Immunization and vaccine development in the last decade

Since the Millennium Summit in 2000, immunization has moved to centre stage as one of the driving forces behind efforts to meet the Millennium Development Goals (MDGs) – in particular, to reduce deaths among children under five years of age and reduce maternal mortality, MDG 4 and MDG 5 respectively. More children than ever before are being reached with immunization: in 2010 it was estimated that 109 million children per year were being immunized globally. And the benefits of immunization are increasingly being extended to adolescents and adults – providing protection against life-threatening diseases such as influenza, meningitis, and cancers that occur in adulthood. For the first time in documented history the number of children dying every year has fallen below 10 million and the number of deaths averted is between 2-3 million.

Meanwhile, Research and Development (R&D) for vaccines in developing countries started receiving substantial international funding from initiatives and partnerships such as the International Finance Facility for Immunization (IFFIm), product development partnerships such as the Malaria Vaccine Initiative, Advance Market Commitment (AMC) and the Global Alliance for Vaccine Initiative (GAVI) to name a few. These initiatives and increased donor funding have proven critical to stimulate regional vaccine research and transfer of technology to increase regional and global vaccine production capacity. In the last decade emerging economies like India and Indonesia have established large productions of non-patented vaccines. In the South-East Asia Region (SEAR), vaccine manufacturers have benefited from transfer of technology for the production of conjugate vaccine against Hib and meningococcal disease. More vaccines have been developed and others are already in the late stages of clinical trials, making this decade the most productive in the history of vaccine development.
In the last decade emerging economies like India and Indonesia have established large production of non-patented vaccine products

This rapid increase of vaccine production in developing countries and the level of complexity to produce and regulate new vaccines are not without challenges for National Regulatory Authorities (NRA’s). Yet despite extraordinary progress in immunization and more vaccines being produced in low and middle income countries, there are still risks of global shortages of vaccines of assured quality. The recent de-listing of vaccines produced in SEA region from the WHO list of Pre-Qualified vaccines demonstrated that achievements still need to be consolidated with stronger Government commitments to support the enforcement of international/WHO standards for vaccine safety and quality.

With the courtesy of Bio Farma
Safe and effective vaccines manufactured in compliance with WHO and international standards for Quality Control, Assurance and Good Manufacturing Practices (GMP) with an oversight by a functioning National Regulatory Authority are universally recognized as essential to immunization programmes. Consistent production of safe and effective vaccines is difficult, and doing so at an affordable price, even more so. WHO has defined the concept of “vaccines of assured quality” in an effort to ensure all stakeholders have a clear understanding of the requirements; a vaccine is of “assured quality” if all the statements below hold truth:

- The vaccine is produced in a country where the National Regulatory Authority (NRA) is independent from the manufacturer;
- The vaccine production is overseen by a fully functional NRA, i.e. the NRA exercise all 6 critical regulatory functions as endorsed by the Expert Committee on Biological Safety (ECBS) in 1995
- There are no unresolved problems reported with vaccine safety, quality and efficacy

The global vaccines market has been growing at a rate of 16% annually and is expected to reach US$ 34 billion in sales by the end of 2012. Increased production capacity and investment in South-East Asia countries has changed the role and influence regional manufacturers have on their domestic, regional and increasingly global access to vaccines of assured quality in developing countries. These factors place SEAR countries in a strategic position which has translated into a more advanced programme of support from WHO in the area of vaccine safety and quality.

In light of the increased importance and impact of regional manufacturing on other countries and global immunization programmes, the Vaccine Safety and Quality (VSQ) unit was formed within the South-East Asia Regional Office of WHO to support Member States. VSQ’s comparative advantage is the fact that most countries affecting the global vaccine supply market are all within short distances in the region. In order to stimulate manufacturing capacity, VSQ has focused on the following key areas of work considered critical to building capacity in the region:

- Vaccine quality and regulatory issues including:
  - Supporting countries to establish, maintain and/or improve functional NRAs
  - Developing surveillance systems for Adverse Effects Following Immunization
- Assessing and improving vaccine procurement, management and cold chain systems
- Improving waste management
WHO has a long history of support to NRA’s and it is the only international development agency that provides this technical assistance not only to NRA’s in WHO Member States but also to UN procurement agencies like UNICEF, PAHO and UNOPS. WHO advises on the safety and quality of vaccines through the vaccine Pre-Qualification scheme. In SEAR, WHO implemented the 5 steps NRA capacity building programme as a priority in vaccine producing countries including India, Thailand and Indonesia. Formal NRA assessments were conducted in the 3 countries and following the assessments, Institutional Development Plans (IDP) were developed and endorsed by the respective national governments. WHO supports Member States to implement their plans and provides support through training programmes for the NRA as well as technical assistance to develop and implement vaccine regulatory procedures. This capacity building programme has been recognized as highly successful with several success stories including:

- WHO developed a guideline for the production of Oral Polio Vaccine (OPV) from bulk supplied by a company and formulated and blended by another company. Three producers of OPV then implemented the guideline and became WHO Pre-Qualified for OPV. Today most of the OPV and monovalent (MOPV) used globally by polio eradication programmes are filled and formulated in India with most raw materials produced in Indonesia.

- Enforcement of GMP by NRA for vaccine manufacturing plants in producing countries. The portfolio of PQ vaccine products has significantly increased along with upgraded production capacity of SEAR vaccine manufacturers.

- India in partnership with Food and Drugs Authority of Canada has significantly strengthened the Market Authorization (MA) procedure through a parallel review of meningococcal vaccine and Thailand did a similar exercise with Australian FDA for the MA of Japanese Encephalitis (JE) vaccine. These activities are part of a package of new approaches and methodology to increase information exchange among regulators from high, medium and low income countries.

- A similar approach was also used in Bangladesh to strengthen Post Marketing Vaccine safety surveillance. A training workshop was organized on Adverse Effects Following Immunization (AEFI) monitoring, investigation and causality assessment followed by a formal meeting of AEFI causality expert group to review reports and conduct formal causality assessment and signal detection that occurred between 2009 and 2011 in Bangladesh.

- In the last five years, countries in SEA have enhanced their access to international expertise on vaccine pharmacovigilence and prominent regional experts on vaccine safety are now participating in several WHO global advisory committees.

- Regional Working Reference Standards established for the production of reference material for the testing of Pertussis and JE initially with India, with Indonesia and Thailand participating. In view of the growing production of vaccines in SEA this activity will expand in 2012-2013 to include China and Vietnam with Governments expressing their interest to join the network for the testing of increased number of vaccines.

These achievements are major milestones to establish a regional and global supply of assured quality vaccines but they remain fragile as demonstrated in 2011 with several products removed from the list of WHO PQ vaccines upon lack of compliance with WHO/International standards for quality system.

*With the courtesy of Bio Farma*
Technical and financial support needs for WHO NRA capacity building programme in SEAR countries 2012-2015

While progress in SEA vaccine producing countries has been measurable and encouraging, NRA’s still need continued support to sustain progress and address new regulatory challenges. The Bill and Melinda Gates Foundation (BMGF) is providing a five year Grant (2011-2016) to WHO for NRA capacity building in India and China. Funding from the grant is being used to implement the road map endorsed by the Government of India (GoI) in 2011, to enforce functions of the vaccine regulatory process. SEARO will contribute actively in coordination with HQ and WHO Country Office to implement the road map.

Although the Gates grant will be instrumental in building NRA capacity in India, its limited scope to support activities in one country in SEA, leaves a fundamental gap in other countries with the potential of influencing the global vaccines market supply. Other countries like Bangladesh, Indonesia and Thailand present various opportunities. Their needs for NRA capacity building are to consolidate, sustain gains and to institutionalize regulatory capacity building activities. With limited funding, SEARO has been able to coordinate and assist NRA’s to implement development plans and to respond to emerging vaccine regulatory needs. With additional funding to the Gates grant, SEARO will be able to provide technical assistance to ensure that vaccine producing SEA countries will have fully functional NRA’s to enforce vaccine safety, quality and efficacy in compliance with International/WHO standards, leading to an increase in the portfolio of vaccines of assured quality.

SEARO has a key role and is well positioned to continue to advocate with governments for sustainable medicines regulatory support and facilitate upgrading of NRA’s. SEARO will intensify its support for NRA’s and NCL’s to comply with regulatory standards by working closely with key government decision makers.

Another area of work which has become increasingly important is the need for non-vaccine producing countries in SEA to establish fast track licensing for UN procured vaccines. WHO has developed guidelines for assisting NRAs to license vaccines procured through UN agencies. In SEA, Bhutan, Myanmar, Nepal, Sri Lanka and Timor Leste procure vaccines through UNICEF supply division. The benefits to countries implementing these guidelines will be: quality assurance assessments, gains in product knowledge, efficient systematic process for releasing vaccines and the ability to respond rapidly with documented evidence on source of vaccine and quality assurance in case of adverse effects following use of the vaccine.

Addressing issues of AEFI associated with new vaccines have posed new challenges for immunization programmes. Newly introduced vaccines have high public expectations for safety and as surveillance systems have improved, health workers increasingly report minor side effects that were not reported previously with other traditional vaccines. Some instances have lead to immunization programmes being brought to a halt because of media and poor AEFI surveillance systems. SEARO plans to assist programmes and NRA/NCL to establish sound national policy for vaccine safety including surveillance systems to detect AEFI cases, improve management of cases and reporting of the same. Once AEFI systems are improved, focus will shift to regional and country capacity building for investigation and causality assessment.

These activities are part of the WHO SEARO Immunization and Vaccine Development (IVD) unit’s work plan and are in line with global strategic plans as part of VSQ support to countries. A concerted effort has been launched to mobilize resources through dialogue with multilateral, bilateral and private foundations in order to carry out the under-funded activities or for which no funding has been identified to date.
Funding requirements for WHO NRA capacity building programme in SEAR countries

Between 2012 and 2015 SEARO will lead work on NRA capacity building and vaccine safety strengthening in the region. In the VSQ technical unit, out of six posts in the HR plan for 2012-2013, one Technical position is funded with WHO funds and another with donor funding. To implement capacity building activities in the four areas of work of VSQ, an amount of USD 750,000 is required in 2012-2013 and USD 800,000 in 2014-2015.

There is no significant increase in the activity budget line during 2012-2013 and 2014-2015 biennium due to opportunities which will capitalize on synergies and building regional expertise and rational methodology with increase in cross-country activities like Market Authorization parallel reviews and regional expert committee of vaccine regulatory representatives from the region.

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<td>2012-2013</td>
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<tr>
<td>Activity support</td>
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