**Summaries of Complementary Presentations on Agenda Item:**

**WHO’s Role in Supporting Emerging Vaccine Manufacturers**

To inform the SAGE discussion on this agenda item, four presentations have been solicited which will provide additional information and viewpoints in four areas.

The first presentation is from the point of view of the local immunization programme in a country where some vaccine production has existed in the public sector for many years, but it has not met the needs in terms of quality, quantity, and vaccine selection. The presentation also emphasizes other important considerations in access to new vaccines.

The second and third presentations consider the need for development of innovative new technologies on the part of emerging vaccine manufacturers and present two case studies: one, in Brazil, where the government has supported access to technologies for the two public sector vaccine manufacturers through partnerships, and the second, a report on technology development and transfer through the International Vaccine Institute from a Vietnamese manufacturer to an Indian manufacturer.

Finally, the fourth presentation uses the example of the financing details of rotavirus vaccines to address the economic issues raised by development of innovative vaccines.

**From the point of view of the local immunization programme**

**Dr Rehan Hafiz, Islamabad, Pakistan**

Vaccine production in developing countries has been largely limited to the production of traditional vaccines in a small number of countries with variable levels of consistency. While countries such as Iran and Tunisia have had a steady repertoire of vaccines, Pakistan in the WHO Eastern Mediterranean Region has oscillated between producing small quantities of measles, TT and, at times, cell culture rabies vaccines in limited quantity. While these countries have benefitted from WHO technical support, the National Regulatory Authorities may not have developed to the appropriate level. India, on the other hand, largely through private sector production, has met global demands for new and emerging vaccines backed by a recognized regulatory authority.

In this context it is critical to define the levels of support that WHO can provide to emerging country vaccine producers as well as the limitations in terms of available expertise and resources. Ministries of Health often perceive WHO as being able to provide inputs and solutions to public sector producers that may not meet certification standards. WHO support thus needs to be defined as not going beyond providing technical assistance and ensuring a viable NRA. WHO pre-qualification must remain as a benchmark for any emerging country producer and WHO must discourage countries from purchasing vaccines either in-country or elsewhere that do not meet the requirements.
WHO cannot support manufacturing from scratch to finish - its mandate is to provide guidance and standards. This whole issue is now all the more complicated given the current repertoire of combination high-end vaccines. For countries to begin to be considered as serious manufacturers they will need to enter this high-end market. As a result, these emerging manufacturers need to make major inputs.

These emerging manufacturers could potentially be either private or public sector manufacturers. Successful emerging manufacturers are linked to the private sector, e.g. India. Private manufacturers understand the stakes, and seek WHO pre-qualification viewing that is their key to success. They may also have the liquidity to allow them to access international expertise prior to applying for WHO pre-qualification.

In terms of support to public sector manufacturers, it is important that WHO no longer ignore their inadequacies. Other groups must also play a role, either on behalf of WHO or in collaboration. PATH and similar entities have years of experience but again their mandates cannot be unlimited.

Should all countries aim to become vaccine producers or is it more practicable to purchase from certified manufacturers? If countries are going to produce vaccines, there should be a potential for enhancing existing facilities, rather than producing only basic vaccines such as measles, BCG and TT. WHO must also find a mechanism to allay inherent fears that supplies may be curtailed or stopped in cases of war/embargoes and other scenarios.

Country level inputs remain an integral and important component regarding vaccine production/usage. The role of National Technical Advisor Groups (NTAGS) becomes all the more critical while analyzing available disease burden data or requesting such data when not available. This provides appropriate tools towards decisions that have major impacts on programmatic issues. With available opportunities for new vaccine introduction through GAVI support, NTAGS are expected to weigh in with the benefits of building national vaccine capacity versus long term sustainability.

**It would be critical to address:**

a. Pragmatism versus desire. Manufacturers must understand changing global markets and vaccine repertoires including newer interventions in developing a product portfolio.

b. Public versus private and public/private. There are few viable vaccine manufacturers who are fully public sector entities.

c. WHO-pre qualification absolute must. Countries should not force themselves to buy vaccines of uncertified quality.

d. NRAs are critical and must form part of the discussion. Despite country desire WHO must point out the reality of needs.

e. Procurement. UNICEF procurement services vs direct procurement? Some countries have mechanisms for public procurement and are by law bound to procure using national procurement mechanisms. WHO can play a strong role in helping develop manuals and documents for procurement, defining minimum requirements such as quality through certification.
Role of Partnerships in Developing Innovative Vaccines: Brazil

Dr Reinaldo Guimaraes, Brasilia, Brasil

In Brazil, the public sector (Unified Health System – SUS) is responsible for 95% of the national human vaccine market. In order to offer and distribute these vaccines, the Ministry of Health created the National Immunization Program (PNI) in 1973. The State offers through this Program more than 15 vaccines to the Brazilian population (BCG by intradermal route; Hepatitis B; Oral poliomyelitis vaccine - OPV; DTPw + Hib; DTPw – Diphtheria-tetanus-pertussis; Haemophilus influenzae b; Oral human rotavirus vaccine – Monovalent G1 (P8); Yellow fever; Measles-Mumps-Rubella (MMR); Influenza; Pneumococcal 10-valent). Besides that, the Ministry of Health offers some vaccines to specific population groups (Hepatitis A; Hepatitis B; Haemophilus influenzae b; DTPa (Acellular DTP); Conjugated 7-valent Pneumococcal; Polysaccharide 23 Pneumococcal; Inactivated poliomyelitis vaccine (IPV); Varicella (Chicken pox); Influenza; Meningococcal group C conjugate vaccine; Pentavalent (DTPw – Hib-Hepatitis B); Rabies; Human immunoglobulins against hepatitis B, antirabies, antitetanus and antivaricella-zoster).

The approved budget for the PNI in 2011 is around US$ 1 billion. It includes 33 000 vaccination centers and 41 specialized immunobiological reference centers. This infrastructure permits the usage of three main strategies for immunization actions: routine, campaign and outbreak response. Since 1999, PNI has administered more than 1.7 trillion vaccine doses and some successful cases can be mentioned, such as the recent H1N1 pandemic influenza vaccine campaign with more than 85.3 million administrated doses or the rubella campaign in 2008 with 96.75% coverage.

Concerning vaccine production, Brazil has ALSO a peculiar situation because the majority of the products of PNI is produced by two public institutions (Butantan Institute and BIOMANGUINHOS). Currently there is no private vaccine manufacturer in Brazil, but Novartis has a project to build one facility in the Northeast region of the country.

These two public institutions have technological and production process expertise for traditional vaccines, such as MMR, DTPw, OPV and yellow fever vaccines. Most recently, in the context of an emerging new generation of vaccines that use the process of antigen conjugation, the two manufactures are collaborating, aiming to incorporate these technologies. This is possible through autonomic research development and through technology transfer agreements.

There are some vaccines that are of priority in the context of these technology transfer processes, such as the ones against rotavirus, influenza, anti meningococcal A and anti-pneumococcal. These transfer agreements begin by incorporating the final products in the vaccine pool of PNI and gradually the SUS absorbs technologies that are developed through a logical step-wise process (fill-finish and usually bulk antigen production). Usually these transfer agreements include explicit deadlines, prices, markets and royalties.

In the research and development field, the country achievement is currently predominantly related to clinical research. However, some pre-clinical initiatives in-house have started, with
multi-national industry collaboration. There is also a well established research line of new adjuvants.

Finally, there are important initiatives in the field of rational vaccine application, aiming to reduce the number of injections that young patients will receive. Currently, we are developing a project for a pentavalent vaccine (DTP + Hib + HepB) and, after that, a vaccine delivering seven antigens in only one injection will be our goal.

**Innovation Initiative Driven by an International Organization**

**Rodney Carbis, Seoul, Republic of Korea**

Emerging manufacturers play a critical role in supplying quality vaccines at affordable prices, and currently the majority of vaccine doses procured by UNICEF and PAHO were manufactured in developing countries. With an increased interest in introduction of new or improved vaccines there is a need for emerging manufacturers to develop or obtain technologies to produce and test these vaccines.

The International Vaccine Institute (IVI) with funding from the Bill and Melinda Gates Foundation initiated a program to make available a high quality affordable cholera vaccine primarily targeting impoverished cholera endemic communities. A Vietnamese manufacturer was producing an inexpensive cholera vaccine for use in public health programs in Vietnam. This vaccine did not comply with the WHO guidelines for production and control of inactivated oral cholera vaccines, and the Vietnamese National Regulatory Authority had not met the WHO NRA indicators for prequalification of vaccines, so this vaccine could not be considered for use in cholera endemic countries. IVI worked with the Vietnamese manufacturer to improve the vaccine and bring it into compliance with the WHO guidelines. This involved reformulation of the vaccine and introduction of new quality control tests that 1) reliably quantified the antigen content or dose and 2) an assay for residual cholera toxin to ensure its removal from the vaccine. A number of modifications to the production process to ensure better compliance with GMP were also introduced.

With an improved production process, new formulation and introduction of assays to control quality and safety, the vaccine was ready for technology transfer to a company in India which had a history of WHO prequalification of vaccines. The recipient company chosen for the technology transfer was Shantha Biotechnics. Staff from Shantha were trained in production and quality control at IVI in Seoul; they then went back to India and demonstrated scalability of the process in their production facility. Three consistency lots were produced in the production facility for licensure of the vaccine in India.

To demonstrate safety and immunogenicity the vaccine was tested in phase 2 trials in SonLa, Vietnam, and in Kolkata, India. The vaccine was shown to be safe and induce vibriocidal antibody responses superior to the existing Vietnamese vaccine. The phase 2 trials were followed up with a phase 3 efficacy trial in Kolkata conducted in 70,000 persons and the vaccine was shown to be safe and protect about 70% of people vaccinated.
The Inactivated Oral Cholera vaccine produced by Shantha was licensed in India in February 2009. It is the world’s first low cost oral cholera vaccine and should add significantly to efforts to control cholera in countries where the disease is endemic.

Emerging manufacturers----potential impact on vaccine market dynamics and price: A closer look at rotavirus vaccines

Dr Deborah Atherly, Seattle, Washington, USA

Background

Each year, nearly 1.5 million children worldwide die from severe, dehydrating diarrhea, and millions more are hospitalized. Diarrheal illness due to rotavirus causes more than 500,000 of these deaths and the vast majority of child rotavirus deaths—greater than 85 percent—occurs in the world’s poorest countries where access to routine medical care is limited and often delivered late. Although two commercial rotavirus vaccines are currently available and have been demonstrated to be safe and effective in low-income, high-disease burden populations, they are not yet widely available or affordable for the developing world. The recent global recommendation by the World Health Organization’s (WHO’s) Strategic Advisory Group of Experts on Immunization (SAGE) for the inclusion of rotavirus vaccines in all countries is expected to further increase demand, but economic barriers to access remain an issue for the countries most in need. Development of a mature market for rotavirus vaccines may help address this issue.

A mature market would include manufacturers from both developed and developing countries that provide WHO-prequalified vaccine in sufficient quantities and in a competitive fashion. Currently, the market is at an early stage, with two multinational vaccine manufacturers participating. However, the entry of manufacturers based in developing countries, such as India, China, Indonesia, and/or Brazil within the next 4-7 years, could potentially bring a lower vaccine cost structure and increased competition resulting in lower prices. In addition, their entry could enhance vaccine supply security and increase uptake in self-producing countries.

Cost Structure and Price Competition

Currently, six rotavirus vaccine candidates are in clinical development—four with bovine reassortant vaccines (BRV), using NIH-licensed technology, and two with neonatal human strains developed locally by academic groups in India and Australia. Each one, if successful, will be produced by a developing country manufacturer. Research and discovery for these products was largely subsidized by the public sector, and clinical development costs for most of these products will be shared with public health partners, thus decreasing the overall risks and cost of R&D. In addition, the agreements forged between manufacturers and product development partners increasingly contain global access conditions, including affordable price guarantees for low-income country markets.
A robust pipeline may also bring price competition as these products enter the market. Based on historical vaccine pricing trends, we are unlikely to see substantial declines in price for the two currently available products, as long as they remain unchallenged. However, in the case of hepatitis B, diphtheria-tetanus-pertussis (DTP)-hepatitis B (hepB), and, most recently, DTP-hepB-\textit{Haemophilus influenzae} type b (Hib) vaccines, price competition began when additional suppliers entered the market. \textsuperscript{iii} \textsuperscript{iv}

\textbf{Supply security}

In addition to the contribution of developing-country manufacturers to decreasing global prices, the participation of these manufacturers could also improve supply security. The vaccine procurement principles established by UNICEF, the largest purchaser of vaccines for children in developing countries, support a healthy market with multiple suppliers from both developing and industrialized countries. A robust market not only creates price competition but also reduces the risk of interrupted vaccine supply due to production problems, which occur more frequently with biologicals than standard pharmaceuticals.\textsuperscript{v}

\textbf{Advantages for large, self-producing countries}

The introduction of rotavirus vaccines manufactured in India, China, Brazil, and/or Indonesia could have a substantial impact on the global burden of disease. These countries have a demonstrated history of successfully manufacturing and introducing vaccine products for their own countries and outside markets. The production costs, economic advantages to the country, and familiarity of the manufacturers with the political and regulatory systems all represent advantages of locally produced vaccines in comparison to products from multinationals. Developing-country manufacturers are also more likely to develop and manufacture affordable vaccines targeted to the needs of the local population.\textsuperscript{vi}

\textbf{Conclusion}

A robust pipeline and a healthy market that includes both developed and developing country manufacturers can contribute to global access through provision of a vaccine supply that is adequate, affordable, secure and acceptable. However, these suppliers will also depend upon sustainable demand in their target markets. Thus, collaboration, oversight and intervention that encompass both the supply and demand dimensions of the market are required.


\textsuperscript{iii} Asian Development Bank. Immunization financing in developing countries & the international vaccine market.

\textsuperscript{iv} Adapted from UNICEF vaccine projections 2005-201.0

\textsuperscript{v} \url{http://www.unicef.org/supply/files/3_Vaccine_Security_Update_R_Matthews.pdf}