP objectives by 2016? .............................................................. 7
  1.2 Increase production capacity: contribution of the WHO Technology Transfer Initiative........... 8
  1.3 BARDA international influenza vaccine manufacturing capacity-building programme: current
      and future plans .......................................................................................................................... 8
  1.4 International stakeholder workshops on sustainable influenza vaccine production capacity ..... 9
  1.5 SAGE updated position paper on seasonal influenza vaccination ............................................. 9
  1.6 International meeting on influenza vaccine effectiveness ......................................................... 10
  1.7 WHO integrated meeting on development and clinical trials of influenza vaccines that induce
      broadly protective and long-lasting immune responses ............................................................ 10
  1.8 Update on LAIV trials and activities ........................................................................................ 11
  1.9 Development of second generation and universal vaccines ..................................................... 12
  1.10 Global Action Plan for Influenza Vaccines II: CDC activities in support of GAP .................... 13
SESSION 2. WHAT CAN BE ACHIEVED BY THE 10TH GAP ANNIVERSARY AND HOW CAN
          PRODUCTION CAPACITY BE MAXIMIZED IN DEVELOPING COUNTRIES .................. 14
  2.1 Introduction: Update and review of challenges ahead and preparation for workshop .............. 14
  2.2 Workshop discussion: roadmap to GAP in 2016 ....................................................................... 14
  2.3 Biosafety and biosecurity in vaccine production facilities: principles and practices ............... 15
  2.4 Presentation by a new member of the network: BCHT China ................................................... 16
SESSION 3. OPTIONS FOR SUSTAINABILITY AND TRAINING ......................................................... 17
  3.1 Assessment of influenza vaccine production compatibilities .................................................... 17
  3.2 How can influenza vaccine manufacturers under the GAP maximize their business potential? 17
  3.3 What type of training is needed in the future? ............................................................................ 18
DAY 2 ................................................................................................................................................... 20
SESSION 4. REGULATORY ISSUES – APPROVAL OF VACCINES ................................................... 20
  4.1 Introduction ............................................................................................................................... 20
  4.2 Regulatory pathways for registration of seasonal and pandemic influenza vaccines: FDA
      approach ..................................................................................................................................... 21
  4.3 Seasonal vaccine approval in the European Union ................................................................. 23
  4.4 TGA registration process for seasonal IIV and LAIV ............................................................... 23
  4.5 Pathway to approval for seasonal IIV and LAIV ................................................................. 25
  4.6 European Union pathways to approval of IIV and LAIV pandemic vaccines ....................... 25
  4.7 The TGA registration process for IIV and LAIV prior to and during a pandemic ............... 26
  4.8 Pathway to approval for pandemic IIV and LAIV in Thailand .............................................. 27
SESSION 5. CLOSURE .......................................................................................................................... 28
## ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIVC</td>
<td>Australian Influenza Vaccine Committee</td>
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<td>ARTG</td>
<td>Australian Register of Therapeutic Goods</td>
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<td>BARDA</td>
<td>Biomedical Advanced Research Development Authority</td>
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<td>BCHT</td>
<td>Changchun BCHT Biotechnology Co.</td>
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<td>BLA</td>
<td>Biologies License Application</td>
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<td>BSE</td>
<td>Bovine spongiform encephalopathy</td>
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<td>CBER</td>
<td>Center for Biologics Evaluation and Research</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CTD</td>
<td>Common Technical Document</td>
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<tr>
<td>CTX</td>
<td>Clinical Trial Exemption (Scheme)</td>
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<tr>
<td>DCVMN</td>
<td>developing country vaccine manufacturers</td>
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<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<td>ECBS</td>
<td>Expert Committee on Biological Standardization</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<td>ERL</td>
<td>Essential Regulatory Laboratory</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<td>GAP</td>
<td>Global Action Plan for Influenza Vaccines</td>
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<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunisation</td>
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<td>GLP</td>
<td>good laboratory practice</td>
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<td>GMO</td>
<td>genetically modified organism</td>
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<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
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<tr>
<td>GPO</td>
<td>Governmental Pharmaceutical Organization (Thailand)</td>
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<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development and Evaluation</td>
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<tr>
<td>HA</td>
<td>haemagglutinin</td>
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<td>HAI</td>
<td>haemagglutination inhibition</td>
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<td>HCW</td>
<td>Health-care worker</td>
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<td>HHS</td>
<td>United States Department of Health and Human Services</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HQ</td>
<td>Headquarters</td>
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<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
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<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
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<tr>
<td>IEM</td>
<td>Institute of Experimental Medicine (Russian Federation)</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
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<tr>
<td>IIV</td>
<td>inactivated influenza vaccine</td>
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<td>IVAC</td>
<td>Institute of Vaccines and Medical Biologicals (Viet Nam)</td>
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<tr>
<td>LAIV</td>
<td>live attenuated influenza vaccine</td>
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<tr>
<td>LMIC</td>
<td>low- and middle-income country</td>
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<td>MA</td>
<td>market authorization</td>
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<td>MDCK</td>
<td>Madin-Darby Canine Kidney Epithelial Cells</td>
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<tr>
<td>MN</td>
<td>microneutralization</td>
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<tr>
<td>MRP</td>
<td>mutual recognition procedure</td>
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<tr>
<td>NIBSC</td>
<td>National Institute for Biological Standards and Control</td>
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<td>NH</td>
<td>Northern Hemisphere</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>NRA</td>
<td>national regulatory authority</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<td>OGTR</td>
<td>Office of the Gene Technology Regulator</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
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<td>PIIV</td>
<td>pandemic inactivated influenza vaccine</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PIP</td>
<td>Pandemic Influenza Preparedness Framework</td>
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<td>pLAIV</td>
<td>pandemic live attenuated influenza vaccine</td>
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<tr>
<td>PPE</td>
<td>Personal Protective Equipment</td>
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<tr>
<td>PQ</td>
<td>prequalification</td>
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<tr>
<td>QIV</td>
<td>Inactivated Quadrivalent Influenza Vaccine</td>
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<td>QSS</td>
<td>Quality, Safety and Standards</td>
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<tr>
<td>R&amp;D</td>
<td>research and development</td>
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<tr>
<td>RCT</td>
<td>randomized control trial</td>
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<tr>
<td>rDNA</td>
<td>recombinant DNA</td>
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<td>RMP</td>
<td>risk management plans</td>
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<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
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<tr>
<td>SARS</td>
<td>Severe acute respiratory syndrome</td>
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<td>SAS</td>
<td>Special access scheme</td>
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<tr>
<td>SFDA</td>
<td>State Food and Drug Administration of the People's Republic of China on the Safety of Drugs and Medical Devices</td>
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<td>SH</td>
<td>Southern Hemisphere</td>
</tr>
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<td>SII</td>
<td>Serum Institute of India</td>
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<tr>
<td>STOP</td>
<td>Substitution, Technical safety measures, Organisational measures, Personal protective equipment</td>
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<tr>
<td>TAG</td>
<td>Technical Advisory Group</td>
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<td>TFDA</td>
<td>Food and Drug Administration of Thailand</td>
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<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<td>TTI</td>
<td>Technology Transfer Initiative</td>
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<td>TSE</td>
<td>Transmissible spongiform encephalopathies</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<tr>
<td>UNICEF</td>
<td>The United Nations Children's Fund</td>
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<tr>
<td>VE</td>
<td>Vaccine effectiveness</td>
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<td>WHO</td>
<td>World Health Organization</td>
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SESSION 1. INTRODUCTION AND UPDATES

The sixth meeting of international partners on prospects for influenza vaccine technology transfer to developing country vaccine manufacturers was held on 18–19 March 2013 in Dubai, United Arab Emirates. The agenda, list of participants, and the presentations are available on the WHO web site. The meeting was chaired by Dr Gary Grohmann.

Marie-Paule Kieny, Assistant Director-General of WHO extended a warm welcome to all participants, all of whom are working collectively to prepare the world for future influenza pandemics, and in particular to help new manufacturers get their vaccines on the market and keep them there. She paid tribute to the two advisory groups to the Global Action Plan on Influenza Vaccines (GAP) that provide policy and technical support, the team at WHO who manage the programme, and the sponsors for their continued commitment.

1.1 What will it take to reach the GAP objectives by 2016?

Dr Kieny proposed that, with three years remaining until the 10th anniversary of the GAP, it was timely to review progress against the original GAP objectives, and decide what is needed to make access to influenza vaccine more equitable across the world in the event of a pandemic. Landmark successes were: the first developing country grants in 2007; the first low-dose adjuvanted pandemic vaccine; the first pandemic live attenuated influenza vaccine (LAIV) produced in a developing country; and the recently registered haemaglutinin-based recombinant vaccine. Other landmarks have been the mid-term review leading to GAP II, and the establishment of the Pandemic Influenza Preparedness (PIP) framework, spearheaded to ensure benefit sharing of virus strains with developing countries, among other objectives.

In analysing how far the original targets were on track, Dr Kieny compared the landscape in 2006 with the situation today, and extrapolated various scenarios for 2016. As a reminder, the original vaccine production targets were to (i): vaccinate 70% of the world with 2 doses of pandemic vaccine within 6 months (herd immunity target) which would require 10 billion doses; or (ii) vaccinate 100% of the population, which would require access to 14 billion doses. Data from two surveys among all influenza manufacturers show an impressive increase in global seasonal vaccine production capacity, from 500M doses in 2005 (produced in 17 countries), to 876M doses in 2009 (19 countries) and 1.5B doses per year in 2012 (21 countries). The prediction for 2016, including capacity from new manufacturers, is 1.7B seasonal doses produced in 25 countries. Translating these data into a pandemic situation, the best case scenario would almost reach the target to vaccinate 70% of the world (2 doses for 4.7B people) in 6 months. However, major issues are unclear, notably assuring a conversion factor of 11 (the conversion factor proposed in the Technical Studies conducted under resolution WHA63.1), and how to sustain such high production without demand.

Dr Kieny listed areas that needed to be strengthened across all three pillars of the GAP if the targets are to be met. For Pillar 1 – increased use of seasonal vaccine to reduce seasonal influenza – SAGE will be an important catalyst in moving the agenda forward, notably in encouraging national policies and practices based on disease burden data, vaccine efficacy in target groups, and a strong communication strategy. Increased production capacity (pillar 2), had been very successful, with current seasonal capacity falling only 280M doses short of the target 1.7B doses. This shortfall may largely be met by the capacity of new low- and middle-income country (LMIC) producers, provided that vaccine quality was sustained and new partnerships were available for uptake of the vaccine. Finally, since the start of GAP there has been an exponential growth in influenza vaccine research and development as shown by the number of patents being applied for not only in the OECD countries but also in developing countries and in particular China and Russian Federation. Sustained research and development on yields and antigen-sparing technologies will be critical under pillar 3 to ensure that the conversion factor from seasonal to pandemic doses is feasible.

In conclusion, Dr Kieny was confident that with concerted efforts to address sustainability challenges and continued R&D, the GAP vision would become a reality.
1.2 Increase production capacity: contribution of the WHO Technology Transfer Initiative

Martin Friede noted that since 2006, LAIV technology had been licensed to three manufacturers, one of whom now had a WHO prequalified vaccine. Five countries had either a pandemic vaccine approved or had completed clinical trials, resulting in a total annual capacity of 320M pandemic doses. The challenges facing these manufacturers are to optimize antigen-sparing capacity and sustain quality every single year. The remaining manufacturers need to maintain the momentum, and overcome the hardest hurdle, registration. The predicted capacity of these manufacturers by 2016 could be an additional 300M doses. Dr Friede added that Saudi Arabia was investing in a local fill-finish influenza plant, and that Argentina also planned to fill-finish vaccine, with long-term plans for full production capacity. While not WHO grantees, this was important news for the global influenza production capacity scenario. A snapshot of the status and progress of each grantee manufacturer over the last year was given. While several of these manufacturers had faced challenges with reproducible production it was pointed out that several of the multinational vaccine manufacturers had also faced production challenges in the last year, demonstrating that influenza vaccine development and production is not easy, even for experienced manufacturers.

The Technology Transfer Initiative manages the grants and directly assists manufacturers by advising on technologies, on-site assessments, negotiations with intellectual property owners, access to cell lines, etc, and is currently assessing other biological technology production to make influenza vaccine production sustainable. The TTi benefits from close collaboration with a wide range of partners – WHO technical departments, regional offices, ministries of health, SAGE, specialized international agencies – and thus has direct access to a wide range of information on vaccine research, regulatory issues, seed strains, intellectual property, etc. It is supported by the GAP Advisory Group for policy direction, and the Technical Advisory Group (TAG) for technical assessments of the grantees.

Dr Friede applauded the manufacturers for the impressive progress they had made, and concluded that the major thrust must now be on obtaining approval of the vaccines and sustainability.

**Discussion**

A question was raised on the decision to produce seasonal and/or pandemic influenza vaccine, and the selection of technologies. While some grantees had begun with pandemic and made the transition to producing seasonal vaccine, others followed the opposite route. The real challenge was developing both at same time until registration, and ensuring that sustainable production was established.

1.3 BARDA international influenza vaccine manufacturing capacity-building programme: current and future plans

Rick Bright thanked WHO on behalf of the US Government and BARDA partners for the successful joint programme to reduce equitable access to vaccine in a pandemic by increasing manufacturing capacity. The strong partnerships forged within the GAP were the backbone of this success. He reiterated the mission and core services of BARDA and how the GAP contributed to the goal of reducing threats to human health.

A chart of BARDA support to GAP since 2006 showed that, despite periodic financial constraints, funding had been maintained and the activities covered had grown. A recap of the status of the diverse technologies of the grantees was presented, and the significant achievements made in 2012. Other activities with BARDA involvement included the establishment of a LAIV reference laboratory at CDC, FDA/QSS support to BARDA’s biomanufacturing training programme, increased on-site training, and collaboration with PATH to support IVAC, Vabiotech and the Vietnamese Ministry of Health on sustainable production of egg- and cell-based pandemic vaccine. Beyond the technical, financial and quality challenges faced by manufacturers, market development is critical if the capacity gained to date is not to be lost. Generating the evidence and promoting appropriate use in target populations such as pregnant women is thus essential.
Dr Bright concluded that since a convincing indicator of success was the return on investment, the impact of the GAP had been tremendous: from 1M doses in 2005, developing countries today had a production capacity of 280M doses, which translates the US$ 30M BARDA investment into US $0.08 per dose capacity. BARDA funds had also leveraged local government support to the tune of US $600 million. This programme has been very cost-effective and the USA remains fully committed to this mission-critical programme in 2013–2016, although the extent of support was not yet known. The invaluable contribution of all colleagues at BARDA was acknowledged.

### Discussion

Dr Bright responded to queries about the on-site training in Viet Nam and the capacity of the trainees. The training in biomanufacturing, initiated in 2010, had been very successful in exposing trainees to a wide range of techniques, but to increase the impact of knowledge gained, in-facility training appears to be needed. Providing training in the local language was deemed to be critical and, where possible, all materials should be translated and on-site interpretation provided as necessary. Regarding opportunities for new manufacturers, the advance planning process for the courses had limited access to places; however, new partners such as BCHT would be assured participation this year. Finally, BARDA fully agreed that seasonal vaccine uptake was critical for sustainability and needed to be developed hand-in-hand with pandemic preparedness.

### 1.4 International stakeholder workshops on sustainable influenza vaccine production capacity

Dan Miller of the Office of Global Affairs, US Health and Human Services described the series of workshops that have been organized by HHS and WHO.

The objective of these workshops is to assist regionally based, independent and sustainable vaccine production capacity in developing countries through discussing the challenges faced by manufacturers and governments such as access to technology, training and retaining a skilled workforce, approval of vaccines by the NRA, development and implementation of policy by governments, and communication on vaccine use Despite a long list of challenges, it was clear that significant progress had been made. The wide range of participants and topics covered were witness to how closely the workshops are aligned with the aims of the GAP. Dr Miller shared the results of the workshop on the health and economic impact of influenza. The key message was that good surveillance underpinned burden of disease studies, their fundamental value being to inform policy. Changing policy required targeted indicators and coordinated approaches, including pooled expertise and the ability to leverage resources.

The last workshop on business modeling emphasized that seasonal vaccine use was the basis for manufacturing continuity and sustainability; that a mix of approaches should be tailored to each context so that the right balance could be achieved between business sustainability and public health goals; and finally that solid partnerships were invaluable for success.

The next workshop on capacity building for communication around influenza vaccination will focus on effective communication systems that can contribute to remove vaccination resistance, promote sharing of information among the various stakeholders (from policy-makers to health-care workers (HCW) and the general population). The ultimate goal is to increase demand for seasonal vaccine. A final HHS workshop will assess overall progress and identify, concretely, how to engage policy-makers, manufacturers and donors to bridge the remaining gaps to achieve the overall goal.

### 1.5 SAGE updated position paper on seasonal influenza vaccination

John Tam of WHO presented the new WHO position paper on influenza vaccine, published in November, 2012. In evaluating the evidence, SAGE used the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) to review the safety, efficacy and effectiveness of seasonal influenza vaccine against different target population groups. Other criteria assessed include burden of disease, cost-effectiveness and operational issues. The GRADE tables
generated are published on the [WHO web site](http://www.who.int). Based on its assessment, SAGE recommended that pregnant women be included as a priority in any existing or planned seasonal influenza programme. Four other groups, which countries may prioritize based on their own coverage goals and local context, are HCW, children under 5 (particularly 6–23 months), the elderly, patients with chronic diseases, and the immunocompromised.

For pregnant women, the challenges to be considered include safety assessment at different trimesters; the duration of protection, particularly for the new born; the need for new or enhanced national policy; global supply with year-round availability, and regulatory issues such as package inserts and labelling. A solid communications and implementation strategy are essential, and avenues being explored are to work in countries with the Expanded Programme on Immunization (EPI), Maternal and Child Health programmes, or for the GAVI Alliance to adopt this target group.

**Discussion**

It was agreed that programme interested in incorporating influenza will need to be evaluated. If GAVI could cover pregnant women, EPI could cover the under fives, and HCW could most effectively be placed under institutional infection control policies. However, avenues to ensure that the other risk groups are vaccinated are less clear. From a regulatory standpoint, vaccinating pregnant women needs particular attention on the adequate assessment of safety and efficacy in both maternal and neonatal outcomes.

1.6 *International meeting on influenza vaccine effectiveness*

Joe Bresee of the Centers for Disease Control and Prevention (CDC) shared the outcomes of the above meeting held in December 2012. To build sustainability on the evidence-based approach in influenza vaccine usage, it is important to assess vaccine effectiveness (VE) to show how vaccines are able to reduce illness.

The many new types of influenza vaccine in development has led to increased attention to VE on two levels: the scientific dialogue on harmonizing approaches and methodologies for comparability of results, and public concern on gaps in knowledge and value of investment. The meeting therefore reviewed the current knowledge on different methodologies and best practices to measure VE. The three main conclusions were that: (1) VE efforts need to be sustained, which requires users to produce yearly estimates of how well the vaccine works and the development of an integrated evaluation system; (2) measuring VE in some target groups and in LMIC is essential; and (3) VE should be determined in specific subgroups such as individuals with HIV and other chronic medical conditions, pregnant women, and young children.

An article will be published with a plan of action to address gaps in knowledge, as well as a WHO guidance document on best practices and standardized methods for conducting VE studies. Other actions will be enhanced technical support, international partnerships to pool VE data, and the development of best practices for communication.

**Discussion**

It was noted that VE estimates were not always properly interpreted. Moreover, while lower VE estimates in certain population groups may lead to difficulties in policy development, it was considered that proper communication, including uncertainty in VE, is the key in the long run.

1.7 *WHO integrated meeting on development and clinical trials of influenza vaccines that induce broadly protective and long-lasting immune responses*

John Tam indicated that the two long-standing meetings on influenza vaccines research and clinical evaluation had now been integrated. The first joint meeting held in Hong Kong (China) in January 2013 reviewed the current status of development and clinical evaluation of novel influenza vaccines that induce broadly protective and long-lasting immune responses as well as strategies to produce and deliver vaccines in novel ways. Special attention was given to the development of possible universal
influenza vaccines. Other topics addressed were an update on clinical trials of pandemic and seasonal influenza vaccines in high-risk groups, vaccine safety as well as regulatory issues. In addition, a research agenda is being developed to address major gaps in knowledge on broadly protective and universal vaccines, viruses with pandemic potential, safety and regulatory issues, production strategies, antigen sparing and immune enhancement, delivery methods, and new approaches in vaccination.

During the meeting, each topic was presented, followed by the identification of gaps in knowledge. Universal vaccines, first and foremost, needed a clear definition while assays for immune responses, cross-protection, and strategies for a regulatory pathway for approval are required in the near future. Regarding vaccines for viruses with pandemic potential, data were presented for a number of clinical trials on H5, H9 and H7 vaccines, but breakthroughs were still needed on those outlined for universal vaccines, particularly on standardized indicators on correlates for protection and strategies for novel vaccine development.

**1.8 Update on LAIV trials and activities**

Dr Friede presented the tremendous development of LAIV vaccines over the last year.

GPO Thailand completed a pandemic LAIV Phase I trial on H5N2 and has started Phase II. Preclinical results from Phase I had shown excellent immunogenicity and protection, and the vaccine had no safety issues; however, low seroconversion in the Phase I trial led to questions on the predicted efficacy of the vaccine. Interestingly, low immunogenicity had also been seen in an NIH/PATH study on LAIV H5N1 (manufactured by Medimmune). Five years later, the volunteers in this study were given a single dose of inactivated H5N1 and the vast majority had very rapid responses. This suggests that, even in the absence of HAI/MN/IgG seroconversion, pLAIV recipients have developed long-lasting B-cell memory and may well be protected from severe illness in the event of natural exposure. Even in the absence of HAI/MN/IgG, evidence of long-lasting B-cell memory was detected. This also confirms that serum/mucosal antibody response to LAIV is an unreliable indicator of vaccine efficacy, and alternative immunological endpoints must be explored.

Preliminary results from the IEM/PATH Phase I study on H5N2 are similar to the GPO vaccine in terms of shedding. Experiments are under way to determine immune response. It will be interesting to compare results of the two vaccines as they become available since the virus sequence is the same but the vaccine was produced in different facilities, viral titres were different, and formulations were different. It was noted that the GPO Phase II trial is using a higher titre than the Phase I trial.

A second IEM/PATH Phase I study on H7N3 has been completed, showing no severe adverse events, very short-lived shedding, and 30–40% seroconversion by HAI. Exploratory T-cell response analysis found no direct correlation with antibody response. The cumulative response (including any serum or cellular response) was 90%, suggesting that standardized T-cell responses should be added to readouts. This will require some harmonization of sample collection and assays.

Given that H2N2 may be the cause of the next influenza pandemic, IEM has also been developing different seed strains, from which two (A/Tokyo and A/California) have been evaluated in mouse immunogenicity and ferret challenge studies. Both were protective against homologous challenge and preparations are now being manufactured for a Phase I clinical trial.

SII/PATH has completed a Phase II efficacy study of seasonal trivalent LAIV in 300 children aged 2–5. This placebo-controlled trial included monitoring for wheezing and other respiratory functions. Currently, a placebo-controlled efficacy study in 1800 children aged 2–5 has started, including monitoring of respiratory functions. It is hoped that future age de-escalation studies will allow the vaccine to be approved for children under 2 years.
In summary, LAIV continues to be a promising approach to pandemic preparedness. There is evidence of strong immune priming and good efficacy data for H1N1. Still to be explored are the number of doses needed, the interval between them, and predictive immunological readouts. Importantly, little data are available on use of LAIV in three priority SAGE groups, namely pregnant women, children under two years, and the elderly.

Discussion
Responding to a query on the safety of LAIV H2N2 compared with H5 and H7, IEM did not expect any safety issues, whether in volunteers or for laboratory biosafety as all clinical studies are carried out in isolation. Results of the prime-boost study were welcomed, as was the call for alternative immunological endpoints. However, since attenuation was different between the Leningrad and Ann Arbor strains, it may be useful to repeat the experiences with recipients of Leningrad strains.

1.9 Development of second generation and universal vaccines
Rick Bright of BARDA complemented John Tam's earlier presentation on a similar issue, highlighting challenging in harmonization towards a universal influenza vaccine. Influenza has a significant impact on millions of people of all ages every year, and vaccination remains the cornerstone of prevention. The well-known limitations of current vaccines – notably cross-protection, efficacy and yield – have led to research into novel technologies. The biggest hurdle, particularly for pandemic preparedness, is time and money: US$ 1 billion and 10–20 years. It is thus essential to be focused and to harness funds.

There are many different types of vaccine in the pipeline. Second generation vaccines are those, such as LAIV and cell-based technologies, that have broader immunity and efficacy, in groups such as young children. Today, quadrivalent vaccines, the cell-based and recombinant vaccines now licensed in the USA, open a new platform for vaccine R&D. BARDA's investment profile has grown from egg-based technology to include cell-based vaccines, recombinant and protein sciences, and finally towards a universal vaccine. Cross-cutting all investments has been antigen-sparing approaches.

The next generation of vaccines needs to be safe, efficacious and affordable; induce broad reaction and rapid response; and be simple to manufacture. Recombinant vaccines, the newest field, have many advantages in that the sequencing is simple, they can be made in different systems, are high-yield, low-cost, amenable to adjuvants, and the production process is rapid, flexible and transferrable. The major challenges are its complex regulatory pathway, safety hurdles, scalability, and potentially lower immunogenicity. In addition, most producers are small biotechs with limited experience and funding.

In order to stimulate discussion on the definition of a universal vaccine, BARDA presented a target product profile that should cover all influenza A subtypes. Characteristics include the route of administration, low antigen requirements, proven safety and efficacy based on novel endpoints, and long-lasting response in several population groups. The whole process should be non-proprietary, and it is critical for new knowledge to be integrated into current knowledge in order to move beyond the traditional licensure model.

However, a universal vaccine is only at the conceptual stage and many issues are unclear. Accelerating progress will involve regulatory science evolving at the same pace as technical developments, and the international community helping small companies on what to focus. BARDA is working on new potency assays, and failing large-scale efficacy trials, other “creative” clinical development approaches may be required.

In conclusion, the landscape of new influenza vaccines is active and rapidly evolving, some technologies have been dropped, others are emerging. Scientific discoveries provide greater opportunities for innovation, but face significant technical and regulatory challenges. R&D is very costly, and leveraging government, nonprofit and industry collaborations are essential for basic science to achieve the monumental goal of developing a universal influenza vaccine.
1.10 Global Action Plan for Influenza Vaccines II: CDC activities in support of GAP

Joe Bresee presented CDC's strategy, activities, and future approaches in support of GAP. Attention was first devoted to building capacity and generating data in support of pandemic preparedness. CDC support to core, non-research activities in 43 projects worldwide have included bilateral arrangements, grants with regional offices, and CDC personnel in countries. The generation of data for decision-making has focused particularly on vaccine evaluations for control and prevention in many developing countries, and will expand to new regions in the near future.

Over the coming years, CDC will increasingly align its efforts with the GAP II goals of evidence-based policy decisions. Dr Bresee highlighted two innovative approaches to achieve this: cooperative agreements to support vaccine introduction in certain countries; and an international influenza vaccine donation partnership. The first approach comprises activities to bridge the gap between disease burden data and implementing a vaccine programme. Activities funded by CDC for multi-year projects include modelling vaccine strategies, cost-effectiveness studies, NRA training, and communications. The Vaccine Donation Partnership aims at an immediate reduction in influenza burden in low-income countries and sustaining these efforts. The strategy is to identify donors to provide vaccine and supplies to a country to build the value of vaccination, followed by an assessment based on concrete data. Criteria for inclusion are countries where influenza vaccine is not widely available, or those who want to expand their influenza programme.

Dr Bresee described the concept and principles of a CDC Foundation that has been created to receive, distribute and monitor donations. Notably, the Foundation will not affect current vaccine programme growth, but rather act as a catalyst to promote vaccine uptake in countries, which must prove their determination to sustain influenza vaccination in appropriate target groups. Key to acceptability and success is an evaluation plan. A pilot feasibility study in several target groups in the Lao People's Democratic Republic had overall success and high acceptability, to the extent that the country has now planned a four-year programme in pregnant women using their own resources. The next steps are to expand the number of countries and partners, data from which will feed into the VE programme at WHO.

The overarching objective is for participating countries to develop sustainable programmes, and ways to attain this include focusing on SAGE recommended groups like pregnant women. The initiative may create new markets to absorb vaccine, allow twinning of markets especially within regions, and represents a solid return on investment.
SESSION 2. WHAT CAN BE ACHIEVED BY THE 10TH GAP ANNIVERSARY AND HOW CAN PRODUCTION CAPACITY BE MAXIMIZED IN DEVELOPING COUNTRIES

2.1 Introduction: Update and review of challenges ahead and preparation for workshop

Guido Torelli recalled the purpose of the meeting to review achievements, identify what remained to be done by 2016, and how best to achieve it. He summarized the concrete successes of GAP to date: six pandemic and two seasonal vaccines approved, and two pandemic vaccines prequalified, not counting the number of facilities under construction. A recent desk review, manufacturer questionnaire and TAG site visits also showed the labyrinth of challenges faced by the grantees, ranging from development, study design, quality management, project management, marketing, and the complex prequalification process. The importance of training emerged at every step. One of the most important challenges across the board related to regulatory issues, and it was clear that the most successful manufacturers were those that had engaged in early dialogue with NRA.

The WHO grantee manufacturers, and the audience at large, were invited to note their ideas on how to improve a range of issues that had surfaced during the above review, the results of which would form the basis of a workshop during the following session of the meeting.

2.2 Workshop discussion: roadmap to GAP in 2016

Guido Torelli noted that quality management and regulatory issues were the overall top priority of the survey distributed during the previous session, followed by project management, study design, marketing, and finally process development. A breakdown by new manufacturers and the audience showed many common denominators, such as training and sharing of information. Specific comments for quality management related to enhanced dialogue with NRAs, clarification of the WHO prequalification process, and NRA strengthening. For project management, specific attention was given to partnering of experienced with less-experienced manufacturers, and the value of a dedicated and empowered project manager.

The need for guidance on study design was unanimous, including rapid access to expertise, standardized methods and protocols for preclinical and clinical studies and efficacy trials. For sustainability, all participants emphasized the need for government support and policy to seasonal influenza, partnership with the ministry of health, and the importance of SAGE recommendations to inform policy. The wider audience promoted the value of LAIV and regional production and procurement for an expanded market. For process development, in addition to the value of shared experiences, networks were noted as key to access reliable information and resolve technical issues.

General issues noted by participants were the need for standardized and coordinated approaches at country level, innovative funding solutions, political commitment to prevent influenza, and solutions to avoid wasting influenza vaccine before its expiry date. Training, the subject of many comments, would be the focus of a specific session later in this meeting.
Discussion
The workshop discussion was rich and varied, covering the following topics.

- Study design: WHO could develop protocols for all clinical trial phases, including preclinical studies, adaptable to local needs, and a list of reliable laboratories that could carry out testing. Some unique processes could be standardized, such as master plans and quality control protocols, and a platform could be established for global access to information on clinical trials.

- A project manager was critical. WHO could outline the skills needed, or facilitate access to experts that could work with local project managers. PAHO highlighted its successful experiences in inter-country sharing of expertise.

- Sustaining manufacturing quality over time was much debated. While sharing information and lessons was good, different levels of capacity suggests a more formal mentoring between experienced and less experienced manufacturers on process development and quality issues.

- Ideas to help change mindsets were to involve government officials in meetings and training courses as they are often the principal client for influenza vaccine in developing countries. PAHO brings manufacturers, regulators and government staff together around the same table to understand and address concerns across the region.

- Since intensive training for regulators in the technology transfer countries began six years ago, the number of NRAs functional under the WHO/HQ prequalification programme has doubled. This was welcome news as developing countries rely on this to sell their products. Training courses range from multi-prong comprehensive programmes to those that address a specific need, and it is hoped that these can continue. In the Americas, NRAs with high functionality support those with less capacity, who can recognize products approved by their more advanced neighbours. Similarly, information on adverse events are shared for licensing purposes.

- In India, despite initial government support to develop the H1N1 pandemic vaccine, its decision to not purchase the vaccine threatens the sustainability of influenza production capacity in India. To date, SII has had to destroy 6M doses which is a waste, both in terms of pandemic preparedness and resources. Sustainability, directly related to a seasonal influenza programme, could work based on SAGE recommendations, but ultimately depends on end-user demand.

- BHCT China felt that WHO guidelines on quality and marketing would lend credible support to approval of their product with the government. BCHT was encouraged to consult the many WHO guidelines on regulatory guidelines endorsed by the ECBS, which may be useful to address issues that WHO grantees manufacturers were experiencing.

The Chair noted the value of this opportunity to voice comments. He summarized the call for a WHO umbrella on specific issues, and the overarching demand for training and harmonization, particularly an accelerated process to accept products. He hoped the lack of issues related to the construction of facilities was a good sign. Martin Friede agreed that it had been a very positive debate, and that the TAG would review how to concretize these suggestions. In addition, he encouraged the grantees to use the DCVMN network to advance these ideas.

2.3 Biosafety and biosecurity in vaccine production facilities: principles and practices
Dr Ali Mohammadi of Global Health and Security Consultants and Advisor to Razi Institute, discussed the principles of laboratory biosafety (working safely) and biosecurity (keeping the work safe). He described the levels of biosafety, containment barriers, and the STOP biosafety principles, i.e. substitution (e.g. hazardous material), technical safety, organizational measures, and personal protective equipment.
While GLP/GMP and biosafety had much in common, there were some basic differences. Regarding safety, for example, GMP focuses on a safe product, and keeping contamination out, while biosafety focuses on a safe environment, by keeping contamination in. Other comparisons were the aims of risk assessments. Dr Mohamidi referred participants to the WHO Technical Report Series 941 on biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines.

Biosafety and biosecurity were largely complementary. Dr Mohamidi contrasted people's perceptions during outbreaks such as SARS or anthrax, when the focus is on public health, with perceptions of security, when thoughts are on guns. Instances when public health and security need to work together include the misuse of an infectious agent. Laboratory biosecurity refers to institutional and personal measures to protect valuable biological materials, including vaccine strains, dangerous pathogens etc. Biosecurity measures also apply to transport, field investigations, manufacturing and health-care facilities. The components of an institutional biosecurity programme were presented, from a risk assessment to material control and accountability and personnel management, with examples of each, e.g. cases of important dignitaries refusing to wear PPE or the fundamental necessity of an inventory.

In conclusion, biosafety and biosecurity were essential practices for all biological facilities, and complemented GLP and GMP. Ways to enhance synergies between them and resolve areas of conflict should be envisaged. The final note was on the importance of training: few members of the audience had attended or organized a course on biosafety and biosecurity in vaccine facilities, and it was thus suggested as the topic for the next workshop organized by the HHS Office of Global Affairs.

2.4 Presentation by a new member of the network: BCHT China

Dr Wu was pleased for the opportunity to introduce BCHT and its LAIV project. The company was established in 2004 and employs 700 scientists, technicians and support staff. It has a marketing organization in China and enjoys international cooperation. Two vaccines have been marketed, a varicella and a rabies vaccine, and BCHT received a licence through WHO in 2012 to develop LAIV. BCHT is highly R&D focused and has strong joint programmes with many universities and institutes. Dr Wu highlighted the quality control activities to meet Chinese, and eventually international regulatory requirements. Government approvals for clinical trials, patents and key projects were presented along with the vaccine development pipeline, including the WHO LAIV and an MDCK influenza vaccine.

BCHT's business interest in influenza vaccine is based on that fact that less than 5% of the population is currently being vaccinated each year. Influenza vaccine was produced in China in 2006, and LAIV presents advantages of a shorter time for mass production in a pandemic outbreak, and intranasal delivery. The ultimate goal is to meet WHO prequalification and high production capacity.

Progress made since receiving the seed strains includes finalization of the IND application and a contract for the facility design and construction. Plans for 2013 are the site inspection by the Chinese regulatory authorities (SFDA), plans for preclinical ferret studies, optimization of the production process, completion of the facility construction and installation of equipment. Subject to contractual arrangements and progress, BCHT expects to market its trivalent vaccine by the end of 2016.

The production process for H1N1, H3N2 and B strains received on-site assistance by IEM. Results of infection titre testing for monovalent and trivalent vaccines showed good consistency. Many hurdles, such as a supplier of eggs that produce a sufficiently high titre, had been overcome, and more will need to be faced. One of the biggest challenges will be to edify the SFDA on this new vaccine, with the support of WHO and BCHT efforts with the government.
SESSION 3. OPTIONS FOR SUSTAINABILITY AND TRAINING

3.1 Assessment of influenza vaccine production compatibilities

Rick Bright presented a study conducted by BARDA with its partners to assess the concept of producing influenza vaccine in parallel to another vaccine in the same production suite in order to increase sustainability. The study only addressed the tip of the iceberg of the issues to consider – regulatory, technology, infrastructure, training, resources – by looking at the feasibility and challenges of, e.g. producing egg-based influenza in conjunction with an egg-based yellow fever vaccine. Based on a review of available knowledge and case studies in developing countries, the study concluded that, while it was technically feasible, and some small-scale examples exist, the approach is highly complex and will remain so for another decade without significant evolution in technologies and regulatory approaches.

3.2 How can influenza vaccine manufacturers under the GAP maximize their business potential?

Claudia Nannei summarized the comprehensive discussions that had taken place with the grantees. Firstly, the market for seasonal vaccine was not fully explored; IFPMA data show that three regions of the world have virtually no distribution, not counting the Western Pacific with a high population and costly vaccine and thus opportunities for new manufacturers to expand their sales. The same IFMPA study released in 2011 noted that the strongest correlation was between vaccine distribution, reimbursement of the cost of the vaccine, and communication, highlighting the importance of a national implementation policy.

In addition, the workshop on Modelling for Sustainable Influenza Vaccine Manufacturing (January 2013) noted that, given excess global seasonal capacity and economies of scale, WHO grantees need to generate added value over a pure cost-of-vaccine model. Conclusions from a cash-flow analysis showed that while significant expansion of production would reduce costs, small-scale manufacturers critically need to consider niche opportunities, produce other vaccines, carefully plan the production process, or increase opportunities for local/regional procurement mechanisms.

In summary, local production is not cheap production. Examples of how manufacturers could exploit their added-value within the local context to overcome market challenges were regional niche markets, prequalified vaccines in high volumes, strategic partnerships with ministries other than health, and with multinationals. International collaboration can help leverage these advantages.

Discussion

The timing of the SFDA site inspections with regard to production capacity was queried. BCHT plans to produce 20M doses of trivalent vaccine, with potential to increase production, possibly through the development of a liquid formulation. Other vaccines were not being followed up since they are of lower priority and may take years to licensure. Technical details of the pilot plant were unavailable, but the company was guided by international expert recommendations, e.g. from IEM and WHO technical advisers. Dr Wu explained that while the company had invested in MDCK technology with Biodem in the past, the focus was now purely on egg-based LAIV.
3.3 What type of training is needed in the future?

A major focus of the last International Partners meeting was on training, and since initiation of the GAP, 280 scientists have been trained around the world. The comprehensive courses, generally carried out in class-based settings with hand-on experience, have had positive feedback. Assessments carried out by the TTi and findings from the last meeting had many elements in common, notably the topic of quality management. Issues to be addressed covered scaling up, the applicability of novel technologies such as tissue culture, the need for follow-up and language barriers. This meeting added the training of trainers, local languages, tailored programmes, and new models such as on-line and interactive video, as ways to improve effective training. Finally, evaluation and follow-up remained critical.

In 2012, on-site courses were held in Indonesia and Viet Nam and a tailored course was held for the Kazakh grantee with interpretation and translated materials. In parallel to the quantity of training, it was now time to use training as a means for behaviour change at the local level. To this end, Mrs Nannei listed a set of parameters for effective training, gleaned from best theory and practices:

- involve trainees to ensure targeted training and adapt teaching methods to learning styles
- include a mix of lessons, role-play, case studies and hands-on practice
- assess skills, knowledge and attitudes at the start, middle and after training
- gather feedback through a range of sources to help evaluate the course
- facilitate mentoring for clarification/additional information after the course.

The audience was invited to provide further ideas on how to improve effective technology transfer.
**Discussion**

Dr Palkonyay announced that grantee manufacturers and regulators would be invited to a training course on quality control testing under the auspices and support of NIBSC and FDA. Other comments were that grantees were gaining expertise not just on influenza, but on vaccines in general, and this knowledge would be transferrable to other vaccines. However, education, which can be gained in short courses, and technology transfer, which involves the complex acquisition of expertise over a number of years, was differentiated.

Regions noted the problem of trainees who were not competent, or who left for the private sector after training. It was proposed that a focus on management to develop a top-down culture of institutional memory was a good approach to allay this issue. The Vaccine Formulation Laboratory adjuvant programme focused on the value of on-site training for a real world situation, access to stakeholders and impact on partners. Experience had also shown the value of building sufficient time into tailored courses to be able to adapt and react to unknown situations; of repeated visits; and of having a specific outcome.

An interesting difference between the content of courses on *training of trainers* and *training of trainees* was that the former should not just be more advanced, but should address the "how" one learns. Communication is key to successful training, and trainers might usefully put themselves in the shoes of trainees. Final comments included the need for materials to be translated into local languages, and the essential role of working together in partnerships.
DAY 2

SESSION 4. REGULATORY ISSUES – APPROVAL OF VACCINES

PATHWAY TO APPROVAL FOR INACTIVATED INFLUENZA VACCINE (IIV) AND LAIV ATTENUATED INFLUENZA VACCINES (LAIV): SEASONAL

4.1 Introduction

Laszlo Palkonyay (WHO) explained the objectives of this information session on regulatory pathways for seasonal and pandemic influenza vaccines, presented by four national/regional regulatory bodies.

Interest in influenza vaccines in the developing world has increased, partly due to pandemic threats, but even countries without manufacturing capacity will still need to license and introduce a pandemic vaccine. The main objective of the session was to help to define an agenda for a future information exchange meeting dedicated to developing country regulatory authorities. The focus will be on grantee country regulators, specifically their national regulatory authority (NRA) personnel involved in day-to-day pre- and postmarket regulation. At least three reasons justify the timeliness of such a meeting given that many grantee manufacturers have secured, or are approaching market authorization of their new influenza vaccines: i) pre- and postmarket regulatory pathways and requirements are often not clear, partly due to the large number of different production technologies used, ii) sustainability of the built-up pandemic production capacity depends entirely on maintained production activities, and iii) specific aspects of postmarket regulation of influenza vaccines, unlike any other vaccine, require market authorization for a new variant before every new immunization season.

In addition to presenting some of the general challenges facing regulators, other important issues have recently emerged such as the need to streamline package inserts, especially for mass vaccination. He underlined that in ensuring public confidence in routine influenza immunization, the potential role of regulators to increase acceptance of influenza immunization should be explored.

A brief summary of the WHO Vaccine Prequalification Programme was provided, which had recently integrated influenza vaccines. The programme, created in 1987, was formally established in the 1990s to serve United Nations procurement, which remains its main objective today. However, it is progressively being used by other vaccine purchasing agencies and countries to aid their decision-making in vaccine procurement. Other activities under the umbrella of the PQ programme include i) post-prequalification to ensure that the quality of the prequalified product is maintained, ii) ensuring sustainability of the supply of affordable vaccines of assured quality for poor countries, iii) and support to regulatory networks targeting vaccine producing developing countries in particular and African regulators. Relevant new aspects introduced into the new policy of prequalification in 2012 are i) increased reliance and collaboration with domestic NRAs during the lifetime of the prequalified product, ii) clear definition of absolute, critical and desirable product characteristics for suitability to developing country immunization campaigns, and iii) a risk-based approach for expedited reviews, which incorporates lessons learnt during the last influenza pandemic in 2009/2010. Over the last two years, three seasonal IIV and one pandemic LAIV were granted WHO prequalification status, three of which are produced by grantee countries, India and the Republic of Korea. Additional seasonal influenza vaccines are expected to be submitted in the near future.

Finally Dr Palkonyay summarized the fields of regulatory elements for seasonal influenza vaccines as i) market authorization (MA) for new products (licensure), ii) MA after major manufacturing and/or clinical indication changes, iii) MA for variant vaccines, i.e. an actual reflection on seasonal strain selection for vaccine components, and iv) MA issues related to potential Southern and Northern hemisphere composition differences.
4.2 Regulatory pathways for registration of seasonal and pandemic influenza vaccines: FDA approach

Via teleconference, David Cho contextualized the Center for Biologics Evaluation and Research (CBER) – the area that regulates vaccines – within the structure of the US Food and Drug Administration. Under CBER’s umbrella, one group looks at safety, efficacy and immunogenicity, and a sister office is responsible for reviewing facilities and manufacturing aspects of vaccines, with input from product experts from the first group as needed.

An overview of the stages of regulation underlined two key terms: the Investigational New Drug Application (IND), and the Biologics License Application (BLA). The former deals with safety, immunogenicity and efficacy, a very interactive and lengthy stage with manufacturers to ensure that all clinical, chemical, manufacturing, and control process data are available, assays have been validated, and package insert information developed to support the license application. Once ready, the application is filed as a BLA, a marketing application similar to the market authorization in Europe. At this point, all requirements have already been discussed and the manufacturer is just formalizing the application for review. Commitment to post-BLA studies is now common, especially for influenza.

Regarding the process for licensing seasonal vaccines, the traditional approval, at an average 10 months, is “based on data… which demonstrate that the manufactured product meets prescribed requirements of safety, purity and potency…” An accelerated approval can be issued “on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint…reasonably likely…to predict clinical benefit” or “subject to the requirement that the applicant study the biological product further to verify and describe its clinical benefit”. Many recent influenza vaccines have been approved under this process. Although this process still takes 10 months, the manufacturer is allowed to carry out efficacy studies post-approval. The BLA process focuses more on safety and immunogenicity, based on HAI.

Recent seasonal influenza vaccines licensed for the USA include i) the first quadrivalent LAIV for...
2–49 year olds, ii) the first cell-culture vaccine in persons above 18 years of age, iii) the first quadrivalent IIV for use in persons above 3 years old, and iv) the first influenza vaccine manufactured using an insect virus expression system and recombinant DNA technology for use in persons aged 18–49 years. Both quadrivalents use two type A and two type B strains.

In most years, at least one strain may be replaced with a new strain, for which a strain change supplement to an existing BLA is required. No clinical data are required for IIV, but some data are required for LAIV (e.g. a 300-person safety trial). This is a much quicker application, as less detail is required. The USA follows WHO recommendations on annual strains, and as a WHO Essential Regulatory Laboratory (ERL), was closely involved in the yearly strain change process.

The timetable of year-round activities from surveillance to production and use showed how the FDA was involved in almost all stages, in collaboration with companies, particularly in post-market. For the 2009 H1N1 pandemic, since seasonal vaccines produced using the same procedure had already been licensed, the FDA used strain change supplements, which allowed a pandemic vaccine to be available only 4.5 months after the first detected cases. The approach was based on the fact that the process, antigen, targeted population and data requirements were the same. Thus no supplementary clinical data were required, excepting a small safety trial for LAIV, and five vaccines were approved in this way.

The production of pandemic vaccine showed remarkable regulatory and manufacturing cooperation. Many lessons were learnt in expediting influenza vaccine which increased focus on areas such as optimized high yields, highly immunogenic vaccine reference strains, alternatives for rapid preparation and calibration of vaccine reagent standards, standardization of assays, and accelerated sterility release testing, in an effort to reduce the time to market in a pandemic event. One of the most important outcomes the 2009 pandemic was the excellent and direct collaboration between all international partners, NRAs and manufacturers for a public health good.

With regard to preparation for a future pandemic, a major issue was to define regulatory pathways in advance. While a vaccine candidate may be considered on a case by case basis, a significantly different strain would require a new BLA, for which Dr Cho listed the considerations. In exceptional circumstances, an Emergency Use Authorization was also an option for an unapproved product. The FDA had a long track record of safety and effectiveness and placed great emphasis on post-market surveillance. He also underlined the important link between seasonal influenza vaccine manufacturing capacity and experience for pandemic response. Remarkable novel approaches would provide critical alternatives to traditional manufacturing technology, but regulatory processes must be in place.

Finally, Dr Cho provided a list of useful and comprehensive guidelines and web-based training offered by CBER, and acknowledged the solid and extensive team work at the core of these activities.

**Discussion**

In the case of supplements to an existing BLA in the case of a pandemic, it was clarified that a new subtype would require a new BLA, subject to individual review. Regarding strain change for seasonal LAIV, despite the fact that European requirements are based on post-market licensing, given the same master strain, composition, and 10-year use, the USA still requires small safety studies for approval.

Since the USA does not require Southern hemisphere vaccines, it has no pathway to approve them, outside the strain selection as an ERL. Regarding the timeline for approval, the Northern Hemisphere vaccine is usually approved within five months of the WHO announcement of the strains. WHO announced that recommendations on nonclinical evaluation of adjuvanted vaccines would be reviewed by the ECBS in 2013, which will be useful for influenza vaccine.
4.3 Seasonal vaccine approval in the European Union

Jim Robertson noted that NIBSC, a national control laboratory within the European network and an ERL, would now be part of the United Kingdom Medicines and Healthcare Products Regulatory Agency. He explained the three procedures in the European Union for registration of influenza vaccines: the NRA, which is now uncommon; a mutual recognition procedure (MRP) which the European Medicines Agency (EMA) forwards for review and processing by a reference Member State while a summary is being reviewed by other members; and the EMA centralized procedure, which is obligatory if the product is to be licensed across the EU. While the centralized procedure is mandatory for some products, those with innovative procedures may be processed either through EMA or an MRP. Most influenza vaccines would use the MRP, although 3 have been licensed through the centralized procedure. Seasonal influenza vaccines licensed in the EU were listed, although the names may vary.

Useful documents are Directive 2001/83 EC (http://www.edctp.org/fileadmin/documents/ethics/DIRECTIVE_200183EC_OF_THE_EUROPEAN_PARLIAMENT.pdf) for mutual recognition, and Regulation No 726/2004 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF) for the centralized procedure. These are updated regularly and can be found, along with a wide range of other materials, some specific for influenza, on the EMA web site (http://www.ema.europa.eu/ema/). If a vaccine is licensed under the national or MRP, a guideline on fast-track procedures (http://ec.europa.eu/health/files/eudralex/vol-2/c/fast_trackfinal_may99_en.pdf) for human influenza vaccines is available. Guidance is also published on the centralized system, on procedures for annual strain variation, as well as an annex on LAIV. Many of these guidelines are being updated to account for the new variations regulation. Within a legal framework, this regulation covers all medicines, with specific points for influenza vaccines depending on type of procedure. The annual update of influenza vaccine falls under type II, since it affects the quality, safety and/or efficacy of the new strain. The EMA also provides guidance on which type of variation to submit, and all its guidelines provide timetables of the operational steps.

Since the 2009 H1N1 pandemic, the Committee for Medicinal Products for Human Use (CHMP) has issued a concept paper on the revision of guidelines for influenza vaccines. A new, single guidance document for IIV and LAIV will replace the currently separate documents on pandemic vaccines, harmonization, cell culture, etc. The most advanced section of the new guideline has been posted for comment on the EMA web site for six months; the nonclinical, clinical and harmonization sections are still being discussed. The EMA has no immediate plans to develop guidance on other types of influenza vaccine, but a lot of information is available on novel approaches such as recombinant DNA and viral vectored vaccines.

Discussion

While the clinical trial requirements for IIV may eventually be abolished, discussion is still ongoing and an agreement would not be reached this year. It was felt that, technically speaking, an emerging developing country vaccine manufacturer was not obliged to start with an egg-based product, provided the novel vaccine was viable.

4.4 TGA registration process for seasonal IIV and LAIV

Dr Gary Grohmann gave an overview of TGA pathways to registration of IIV and LAIV, although the latter was not currently registered in Australia. The legally binding TGA Act promotes a national system of controls relating to the quality, safety, efficacy and availability of therapeutic goods used in or exported from Australia. Being based on the British and hence European pharmacopoeias, most EU monographs and WHO documents are accepted. However, TGA operates on 100% cost recovery from industry and largely uses external evaluation services.
Within the overall organizational structure, three groups work closely together for vaccines: market authorisation; monitoring and compliance (with increasing emphasis on postmarket activities); and regulatory support. Dr Grohmann explained the medicines regulatory framework, whereby all products must be registered on the Australian Register of Therapeutic Goods (ARTG). TGA uses a low to high risk-based continuum. Determinants for risk include ingredients, dosage form, indications, capacity for misuse and the significance of side effects. Complementary medicines are generally low risk (listed medicines), over-the-counter of medium risk, but all prescription medicines including vaccines are considered high risk (registered medicines). The difference between these in terms of labelling is that listed products have an AUSTL number while those registered show AUSTR and require more rigorous clinical, safety and quality data.

Clinical evaluation units evaluate clinical data for new products, variations on existing registrations, product information and consider use of unregistered medicines under the emergency special access scheme, e.g. pandemic vaccines.

Three types of application exist. Category 1 comprises new prescription medicines or any major manufacturing change. Category 2 products are prescription drugs supported by two evaluation reports from credible sources. Category 3 includes new data on registered medicines, but not requires no clinical data, e.g. a strain change. The clinical data expected per category was listed, and while minor, self-assessed changes in Category 3 would not need to be submitted to TGA, all must be notified and approved before implementation. A useful algorithm can be used by potential candidates to assess in which category the product belongs. The timeline of from pre- to post-submission has been significantly shortened to 7–8 months for Category 1, and 15 days for Category 3.

TGA uses the same common technical document format as the EU, technical guidelines – particularly from ICH and EU, and the Australian Regulatory Guidelines for Prescription Medicines. Requirements for the five modules (quality, clinical, nonclinical, summaries, and regional administration) under the CTD numbering scheme were described. The e-submission pathway was encouraged as it facilitates the transfer of data and feedback.

The first part of the complex review process is the most important as the application is rejected if anything is amiss, and no further data are accepted. These next phases are for detailed evaluation and decision-making during which a nominated Delegate may seek advice from experts and advisory committees and ensure final labelling. Questions may be addressed to the sponsor who may submit supplementary data at that point. All products must have TGA-approved product information for health professionals and a Consumer Medicine Information document for patients. The sponsor has the right of appeal against the Delegate's decision.

Dr Grohmann also described TGA's lot release activities, to which all vaccines are subjected. Influenza lots are tested for potency and endotoxin levels. He briefly pointed to the familiar product vigilance and risk management cycle that manufacturers are expected to have in place, especially for new vaccines and those involving children. Risk management plans (RMP) are a key to the TGA framework. Two key documents, based on the EU guidelines, along with their updated good pharmacovigilance guidelines, are available on the TGA web site.

The Adverse Drugs Reactions System database analyses solicited reports, data from various cohorts as well as reports submitted from the general population. All are carefully reviewed, triaged, coded and posted with acknowledgement on web site. The WHO classification is used for causality assessment; where an event is unclear, the report is accessible but not used in consideration of a safety signal.

The Australian Influenza Vaccine Committee advises TGA on the appropriate strains for IIV and QIIV, for pandemic situations and stockpiles. TGA also takes into account the WHO recommendation for SH strains when making a decision. This, and all information presented, can be found on the TGA web site at http://www.tga.gov.au.
4.5 Pathway to approval for seasonal IIV and LAIV

Dr Pramote Akarapanon of the Thai Food and Drug Administration stated that all new vaccine applications required a full CTD. The key quality, clinical and nonclinical data required were listed, along with the national and international guidelines used to assess the criteria. The standard review process is completed within 480 working days. For manufacturing changes, TFDA Variation Guideline 2012 advises on requirements for submission of major and minor variation applications, both of which require prior approval and notification.

Major variations to a registered product are those that may affect significantly or directly its quality, safety and efficacy, while minor variations concern administrative data or changes with minimal/no significant impact on these aspects.

Regarding annual strain changes, the Marketing Authorization Holder submits the variation application in line with WHO recommendations. Being in a tropical area, Thailand uses both Northern Hemisphere and Southern Hemisphere formulations for which the following issues are considered: specification, virus seed lot system, process validation and evaluation, inactivation and stability. The timetable for SH starts with notification of the reference strain in September, variation application in December and TFDA approval in March.

All data are available on the TFDA web site at http://www.fda.moph.go.th/eng/index.stm.

PATHWAY TO APPROVAL FOR IIV AND LAIV: PANDEMIC

The Chair opened the second part of this regulatory session on different processes for pandemic vaccines, both before and during a pandemic. In reflecting on priorities for future consideration, Dr Palkonyay outlined in his brief introduction the importance of flexibility in regulatory approaches, policies that the grantees’ NRAs develop to deal with the different, equally justifiable development strategies chosen and pursued by the manufacturers: a “seasonal to pandemic” and a “(pre-)pandemic to seasonal” vaccine development route.

4.6 European Union pathways to approval of IIV and LAIV pandemic vaccines

In the EU, the core dossier based on a mock-up vaccine is designed to reduce the time taken to approve an actual pandemic dossier after a new pandemic is declared by WHO. The background to this was the relatively low immunogenicity of H5 and H9 vaccines meaning that in a pandemic, the dose needed would be unclear, requiring a new licence. Under the new process, industry has been
encouraged to prepare and test monovalent mock-up vaccines. This was put into practice in 2009, along with a mutual recognition procedure since the immunogenicity of the pandemic H1N1 strain was identical to an existing unadjuvanted vaccine.

Another procedure set up prior to 2009 was the prepandemic authorization scheme, whereby companies were invited to produce and stockpile H5 vaccines. The main difference with the core dossier was that prepandemic authorization required a full level of clinical assessment versus the core dossier approach which requires only limited clinical data from the manufacturer.

In a pandemic, the intention is to replace the mock-up strain with the pandemic strain. It is anticipated that new strain would not substantially affect safety or the immunity conferred. A combination of the full package of mock-up data plus data on the pandemic vaccine is deemed sufficient to demonstrate risk–benefit, and thus the only new data required would be on the quality of the final pandemic vaccine. Some companies also did small clinical studies to assess immunogenicity of their vaccine. These procedures are described in two primary guidelines, one focusing on the content of pandemic influenza vaccine marketing authorization applications, and the other on submission of applications through the centralized procedure. While H1 vaccines did not have to be approved by the EMA, for cases such as rDNA and the genetically engineered H5N1, EMA approval is mandatory.

The 'emergency procedure' was set up for fast-track approval of a new vaccine developed after a pandemic has been declared. Authorization is quicker as the information submitted by the manufacturer is assessed in 70 instead of 210 days. Two vaccines underwent emergency procedure in 2009 but were later withdrawn.

Dr Robertson described the vaccines currently on the market for pandemic use, licensed via mock-up or prepandemic procedures through the national or centralized system. He drew attention to new EMA guideline in preparation that will bring together all existing documents related to influenza vaccines. Other EU activities described relating to licensure included the role of a special Task Force and an accelerated process for strain exchange.

4.7 The TGA registration process for IIV and LAIV prior to and during a pandemic

Dr Grohmann explained that the Australian system accepted the EMA guidelines for licensing pandemic vaccines. The registration pathway for a pandemic vaccine followed the same five modules required for a seasonal CTD, but the process could be significantly accelerated if all the required data were in place.

Two steps in the decision tree were presented. The first is the same as in the EU, i.e. companies are encouraged to submit applications of new methods of manufacture of vaccines against pandemic strains. A core dossier requiring quality, safety and efficacy data for a mock-up vaccine is authorized during the interpandemic period and when the pandemic strain emerges, fast-track approval requires only quality data related to this strain, along with commitment to gather clinical information during the pandemic. Dr Grohmann discussed the principles and differences of mock-up to interpandemic and pandemic vaccines that influence whether a vaccine is accepted. A new method involving reverse genetics must be reviewed by a second regulator from the Office of Gene Technology Research, although discussions are ongoing to demonstrate the safety of the technology. The different scenarios are then assessed, e.g. whole vs split virus, adjuvant, concentration, dose regimen, which form the mock-up vaccine package.

The second step is when a pandemic strain emerges. After WHO announces the reference virus, manufacturers are expected to produce three pilot batches and complete animal safety tests within three months. TGA will then register the vaccine based on an approved mock-up vaccine, but only for
H5. The sponsor of the vaccine is expected to initiate human immunogenicity and safety studies, and although they may not be completed, should commit to including all age groups (especially children) and certain diseased conditions to give confidence in the registration decision. In addition to the usual production considerations, all vaccines must be TSE compliant and are subject to batch release.

Vaccine registration outside a pandemic has several options: the timely Category 1 route; a clinical trial exemption, where data are assessed before completion of the trial; the special access scheme that would bypass clinical and safety data, or an emergency provision. Several other exemptions under the TGA Act allow emergency provisions; for example in a pandemic, available vaccine could be authorized for immediate use. Requirements for each of these options were enumerated.

Concern about TSEs, genetically modified viruses and adverse reactions are solved by requiring an RMP and effective collaboration among the various regulatory and advisory bodies. Although live viral vectors are not registered in Australia, it is appreciated that they can provide an effective means of antigen expression. Potential issues that need to be considered include recombination with wild type strains, implications of prior infection, available tests, and public acceptance. TSE compliance criteria were notably traceability and use of serum from BSE-free countries in master and working cell banks.

Australia has registered an H5 alum-adjuvanted, stockpiled vaccine and several H1 vaccines.

In summary, pandemic vaccines other than H5 would likely require clinical trial data depending on the severity and speed of the pandemic. New live or recombinant vaccine could be accepted quickly on the basis of registration in the EU and USA with supporting safety data. Approval for strain change is a Category 3 application and based on the advice of the AIVC and/or WHO. RMP is essential for children and for any new vaccine. And finally, outside a pandemic, normal registration is expected while CTX, SAS or emergency provisions are possible. All information resources are available at www.tga.gov.au (TGA) or http://www.ogtr.gov.au/ (OGTR).

4.8 Pathway to approval for pandemic IIV and LAIV in Thailand

In a pandemic, a fast-track review process can be implemented for marketing authorization of a product of major public health interest, in which case the TFDA ensures a decision within 280 days. In this notification, a full dossier is required covering quality, nonclinical and clinical data. During the H1N1 pandemic, e.g., a PIIV split virion vaccine was approved in 100 working days. The TFDA may announce an Emergency Use Authorization of a medicinal product, whereby assessment of efficacy and safety are based on the principle of risk-benefit. This authorization is only applicable in a pandemic situation and only if no other medicinal product can control or prevent the disease. The product must be monitored for safety and efficacy.

Outside of a pandemic, Market Authorization Holders can apply for approval of a vaccine prepared from viruses with the potential to cause a pandemic, which is evaluated under the standard review of new vaccines. Once a pandemic situation is declared, they can apply for a strain change to the pandemic strain and the TFDA will facilitate a priority review.

**General discussion on pandemic pathways**

The issue of whether a trivalent vaccine including H1N1, as opposed to a monovalent vaccine was the best option during the last pandemic was debated. TGA noted that approval for H1N1 pandemic vaccine was very rapid due to prior experience of industry with the strain, and the vaccine was available within three months. Development of a monovalent vaccine thus followed the existing trivalent vaccine. TGA differentiates between emergency and severity and if a pandemic is not severe, a clinical trial is required. After discussion with its advisory committee, TGA is ultimately responsible for deciding the strain selection and subsequent discussion with manufacturers. Advance release of vaccine may occur under the special access scheme, e.g. for health-care workers. Other regulations and regulatory agencies such as those covering the use of genetically modified organisms and
environmental contamination can also impact time to approval, and virus made by reverse genetics is considered in some countries to be a GMO.

Much discussion took place on who can order the switch from seasonal to pandemic production. The 2009 H1N1 was relatively straightforward as seasonal production was believed to be near completion. In Australia and the USA, and in countries where governments have contracts with manufacturers, the government has a clear mandate to make this decision; however the legal situation in the EU, and for multinational manufacturers was less clear. The role WHO might play in making this decision at intercountry level should be agreed in advance of the next pandemic. To this end, the Chair reiterated the importance of close relationships between international agencies, governments, regulators, programme managers and manufacturers in advance of a pandemic.

The EMA Guidelines are being revised based on experience gained during the H1N1 pandemic, when no LAIV was available in Europe. The same applied to Australia, but if a seasonal LAIV were available in a pandemic, it could be approved subject to sufficient safety data. Regarding pandemic guidelines for NRAs in developing countries, the criteria and declarations for phase changes are discussed in new guidelines that would be published soon.

While surveillance data may be essential, H1N1 did not circulate widely in areas of Africa and China, where physicians felt that a strain change without an RCT meant "not tested thus not safe". This underlines the need for better communication and understanding of cultural influences.

IVAC asked whether its H1N1 pandemic vaccine candidate could be used if a pandemic struck before completion of clinical trials. WHO responded that, as for other grantees, while a lot of data had been produced, more were needed, and some regulatory aspects such as oversight of clinical trials remained weak. WHO would also be pleased to receive any specific requests for assistance from the country.

Indeed, to support weaker NRAs, especially in a pandemic environment, pooling of NRA expertise and a form of mutual recognition was essential for rapid distribution of available vaccines and to ensure that NRAs are involved in international mass vaccination campaigns. In this regard, a study on the use of large volumes of vaccine outside the cold chain was considered very useful.

A number of areas were highlighted where grantees and NRAs could benefit from WHO programmes related to this session. First, NRAs were invited to provide input to the operational sections of the new draft WHO prepandemic guidelines, which included issues such as severity and the switch from seasonal to pandemic production. Grantees could also join the list of those who receive the composition of seasonal vaccines immediately following the dedicated WHO strain selection meetings organized twice a year in February and September for Northern and Southern hemisphere vaccines respectively, as well as teleconferences organized to discuss issues emerging during the period of these strain changes. Participants were also invited to consult the WHO web site for information on where to obtain viruses, reassortants and reagents.

It was proposed that terminology such as "fast track" and "emergency" should be more clearly defined, especially for ultimate acceptability of vaccination. For emergencies, it was stated that the International Health Regulations issued declarations in a global emergency health situation.

**SESSION 5. CLOSURE**

In his closing remarks, the Chair particularly thanked all the speakers for their presentations, and Dr Marie-Paule Kieny and her team for such a well-organized and informative meeting.
ANNEX I

SIXTH MEETING WITH INTERNATIONAL PARTNERS ON PROSPECTS FOR INFLUENZA VACCINE TECHNOLOGY TRANSFER TO DEVELOPING COUNTRY VACCINE MANUFACTURERS  
18-19 March 2013, Grand Hyatt Dubai Hotel

Chair: G. Grohmann

DAY 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Session 1 - Introduction and updates</th>
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<tr>
<td>8:45</td>
<td>9:00 Welcome address and opening remarks</td>
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<tr>
<td>9:00</td>
<td>9:15 Global Action Plan for Influenza Vaccines - update</td>
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<td>9:15</td>
<td>9:30 Progress under GAP Pillar 2 “Increase Production Capacity”</td>
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<td>9:45 BARDA international influenza programmes</td>
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<td>9:45</td>
<td>Updates of recent meetings and workshops</td>
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<td>9:45</td>
<td>10:05 IHIS/WHO workshop series: review of recent workshops</td>
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<td>10:05</td>
<td>10:20 SAGE: updated position paper on influenza vaccination</td>
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<td>10:20</td>
<td>10:35 Recent meetings: 1. Influenza vaccine effectiveness (December 2012)</td>
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<td>10:35</td>
<td>10:50 2. Development and clinical trials of influenza vaccines that induce broadly protective and long-lasting immune responses (January 2013)</td>
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<td>10:50</td>
<td>Coffee break</td>
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<tr>
<td>11:15</td>
<td>11:30 Update on ongoing LAIV trials</td>
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<td>11:30</td>
<td>11:45 Progress in the development of 2nd generation vaccines and “universal” vaccines</td>
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<td>11:45</td>
<td>12:00 CDC work in support of the GAP</td>
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<td>12:00</td>
<td>Session 2 - &quot;What can be achieved by the 10th GAP anniversary, and what will it take to maximize increase of production capacity in Developing Countries (GAPY10)?&quot;</td>
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<td>12:00</td>
<td>12:30 Introduction: Update and review of challenges ahead</td>
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<td>Lunch</td>
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<th>Time</th>
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<tr>
<td>14:00</td>
<td>15:00 Workshop discussion: Roadmap to GAPY10 - potential solutions</td>
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<td>15:00</td>
<td>15:15 Biosafety and Biosecurity in vaccine production facilities, Principles and Practices</td>
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<td>15:30 Presentation by new member of the network: BCHT, China</td>
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<td>Coffee break</td>
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<td>16:00</td>
<td>16:15 Barriers and opportunities for multi-product facilities</td>
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<td>16:45 Business planning</td>
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<td>16:45</td>
<td>17:15 Training: what type of training is needed in the future</td>
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<td>17:15</td>
<td>17:30 Discussion and wrap-up</td>
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End of Day 1
SIXTH MEETING WITH INTERNATIONAL PARTNERS ON PROSPECTS FOR INFLUENZA VACCINE TECHNOLOGY TRANSFER TO DEVELOPING COUNTRY VACCINE MANUFACTURERS
18-19 March 2013, Grand Hyatt Dubai Hotel

Chair: G. Grohmann

**DAY 2**

<table>
<thead>
<tr>
<th>8:00</th>
<th>Session 4 - Regulatory issues - approval of vaccines</th>
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<tr>
<td></td>
<td>Information session on national approval processes.</td>
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<td>Definition of an agenda for a future dedicated information exchange meeting</td>
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**Pathway to approval for seasonal IIV and LAIV**
- Approval of new vaccines
- Approval after major manufacturing changes
- Yearly approval for strain change

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<td>L. Palkonyay</td>
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**Presentations of national regulatory processes:**
- **USA** [covering both seasonal and pandemic vaccines]
  
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<th>8:15</th>
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<th>D. Cho (by teleconference)</th>
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<td>8:45</td>
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<td>Australia</td>
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<td>Discussion</td>
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**Pathway to approval for pandemic IIV and LAIV**
- In a pandemic situation
- Outside of a pandemic situation

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**Presentations of national regulatory processes:**
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<td>11:15</td>
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<td>General discussion</td>
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<td>Wrap-up</td>
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<td>Concluding remarks</td>
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<td>M.-P. Kieny</td>
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ANNEX II

SIXTH MEETING WITH INTERNATIONAL PARTNERS ON
PROSPECTS FOR INFLUENZA VACCINE TECHNOLOGY TRANSFER
TO DEVELOPING COUNTRY VACCINE MANUFACTURERS
18-19 March 2013
Grand Hyatt Dubai Hotel

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