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Expert Committee Consultation to Develop a Fast-Track Mechanism for the Licensing of Vaccines Procured through UN Agencies

New Delhi, 13-15 September 2005

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EXECUTIVE SUMMARY

National Regulatory Authorities (NRAs) play a critical role in assuring the quality, safety and efficacy of vaccines, and their legal authorization for use. It is recognized that NRAs in many countries in the developing world do not meet expectations in this regard, even where medicines other than vaccines are adequately regulated.

Many countries without a functional[1] NRA procure vaccines through UN procurement agencies which supply vaccines only from the list of WHO pre-qualified products. Therefore, these countries use vaccines that meet international standards of quality, safety and efficacy. While the WHO pre-qualification procedure ensures that these vaccines meet WHO recommended standards it does not replace the oversight role of the NRA of the country that imports vaccines. WHO recommends that this NRA must have an independent and functional system that meets at least two functions[2] even if most of the vaccines are procured through UN agencies (eg. UNICEF, WHO/PAHO, etc). The marketing authorization and licensing activities that primarily ensure that proper product evaluation and facility licensing have been undertaken require a defined expertise that does not exist or is not developed in most developing countries. Registration and licensing procedures in countries that procure their vaccines mainly through UN agencies may follow a fast-track procedure. This procedure follows certain steps of product evaluation which are undertaken by the WHO prequalification (PQ) procedure. The aim of the fast-track procedure is two-fold: a) to comply with national regulations and international standards of product registration/licensing and b) to continue to provide timely access to EPI vaccines that meet assured quality standards.

In addition, immunization schedules are continuously being updated and adapted to new epidemiological situations and/or to introduce new vaccine products as they become available and affordable for public health programmes. Consequently, some vaccines are not used in some markets. For example, in industrialized countries, the whole cell pertussis vaccine is

[1] Definition of functional NRA : system independent and functional as assessed as per the WHO recommended functions (according to the main source of vaccines: Producing, Procuring or UN agency).

[2] 1) Marketing authorization (M.A.) and licensing activities, 2) Postmarketing surveillance including monitoring adverse events following immunization (AEFI)

either no longer used or no longer licensed or both, for their domestic market. As this is a critical product for immunization programmes in developing countries, WHO had concerns regarding its registration/ licensing and the sustainability of the global supply to the developing world. WHO has worked, with the European Agency for Medicinal Products (EMEA), on a regulatory pathway to regulate vaccines that are produced by EU manufacturers and not used in the EU market. This regulatory pathway will generate an EMEA "scientific opinion" that will allow the registration/ licensing of these vaccines in the absence of a formal EU Marketing authorization. The use of this new mechanism also requires that manufacturers monitor and report adverse reactions that could occur with the use of the vaccine. It is, therefore, extremely important that post-marketing surveillance of the efficacy and safety profile of the vaccine be conducted in the importing countries. Further strengthening of this expertise in countries actually using the vaccine is required.

Six SEAR countries[3] were selected for participation in this expert committee consultation aimed at identifying issues related to the registration and licensing of UN-procured vaccines and at formulating recommendations for developing a guideline that will help countries to meet international regulatory standards for the licensing of WHO pre-qualified vaccines procured either through UN agencies or directly. This expert consultation reviewed and detailed the modality of a "fast-track system" for the registration and licensing of UN-procured vaccines that can address the limited regulatory capacity of developing countries and ensure access to assured quality vaccines.

The guideline to establish a "fast-track system" for the registration and licensing of UN-procured vaccines is intended for all concerned NRAs, UNICEF, and vaccine manufacturers for the SEA Region with a view to extending this process to other WHO regions. The consultation was the first of its kind for vaccines.

[3] Bangladesh, Bhutan, India, Maldives, Nepal, Sri Lanka

1. OBJECTIVES AND EXPECTED OUTCOME OF THE CONSULTATION

The expert committee consultation was aimed at enabling the participating countries to review current WHO recommendations for licensing vaccines and to identify the steps required to be taken by the importing countries when the vaccines are procured through a UN agency through the following activities:

- Review of participating country's regulatory status regarding the marketing authorization (MA) and licensing activities
- Discussion and brainstorming on the constraints, strengths and options for developing and implementing a fast-track system
- Discussion of issues related to procurement of UN vaccines and impact of a registration/licensing system as recommended by WHO or international standards consistent with WHO recommendations
- Development of an outline of guidelines to fast-track registration/ licensing of UN- procured vaccines as per WHO recommendations on quality, safety and efficacy
- Development of a regional workplan as well as a national workplan for each participating country, with clear definition of national needs, and identification of any corrective actions necessary through training, and collaboration between countries and in conjunction with WHO, UNICEF and vaccine manufacturers
- Development of recommendations for the ongoing work, and to extend the initiative to other WHO regions.

A medium- to long-term additional objective of the consultation was to ensure that national regulatory capacity be developed in countries planning to license non-prequalified vaccines procured from countries with functional NRAs. Countries are expected to establish accredited scientific and technical review committees as well as research ethics committees to ensure competent data monitoring systems for Adverse Events Following

Immunization (AEFI) and compliance with principles of Good Clinical Practice (GCP) consistent with international ethics norms during clinical trials.

Each participating country was asked, prior to the consultation, to identify current vaccine regulatory challenges and specific issues to meet international standards: what is required in terms of personnel, institutional arrangements and training to achieve these international standards consistent with WHO recommendations. The consultation took the form of interactive presentations, plenary and group discussions. Opportunities were explored for long-term collaboration between countries in the Region based on the plans developed by country participants. Initiatives such ASEAN (Association of South East Asian Nations), DCVMN (Developing Country Vaccine Manufacturers Network), DCVRN (Developing Countries' Vaccine Regulators Network) were also presented and discussed.

The specific objectives of this expert consultation were 1) to develop an outline of a guideline that Member States can implement to register/license UN procured vaccines and meet international standards consistent with WHO recommendations and 2) to discuss the vaccine regulatory status of each participating country, with a clear definition of national needs, and identification of any corrective actions necessary through training, financing, and collaboration between countries and with WHO. During the course of the consultation, the following activities were carried out:

- Mapping of the current expertise and activities in the participating countries in the field of registration/licensing of vaccines according to their procurement system (UN, mixed or direct)
- For countries using UN-procured vaccines, to promote standards of scientific and technical evaluation
- To update all participating countries on the latest knowledge regarding regulatory practices and related issues, with particular reference to novel vaccines
- To identify short- and long-term activities necessary to address vaccine regulatory issues for marketing authorizations and licensing activities for UN-procured vaccines, and for licensing of new vaccines.

2. PARTICIPANTS

(a) Country participants

The following countries participated: Bangladesh, Bhutan, India, Sri Lanka, Nepal and Maldives. The Ministries of Health of the participating countries were requested to nominate the most appropriate participants according to the following profile: (i) representative of the national regulatory authority, with responsibility for vaccines and biologicals; (ii) a key person with knowledge of procurement and/or a representative from the national immunization programme.

(b) WHO facilitators and external participants

WHO/SEARO was represented by Dr Brent Burkholder, Mr Stephane Guichard and Dr Jaspal Sokhey.

WHO/HQ/FCH - Immunization, Vaccines and Biologicals was represented by Mr Lahouari Belgharbi and Dr Nora Dellepiane from the Quality Standards and Safety team (QSS) and Mr Miloud Kaddar from the EPI+ team.

The Developing Country Vaccine Manufacturers Network (DCVMN) was represented by Dr Suresh Jadhav from the Serum Institute of India (SII), Pune, India.

Dr Christopher Rolls from the Therapeutic Goods Administration (TGA), Canberra, Australia acted as WHO external facilitator.

The UNICEF Supply Division in Copenhagen was represented by Ms Elizabeth Molari, while International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) was represented by Dr. Anil Dutta from Sanofi Pasteur International, Lyon, France.

The expert committee consultation was inaugurated on 13 September by Dr. Samlee Plian bangchang, Regional Director WHO South-East Asia Region. In his address the Regional Director urged that mechanisms be developed for licensing vaccines which ensure vaccine quality. "At the same time, these mechanisms must not be a burden on the capacity of the regulatory system in your respective countries. Our common goal is to deliver safe, effective vaccines to children in need. Your task is to develop "fast-track" systems which satisfactorily address both these targets of quality and efficacy", he added.

DAY 1: SUMMARY PRESENTATIONS AND DISCUSSIONS

3. REGULATORY CHALLENGES FOR VACCINES INCLUDING NOVEL VACCINES: *DR. NORA DELLEPIANE*

In the past, vaccines were developed and used first in the industrialized world and gradually reached the developing world. Regulatory authorities in these countries based their decisions on those taken in the industrialized world. This paradigm is rapidly changing with markets in industrialized and developing countries diverging in the type of vaccines used. With this differentiation in vaccines used, some authorities in industrialized countries have decided not to license those vaccines that are not going to be used domestically (no license renewal when the existing licenses expire). Other authorities may be licensing for export purposes only, which implies that some of the post-marketing regulatory functions cannot be properly exercised (i.e. monitoring of the safety profile of the product).

In view of this new scenario, manufacturers are increasingly looking at developing countries to conduct clinical trials, to produce or finish vaccines (filling, packaging) and to distribute vaccines worldwide. Different approaches are taken such as joint ventures, installation of facilities by Industrialized Countries (IC) manufacturers in developing countries, etc. Furthermore, manufacturers in developing country are expected to increasingly take over the supply of traditional EPI vaccines and combinations and are working on the development of novel vaccines. For all of the above-mentioned reasons, authorities in developing countries are faced with fully regulating vaccines including the oversight of clinical trials that may be conducted in their countries.

The challenges faced by authorities in developing countries include limited expertise for the assessment of pre-licensure data, for the review of submissions for licensure purposes and for post-marketing oversight of the efficacy and safety profiles of these newly introduced products.

4. PROCEDURE FOR ASSESSING THE ACCEPTABILITY OF VACCINES TO BE SUPPLIED THROUGH UN AGENCIES: *DR. NORA DELLEPIANE*

WHO advises UNICEF and other UN procuring agencies regarding the acceptability in principle of vaccines from different sources for supply to these agencies. It provides an independent opinion or advice on the

quality, safety and efficacy of the vaccines. The goals of the existing procedure are to ensure that vaccines used in national immunization programmes are safe and effective and that they meet the specific needs of the programme, reflected by the tender specifications.

The procedure is based on the following principles: 1) reliance on regulatory oversight by the NRA in the producing country, 2) understanding of the production process and quality control methods, 3) ensuring production consistency through GMP compliance and testing of final product characteristics, 4) evaluation of clinical information to ensure safety and efficacy for the target population and 5) checking that it meets tender specifications. A pre-requisite for eligibility to undergo the pre qualification process is the assessment of functionality of the responsible regulatory authority. Once this is ensured, the evaluation procedure consists of three steps: review of a Product Summary File, checking consistency of final product characteristics and site visit to the manufacturing facilities. If the three steps are satisfactorily accomplished and depending on commitment by the manufacturer and regulatory authority to immediately communicate to WHO any problems with the product (adverse events, GMP non-compliance, etc.) the product is accepted and added to the WHO list of pre-qualified vaccines. The procedure includes continuous monitoring of performance in the field and reassessment at regular intervals.

5. LICENSING PROCESS AND EXPERIENCE FROM ASEAN COUNTRIES AND THERAPEUTIC GOODS ADMINISTRATION (TGA) AUSTRALIA :

DR. CHRISTOPHER ROLLS

In Indonesia, the establishment of regulatory functions on Marketing Authorization (MA) was initiated in 1971 and the country has a fully functional NRA. In 2000, in keeping with the trend towards global harmonization of regulatory issues, ASEAN began harmonization initiatives which include the development of a Common Technical Dossier, to be implemented in 2008.

The practical implementation of the WHO indicators and sub-indicators for licensing in Annex 1 was specifically illustrated through the demonstration of each factor with an example from the Australian licensing process.

6. NATIONAL REGULATORY AUTHORITY (NRA) STATUS IN SEAR: *MR. STEPHANE GUICHARD*

Member States in the South-East Asia Region (SEAR) present a varied pattern in terms of vaccine needs, vaccine financing and procurement policies. India, with a birth cohort of 25 million outstrips vaccine utilization compared to the other countries. Indonesia and Bangladesh are the two other countries with large populations and Maldives and Bhutan are countries with a population of less than a million each.

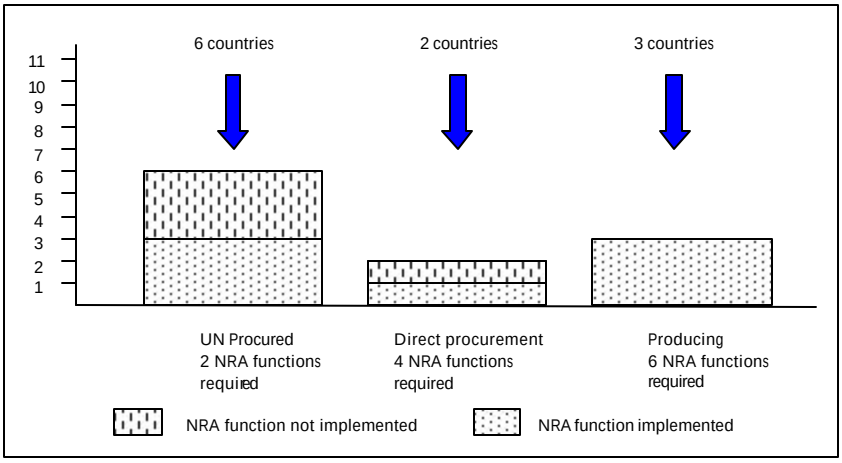
Of the 11 Member States in the region, six are self-reliant in financing their vaccine requirements. Among these, three rely on their domestic production, with India and Indonesia being major vaccine suppliers to UN agencies. Sri Lanka and Nepal procure vaccines through International Competitive Bids but their suppliers are limited to those that are WHO pre-qualified. India procures through a bid process but only local manufacturers are invited. Among seven countries that purchase UN supplied vaccines, Bangladesh and Nepal have established procurement services agreements that include handling charges and custom fees while the five other UN-supplied countries benefit from the UNICEF humanitarian assistance scheme that includes waiver of tax and handling charges. Financing sources and procurement policies are summarized in Table 1

Table 1: *Financing sources and procurement policies in SEA countries*

Country	Financing source	Procurement policy	Supply sources
Bangladesh	Domestic (WB loan)	UNICEF procurement agreement	Imported (WHO PQ)
Bhutan	External (donor)	UNICEF (Humanitarian assistance)	Imported (WHO PQ)
DPRK	External (donor)	UNICEF (Humanitarian assistance)	Imported (WHO PQ)
India	Domestic	Direct	Domestic
Indonesia	Domestic	Direct	Domestic (WHO PQ)
Maldives	External (donor)	UNICEF (Humanitarian assistance)	Imported (WHO PQ)
Myanmar	External (donor)	UNICEF (Humanitarian assistance)	Imported (WHO PQ)
Nepal	Domestic	Direct + UNICEF procurement agreement	Imported (WHO PQ)
Sri Lanka	Domestic	Direct	Imported (WHO PQ)
Thailand	Domestic	Direct	Domestic + imported
Timor-Leste	External (donor)	UNICEF (Humanitarian assistance)	Imported (WHO PQ)

Country vaccine procurement policies have a direct impact on regulatory requirements to ensure the safety, quality, and efficacy of vaccines. Between 1999-2003, WHO conducted assessments of all National Regulatory Authorities in SEAR countries. Following each assessment, country institutional development plans were developed and implemented. NRA staff participated in a GTN course on vaccine regulation and in-country technical assistance was provided to strengthen particular functions such as AEFI monitoring and GMP. NRA status in SEA countries is displayed in Figure 1. I am surprised to see that al three producing countries fulfill all functions as Thailand does not according to the last assessment in 2003.

Figure 1: ***NRA status in South-East Asia countries in 2005***



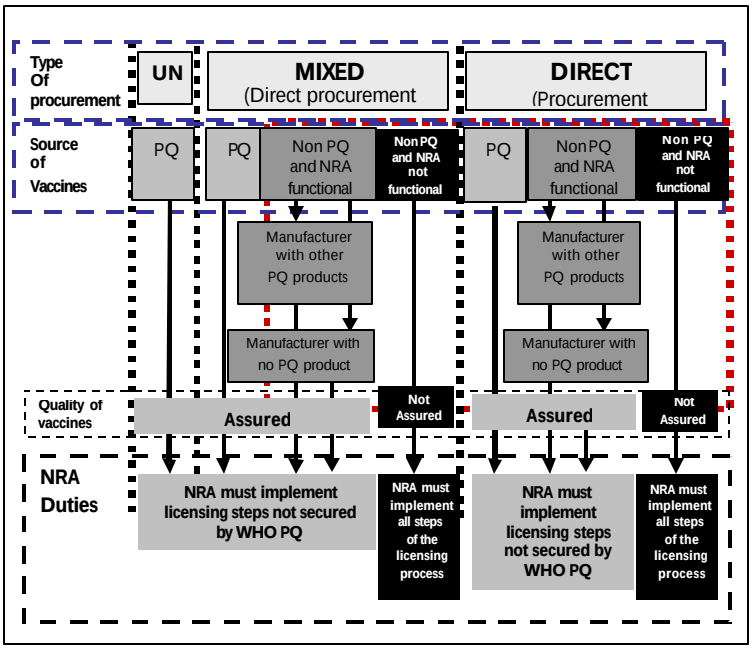
7. FAST-TRACK SYSTEM AND SCENARIO OPTIONS FOR UN PROCURED VACCINES AND VACCINES PROCURED OUTSIDE UN PROCUREMENT SYSTEM FROM COUNTRY WITH FUNCTIONAL NRA*:*

MR. LAHOUARI BELGHARBI, AND GROUP WORK

Scenarios of the various procurement options including UN procurement, Mix procurement and direct procurement was presented and discussed (See figure 2). Different options for using a fast-track system for their licensing were discussed. The third option where vaccines are procured from country with a non- functional NRA and with no information about the quality of the product was dismissed as such sources were not

considered to be of assured quality. Both options, UN procured and mixed procurement where vaccines could be procured from a country with a functional NRA either from a manufacturer with no prequalified products or from a manufacturer that may have other prequalified products (but not the product in question) were considered as meeting the assured quality definition. For these two viable options discussion of a fast-track system and relevant functions were discussed among participants and further developed in the subsequent sessions.

Figure 2: ***Procurement policy and NRA responsibilities***



DAY 2: SUMMARY PRESENTATIONS AND DISCUSSIONS

8. DEVELOPING COUNTRY VACCINE MANUFACTURERS NETWORK: *DR. SURESH JADHAV*

What is the Developing Country Vaccine Manufacturers Network (DCVMN) and its objectives?

Dr S. S. Jadhav, President, DCVMN presented Network's objectives, and its perspective on regulatory requirements for licensing.

DCVMN was established in 2000 as an initiative of WHO. The main mission was to provide quality vaccines at affordable prices to the developing world, to supply vaccines in which industrialized countries have limited interest, and to obtain recognition that DCVMN members have an essential role in assuring quality and availability of vaccines to immunize every child.

Currently, DCVMN has 29 member producers from all over the world, and four resource institutes to provide training, technology transfer, and advice (NVI, PATH, IVI, NIH). The majority of vaccines procured by UN agencies are from the network members who are pre qualified. Some of the newer combination and conjugate vaccines are in development and will be available in the near future.

DCVMN members are part of the global vaccine community and supply vaccines all over the globe. They seek help from WHO and other UN agencies regarding finance, Intellectual Property Rights (IPR) issues, access to new technologies, help to design clinical trials, and fast-track procedures for licensing and testing of vaccines, and suggest that this could be done by recognizing regional authorities and laboratories to perform this function.

Thus, by recognizing the technical capability, trained manpower, and cheap resources of DCVMN, they can participate in the development of new vaccines, pandemic vaccines, vaccines in shortage, for which they will need encouragement from international agencies both financially and technically.

The move to develop a fast-track licensing process for UN-procured vaccines will certainly help DCVMN members to continue to move forward.

9. NOVEL VACCINES AND DEVELOPING COUNTRIES VACCINE REGULATORS NETWORK: *MR. STEPHANE GUICHARD*

The introduction of novel vaccines like rotavirus, papillomavirus, pneumococcal conjugate, etc. raise several challenges for licensing and clinical trial procedures.

(a) Licensing challenges

Manufacturers in European countries producing novel vaccines needed in developing countries but which are not used in their domestic markets will not be able to license such vaccines in Europe. Hence, the European Medicines Agency (EMEA) has developed, in collaboration with WHO, and to serve the needs of public health in developing countries, an alternative regulatory pathway which involves a product evaluation that mimics the centralized procedure for licensure except that the outcome would not lead to a marketing authorization but to a "Scientific Opinion (SO)" on the licenseability of the vaccine.

The SO procedure would be handled in the same way as the centralized procedure for licensing of pharmaceuticals in the European Union. There is a provision for inviting experts recommended by WHO to evaluate specific aspects of the dossiers, particularly the clinical aspects. WHO will also be invited to send a representative as an observer to the Committee for Medicinal Products for Human Use (CHMP) meeting that will discuss the outcome of the evaluation and will decide whether the SO can, or cannot, be granted. As part of the post-marketing activities to be conducted by EMEA, the European authorities commit (in the case of vaccines) to perform batch release for UN-supplied vaccines. As there will be no marketing authorization in the Community, the rules for batch release do not apply. However, in this case as well, they will follow exactly the same procedure (protocol review and testing) and will issue a "Certificate of compliance" This certificate will be issued in most cases by the Official Medicines Control Laboratory (OMCL) of the relevant producing country, but there may be exceptions. An interesting advantage of the new procedure is that any manufacturer can apply from within or outside the Community as long as it has a representation in the European Union. Concerning post-marketing surveillance, the EMEA will make the granting of the Scientific Opinion conditional to the manufacturer's commitment to conduct active surveillance for AEFI in countries purchasing the vaccine directly. For UN-supplied vaccines, WHO is considering the possibility of establishing agreements with countries that have good surveillance systems to perform active surveillance of novel vaccines at least in the early stages of their supply.

b. Clinical trials

Manufacturers in industrialized countries conduct clinical trials in developing countries because the novel vaccines being developed are to prevent diseases that occur mostly in developing countries. (They also do it

to extend their markets and because it is often cheaper and less complicated, and they may do it for vaccines that might not be intended for use in that developing country, for example, for initial dose ranging studies, etc.). During vaccine development, clinical trials might be conducted in any country irrespective of the expertise/strength of their National Regulatory Authority (NRA). The selection of the country depends on the epidemiological rationale and logistical feasibility of running trials. However, most developing countries do not enforce Good Clinical Practices, resulting in the possibility of different trial standards and practices in each country. To rationalize and harmonize clinical trials in developing countries, WHO established in 2005 the Developing Country Vaccines Regulators Network (DCVRN) with the objective to promote the strengthening of the procedures for monitoring and evaluation of clinical trial protocols, clinical trial performance and clinical trial data. Actually, this is not the issue. The issue is that in cases where the clinical trial data will never be used in support of licensing in a country with a well-functioning NRA, there may be no regulatory review of the trial at all, and even if there is, it could be after the fact. The country eligibility criteria includes:

- The country has a producer of WHO pre-qualified vaccines
- The NRA is functional (meets the six critical regulatory functions or has a government endorsed workplan with timelines to achieve this)
- There is domestic expertise in research on new vaccines and combination vaccines
- There are recognized medical institutions for clinical research on the control of infectious diseases in the country.

The DCVRN is constituted of nine countries, namely; 1) Brazil, 2) China, 3) Cuba, 4) India, 5) Indonesia, 6) Korea, 7) Russia, 8) South Africa, and 9) Thailand. At this initial stage, the DCVRN has been assigned to address the following issues:

- Development of procedures, checklists for review and approval of clinical protocols
- Development of guidelines for review of clinical trial data protocols for monitoring clinical trials, etc.
- Discussion on regulatory considerations for the evaluation of clinical data for new vaccines (i.e. rotavirus, HIV, HPV, etc.)
- Assistance to other countries in the evaluation of clinical data of novel vaccines

10. VACCINE MARKET TRENDS AND SOURCES:

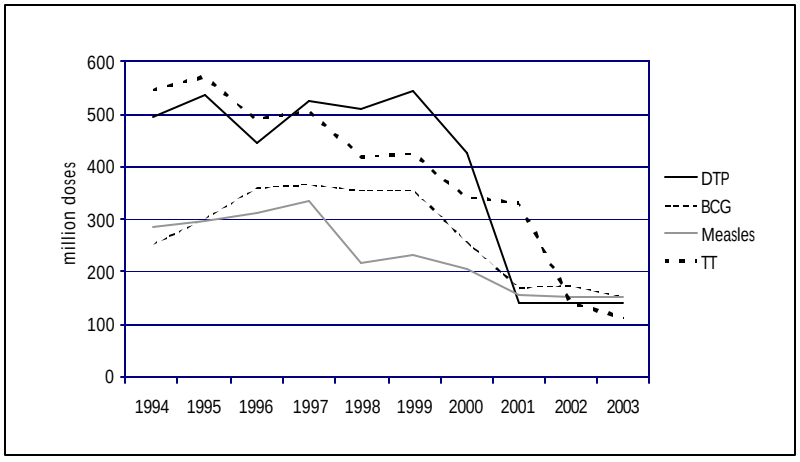
MS. ELIZABETH MOLARI

UNICEF's involvement in the vaccine market relates to buying 40% of the global volume of vaccine doses, mainly basic vaccines, but representing only 5% of the total market value. In 2004, UNICEF bought around 2.8 billion doses of vaccines for a total value of approximately 370 million USD.

The vaccine market has undergone significant changes in the last few years. Shortages of traditional EPI vaccines began to emerge in the late 1990s due to a number of converging factors. New, more sophisticated and more expensive vaccines were introduced in industrialized country markets. Up to that point, children in both developing and industrialized countries received the same vaccines.

As long as industrialized and developing countries gave the same vaccines to their children, it was possible for UNICEF to procure vaccines at low prices, because industrialized country markets paid higher prices for those vaccines and passed on a price advantage to developing country markets. With industrialized countries now buying new vaccines, the low prices at which UNICEF had been able to buy traditional vaccines were threatened. Vaccine manufacturers began phasing out the production of the traditional, less expensive vaccines used in developing countries.

Figure 3: ***The doses of basic vaccines offered to UNICEF dropped significantly at the end of the 1990s***



A new paradigm can be seen in the vaccine supply market. More than 20 new vaccines are currently under development and some of these will be for diseases that affect developing countries only. The trend of manufacturers to cease or greatly reduce production for developing countries has been reversed. This type of investment and activity is unprecedented in this market.

In 2004-2006, there have been significant improvements in vaccines availability but the market is still considered to be fragile.

DAY 3: SUMMARY PRESENTATIONS AND DISCUSSIONS

11. UNITED NATIONS PROCUREMENT SYSTEM (EXAMPLE OF UNICEF SUPPLY DIVISION PROCUREMENT PROCESS): *MS. ELIZABETH MOLARI*

(a) UNICEF Procurement Process

The objectives of UNICEF's vaccine procurement system are as follows:

- Ensure an uninterrupted, sustainable supply of affordable, quality vaccine: Vaccine Security
- Ensure continuous and effective communication with vaccine manufacturers
- Consolidation of Long-Term Strategic Procurement and Relationships with manufacturers
- 'Most Favoured Nations' pricing for poorest countries
- Compliance with Vaccine Procurement Principles
- Compliance with UNICEF's Financial Rules and Regulations
- Compliance with Public Procurement Principles

There are several steps in the procurement process:

- Definition of the demand
- Invitee list
- Pre-tender meeting

- Issuance of tender
- Tender type – Request for Proposal (RFP)
- Tender document structure
- Technical review of proposals
- Commercial review of proposals
- Clarifications and negotiations meetings
- Evaluations
- Recommendations for award
- Review/approval of recommendations
- Notification of awards to those submitting proposals
- Establishment of contracts

(b) UNICEF 2007-2009 vaccine tender plan

June – November 2005

Review and development of:

- Strategy
- Quantities
- Commercial and Technical Terms and Conditions through discussions with partners, messaging to manufacturers and discussions with advisers

December 2005

- Pre-tender meeting with manufacturers:
- Present tender process, terms, quantities, etc. to manufacturers
- Programme (WHO, UNICEF) and Quality (WHO) participate
- Manufacturers provide feedback
- Adjustments are made

Early February 2006

Tender Issuance

End March 2006

Closing of Tender

April – July, 2006

Evaluation and Negotiation

August – September 2006

Issuance of awards, debriefings

January 2007

Deliveries commence

12. PROCUREMENT OF VACCINE FOR PUBLIC SECTOR:

MILOUD KADDAR

(a) Brief summary on group procurement of vaccines

Procuring and purchasing pharmaceuticals, vaccines and other health commodities is a considerable and growing challenge, especially for low and middle-income countries. The situation with vaccine procurement is especially acute. As donor agencies have increasingly targeted the poorest countries – for example, the Global Alliance for Vaccines and Immunizations (GAVI) and its Vaccine Fund are limited to countries with a gross national income per capita of $1,000 or less – more and more countries are dealing directly with the global vaccine market. In this market the number of large, well-known vaccine producers in the Western economies has reduced dramatically to focus mainly on new, expensive and sophisticated vaccines while more and more emerging suppliers are becoming significant actors in supplying the public vaccine market (both UNICEF-PAHO markets and developing countries). These forces can result in new opportunities and challenges but also in the consequent problems of high or unpredictable prices and irregular supplies from manufacturers. In addition to these market challenges, national immunization programmes must often cope with the irregular release of government funds for vaccines, budget shortfalls, limited in-country capabilities in vaccine procurement, regulation and management.

These issues in vaccine procurement are likely to grow, as new, sorely needed but likely more expensive vaccines, such as rotavirus, papillomavirus, pneumococcal conjugate, and later, HIV/AIDS and malaria vaccines, become available.

One way that countries can address these challenges is to join a regional group or group procurement mechanism. The concept of group purchasing for pharmaceuticals or vaccines has garnered increasing interest in recent years. The establishment of regional pooled procurement schemes for selected essential drugs and vaccines is being explored in Africa, and in Middle Eastern countries and in the South/South-East Asia Region. The feasibility of group procurement for vaccines is also being explored among Central and Eastern European countries and South-East Asia countries. Group procurement is viewed as a potential means of increasing competition among suppliers, reducing prices, increasing transparency in the procurement process, ensuring quality, and improving the regularity of supply of essential products to countries. Via price reductions accomplished in part through economies of scale, group purchasing can also potentially enable countries to introduce newer, more expensive products at an earlier stage than they would be able to on the open market.

The presentation reviewed the potential models and stages of group procurement mechanisms, identified advantages and obstacles to set up an intercountry system and described the potential for such an activity in SEAR countries. Regulatory issues were also discussed and clarified. In the short term, Maldives and Sri Lanka are interested and started identifying the practical arrangements to be made to start an initiative of group procurement in 2006. WHO/SEARO, as part of its strategy to improve access to high quality vaccines at affordable prices, is committed to support group procurement mechanisms tailored to the national regulatory and financing capacity of participating countries.

13. STATUS OF REGISTRATION SYSTEM IN COUNTRIES:

GROUP WORK

Country	All vaccines (not including UN vaccines)	UN-procured vaccines	Comments/remarks
Bangladesh	➢ Free sales certificate (CPP)	➢ Lot/batch certificate of the exporting country ➢ WHO prequalified list	➢ Waiver by a expert committee
Bhutan	➢ No registration for drugs	➢ No registration for any vaccines; however all vaccines will be registered. ➢ No documentation required as EPI is using only WHO prequalified vaccines ➢ Lot release certificate received	➢ NRA not functional, established in 2003. Drug Law revised and not yet issued and enforced. Waiver by board for emergency; howe ver there will be no waiver.
India	➢ Import license ➢ Full dossier ➢ Testing protocol ➢ Testing ➢ Lot release certificate of the exporting country ➢ Summary lot protocol ➢ Fees	➢ Same standards apply; however there is a waiver provision that may be applied in case of "public health, priority", etc	➢ AEFI weak, monitoring clinical trials sites for new vaccines. Waiver by DCG(I)
Maldives	➢ Any medicine must be registered; however for public use there is a waiver ➢ If no information, Govt. will take decision to use the product	➢ As for drugs, but no vaccines are registered ➢ Use only WHO prequalified sources ➢ Batch release certificate and summary lot protocol	➢ Lack of capacity to evaluate, legislation needs to define these functions, more networking among countries. Waiver by Ministry of Health, advice by a advisory expert committee
Myanmar	➢ All vaccines should be registered ➢ Import license ➢ Full dossier ➢ Testing protocol ➢ Quality control ➢ Fees	➢ No registration required	➢ No batch release. Waiver by the MoH, opinion/advice by a technical committee.
Sri Lanka	➢ All vaccines must be registered ➢ Lot release ➢ CPP (free sale certificate) ➢ SOP ➢ Testing protocol ➢ Quality control ➢ GMP certificate ➢ Fees	➢ Registration required ➢ For EPI, WHO prequalification mandatory ➢ No fees ➢ No objection clearance (for emergency or humanitarian aid) ➢ Same as for other vaccines	➢ Issue with scientific opinion, need to amend the existing regulation, norms for evaluation process. There is no provision for waiver in the drug act. NRA. Director General of services.

14. OUTLINE TO DEVELOP GUIDELINE FOR UN-PROCURED VACCINES: *MR. LAHOUARI BELGHARBI, AND GROUP WORK*

Participants reviewed WHO's recommended indicators for licensing and identified those which involved the NRA directly, those which are covered by the prequalification procedure (PQ) and those which are the shared mandate of the NRA and WHO PQ. The outcome of this session is displayed in Table 3.

Table 3: *Source of information/guidance to implant WHO recommended indicators for licensing*

Source of information and/or guidance	The nine WHO indicators for vaccine licensing								
	1. MA system established and operational	2. Submission of MA applications	3. Assessment of MA applications	4. Appropriate assessment expertise	5. Same criteria/ standards for evaluation of MA applications regardless of the source	6. GMP assessment in MA process	7. Requirement for variations to be submitted and assessed	8. Clear and comprehensive approval information on authorized products	9. List of authorized products and companies.
WHO PQ									
NRA									
Shared NRA/PQ									

15. SCENARIO 1 - FAST-TRACK SYSTEM FOR UN SUPPLIED VACCINES: *MR LAHOUARI BELGHARBI AND DR CHRIS ROLLS*

National Regulatory Authority (NRA) responsibilities	Procurement agency (eg. UN agency) responsibilities	WHO responsibilities
Registration ➢ Amend regulation to allow "fast-track" registration of UN supplied vaccines ➢ Submission mechanism to be proposed (address to whom, number of copies, point of contact etc.) ➢ Applied only to WHO prequalified vaccine products	➢ Inform country that WHO/UNICEF recommend fast-track registration for UN vaccines. ➢ Develop, in coordination with WHO, a schedule of	➢ Draft guidelines including a common process and format for issuing registration certificate (by February 2006) ➢ Consultation,

National Regulatory Authority (NRA) responsibilities	Procurement agency (eg. UN agency) responsibilities	WHO responsibilities
➢ Required documentation ➢ Lot release certificate and Summary Protocol for three consecutive batches ➢ Information on proposed Vaccine presentations (container, label, leaflet, etc.) **Other conditions** ➢ No customs or VAT fees on vaccine imported as UN supplies for humanitarian assistance. ➢ Timeframe; as per published submission schedule for UN procurement agency ➢ License duration; as per UN contract with UN supplier vaccine manufacturer. ➢ NRA response period; 15 working days from receipt of complete documentation. ➢ License conditions; certificate will specify ONLY UN Supply ➢ In case of rejection; reasons for rejection, opportunity for manufacturer to respond, reconsideration mechanism.	submission of "fast-track" registration application ➢ Adopt WHO recommendations on fast-track system to register UN vaccines ➢ Provide guidelines when initially applied	finalization, and publication on WHO website (Q2 2006) of guidelines and proposed schedule for submission of "fast-track" applications ➢ List of NRA contact details for "fast-track" applications ➢ Explore possibility to publish NRA status for assessed countries
Check documentation for completeness ➢ UN procured vaccine? Check pre qualification status (WHO Web-Site) ➢ Check authenticity of documents ➢ Checklist of content ➢ Product name and presentation, applicant details ➢ Lot release certificate and summary protocol for 3 consecutives batches ➢ An example of the Vaccine presentation - Container - Label - Leaflet **Review of submitted Certificates, Protocols, presentations** ➢ Lot Release Certificate (x 3) ➢ Relevant Authority		

National Regulatory Authority (NRA) responsibilities	Procurement agency (eg. UN agency) responsibilities	WHO responsibilities
➢ Cross-check that they match Summary Lot Protocols **Summary Lot Protocol (x 3)** ➢ Review specifications against appropriate TRS **Vaccine presentation** ➢ Review leaflet against Model Insert ➢ Review label and inner box against appropriate TRS ➢ Review sample, label, and inner box for consistency and match description on supplied Summary Lot Protocols ➢ Vaccine Vial Monitor (VVM) ➢ Does the type(s) of presentation match the application form? ➢ Report based on this review – indicate compliance/non-compliance ➢ Issue Certificate ➢ Add to List of Authorized Products		

16. SCENARIO 2: ASSESSMENT CHECKLIST FOR VACCINES PROCURED FROM A COUNTRY WITH FUNCTIONAL NRA (IN ADDITION TO REQUIREMENTS FOR FAST-TRACK): *MR. LAHOUARI BELGHARBI AND DR. CHRIS ROLLS*

National Regulatory Authority (NRA) responsibilities		
➢ Registration Fee (Optional) ➢ Confirmation of NRA competence (assured by PQ status) ➢ Provided by manufacturer - NRA competence (for non-PQ) [date and result of WHO assessment] Just a question – will manufacturer be able to access this information as it is meant to be confidential?		

National Regulatory Authority (NRA) responsibilities		
- GMP Certificate from country of origin • Optional – Inspection report • Inspection only if necessary and have expertise ➢ Licensing status elsewhere - Country of origin - Other competent countries - Regulatory history (e.g. date of first registration, major updates, recalls) - Certificate of Free Sale - Recognition of another NRA License		

RECOMMENDATIONS AND FUTURE WORKPLAN

The following recommendations were made at the consultation :

17. PRIORITY ACTIVITIES – *PLENARY*

- WHO to recruit a specialist in vaccine licensing to develop guidelines for the licensing of UN-procured vaccines (end of December 2005)
- Submit draft guidelines to expert group committee and other task forces involved in harmonization of vaccine procurement (i.e. Association of South East Asian Nations) by end of February 2006
- Finalize guidelines by May 2006
- Implement guidelines staring August 2006 in priority countries (Myanmar, Bangladesh, Bhutan, Maldives and Bangladesh).
- Maldives and Sri Lanka to finalize agreement on Group Procurement: Memorandum of understanding between Sri Lanka and Maldives
- SEARO to conduct an investigation on favourable factors and potential obstacles to setting up a broad Group Procurement in the Region, April 2006

18. STRATEGIC CONSIDERATIONS – *PLENARY*

(1) SEARO to support countries in harmonizing their legislation and practices in licensing vaccines and selecting suppliers of assured quality vaccines.

(2) Through DCVRN, encourage mutual recognition of licenses to facilitate access to vaccines of assured quality

(3) Establish NRA forum in the Region to share data on vaccine safety profile and emerging vaccine regulatory issues.

19. ONGOING ACTIVITIES – *PLENARY*

(1) NRA assessment follow-ups to be conducted in 2006-2007 to monitor achievements regarding vaccine regulatory issues

(2) Training of NRA experts on clinical trials, quality control of conjugated vaccines and biological standardization.

(3) Regional working reference reagents for JE and pertussis vaccine established

(4) Conduct GTN course with Central Drugs Laboratory (CDL), Kasauli, India, on vaccine lot release

(5) WHO assessments and training activities to improve national and regional procurement capacities

(6) UN to inform countries of other Group Procurement experiences and draft guidelines based on best practices.

Annex 1

PROVISIONAL AGENDA

Expert Committee Consultation to develop a fast-track mechanism for the licensing of vaccines procured through UN agencies
WHO/SEARO, New Delhi, 13-15 September, 2005

Day 1 – Tuesday, 13 September 2005

Time	Session	Presenter
0830-0900 hrs	Registration	SEARO IVD
0900-0930 hrs	Opening session	SEARO IVD RD
0930-0940 hrs	Group Photograph	
1000-1030 hrs	Welcome remarks ➢ Presentation of the agenda ➢ Adoption of the agenda ➢ Open question time to chair and the secretariat ➢ Nomination of chairman and rapporteurs	IVD, HQ/ATT Chairperson
1030-1300 hrs	Global and regional issues for NRA systems: Licensing of WHO pre-qualified vaccine	
	Objectives and expected outcome of day 1 session	Chairperson
	Regional and country status	
	Country procurement policies and NRA status	S.Guichard, WHO/SEARO
	Regulatory challenges for vaccines including novel vaccines	N.Dellepiane, WHO/HQ
	Discussions: What are the above challenges that can be addressed by the countries, list constraints and issues for the countries	Plenary
	Ensuring quality of vaccines used in National EPI	

	WHO pre-qualification process –the process and expertise used, pre and post evaluation including NRA assessment	N.Dellepiane, WHO/HQ
1400-1530 hrs	Licensing process and experience from ASEAN countries and TGA Australia	Chris Rolls TGA Australia
	Brainstorming: Identify key elements that remain the responsibility of the NRA of the importing country	Group Discussions
1600-1700 hrs	**Brainstorming:** How will countries comply with the WHO recommended regulatory functions and their specific licensing system components in a "Fast-track" process	Group Discussions
	Recommendations (wrap up) for NRA to license vaccines procured through UN agencies in a "Fast-track" process	Plenary
1700 hrs	**Closing day 1**	

Day 2 – Wednesday, 14 September 2005

0830-0900 hrs	Objectives and expected outcome of day 2 session	Chairperson
0900-1030 hrs	Licensing of vaccines for countries that have mixed procurement system (including UN procured vaccines)	
	What is Developing Country Vaccine Manufacturers network (DCVMN) and its objectives?	DCVMN rep
	Scenario for mixed procurement systems (including UN procured vaccines)	L.Belgharbi, WHO/HQ
1100-1300 hrs	Brainstorming :	
	How will countries comply with the WHO recommended regulatory functions and their specific licensing system components	Group discussions
1330-1530 hrs	Licensing of novel vaccines:	
	➢ Issues with novel vaccines ➢ WHO response: Developing Country Vaccine Regulatory Network (DCVRN)	S.Guichard, WHO/SEARO

	Brainstorming: How will countries license novel vaccines?	
1600-1730 hrs	Recommendations:	
	For countries that have a mixed procurement system (including UN procured vaccines)	
1730 hrs	Closing Day 2	

Day 3 – Thursday, 15 September 2005

0830-0930 hrs	Objectives and expected outcome of day 3 session	Chairperson
0930-1030 hrs	Global and regional issues: UNICEF procurement system and vaccine group procurement mechanisms	Ms.E.Molari, UNICEF, Supply division Copenhagen
	UN procurement system; UNICEF procurement systems, vaccine sources and trends.	
	Vaccine market trends	M.Kaddar, WHO/HQ
	Example of different group procurement mechanisms: advantages and disadvantages	
1100-1130 hrs	Discussion:	Plenary
	How can countries benefit from group procurement	
	What are the regulatory implications?	
	Recommendations on procurement	Plenary
1130-1300 hrs	Final recommendations and action plan	Chairperson and rapporteurs
1400-1430 hrs	Closing of the Expert Committee	

Annex 2

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