

**Any way you look at it...
vaccine quality is critical**



**World Health
Organization**

WHO: ensuring vaccines of assured quality

Recent progress in vaccine development and use has given great cause for optimism in further reducing disease and death through vaccination. According to estimates generated by the World Health Organization (WHO) Immunization Department, immunization could be preventing 4-5 million child deaths per year by 2015. The vaccine pipeline is robust, as many vaccines holding great life-saving potential are now available for use or undergoing testing in late-stage clinical trials. Vaccination coverage is steadily increasing with 81% of infants having received three doses of diphtheria-tetanus-pertussis vaccine in 2007. Innovative funding mechanisms, coupled with unprecedented levels of funding, serve both as an incentive to vaccine manufacturers and an essential element in improving immunization coverage across the world.

These successes, however, come with challenges: generating the standards to which vaccines of assured quality and safety must comply; ensuring that all people of the world have access to the full range of quality vaccines that will protect them against the diseases from which they are most at risk; and effectively managing the vaccine safety concerns that can now cross the globe in minutes.

WHO is working with its Member States and immunization partners to ensure that these challenges are met.

Ensuring access to vaccines of assured quality is a critical component of the *WHO/UNICEF Global Immunization Vision and Strategy*.

Generating vaccine standards

Ensuring that appropriate, internationally agreed, technical specifications for vaccines are developed and available to countries in a timely and efficient manner is a core function of WHO. Established through the work of WHO's Expert Committee on Biological Standardization, written standards – which are essentially specifications for how vaccines should be produced, and how they should be tested, both in the laboratory and in human clinical trials – serve as guidance to national regulatory authorities (NRAs) and vaccine manufacturers. Standard vaccine preparations are also established by the Committee and provide the basis for the laboratory comparison of vaccines worldwide. In recent years, increasing efforts have been made to ensure that countries across the world are aware of, understand and comply with these standards.

This publication was produced by the World Health Organization Department of Immunization, Vaccines and Biologicals.

It is available on the Internet at: http://www.who.int/immunization/newsroom/key_immunization_resources/en/

Printed: May 2009 in Switzerland
Photography: www.istockphoto.com/www.shutterstock.com/www.phototakeusa.com
Design and layout: www.allmeo.com

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Ensuring access to quality vaccines and immunization equipment

WHO approval - increasing the supply of quality vaccines and facilitating market efficiency

Set up over 20 years ago, WHO's "seal of approval" (prequalification) is a mechanism for ensuring that all countries can be supplied with vaccines of assured quality.

The process is as follows:

1. a manufacturer sends in an application for the evaluation of a specific vaccine;
2. the WHO evaluation team scrutinizes information on production methods, vaccine composition, quality control and clinical evaluation;
3. the vaccine is independently tested for consistency by WHO-qualified laboratories; and
4. site visits of manufacturing facilities are carried out by WHO experts.

All vaccines which obtain WHO prequalification undergo random testing and reassessment at regular intervals to ensure continued compliance with requirements. Only vaccines manufactured in a country with a functional NRA can be prequalified.

All prequalified vaccines can be supplied to countries through United Nations agencies or procured directly by countries. The system helps developing country producers play a greater role in global vaccine supply. Increased competition created by additional manufacturers also benefits purchasing countries by driving down prices.

More than 20 manufacturers have vaccines which are prequalified by WHO; about half of them are based in developed countries and half in developing countries.

The prequalification programme must continually evolve in order to keep pace with the growing number and complexity of applications being submitted year after year. A number of measures have been taken to meet the demand in a timely manner. The prequalification process takes on average 18 months. Fast-track procedures can be implemented under special circumstances, such as disease outbreaks or an acute shortage in global vaccine supply.



A parallel system for immunization equipment

A similar process to that which exists for vaccines is in place for immunization equipment. Established in 2005, the Performance, Quality and Safety system provides an assurance of the quality of the manufacturing process of the product and adherence to WHO performance specifications. Products submitted to WHO for prequalification undergo a rigorous evaluation process, with those which meet all criteria listed on the WHO web site. Manufacturers can submit applications for evaluation of injection devices, temperature monitoring devices, and cold chain and waste management equipment.

Working towards first-class regulatory systems in all countries

Effective regulation of vaccines is another means by which access to vaccines of assured quality can be improved. Recognizing that many countries lack the resources to undertake this role, in 1997, WHO launched an initiative to strengthen under-performing NRAs. The work involves collaboration with regulatory authorities to identify strengths and weaknesses in assessing vaccines for safety, quality and efficacy. Priorities are then defined and a development plan, which includes training and technical support, is drawn up. Reassessment to determine progress

generally takes place within two years. Priority is given to countries with vaccine manufacturers.

Another aspect of efforts to strengthen regulators at country level, particularly in developing countries, relates to clinical trial oversight. Increasingly, vaccines are being developed to protect against diseases that are endemic in developing countries. To ensure suitability for introduction into immunization programmes, clinical trials must be undertaken in the target countries. The NRA of the trial host country is responsible for authorizing and monitoring such trials. Until recently, however, many developing countries had limited experience in this area.

In 2002, WHO began working to address this gap through the creation of networks. Through such mechanisms, NRAs in developing countries with a need to build competence in clinical trial oversight meet with and learn from other experienced NRAs, vaccine developers and sponsors of clinical trials. The first network that was established was the Developing Countries Vaccine Regulators Network. It is global in scope, with representation from Brazil, China, Cuba, India, Indonesia, the Republic of Korea, the Russian Federation, South Africa, and Thailand. Expansion of membership to other developing countries is under consideration. Topics addressed at the network's biannual



meetings include issues relating to candidate vaccines against human papillomavirus (HPV), rotavirus, typhoid, Japanese encephalitis, tuberculosis, HIV/AIDS, and dengue. Also discussed at length are general regulatory procedures applicable to the oversight of clinical development of new vaccines.

In 2006, a regional network called the African Vaccine Regulatory Forum (AVAREF) was created. Clinical trials of vaccines against diseases including tuberculosis, malaria, meningitis, and HIV/AIDS, are under way in many of the 19 AVAREF countries, where regulatory oversight is weak or altogether absent. As well as providing assistance to countries in building regulatory capacity, AVAREF is now driving harmonization of regulation of clinical trials of medicines in the region and is establishing a system integrating ethical review, regulation and registration of clinical trials in Africa.

Managing vaccine safety concerns

The ease and rapidity with which information on vaccine safety concerns spreads across the world has meant that all those involved in immunization programmes are giving increased attention to effective management of adverse events following immunization (AEFIs). The impact on vaccination

coverage, if not effectively dealt with, can be swift and bring disastrous consequences.

WHO's efforts to effectively manage such concerns include coordinating scientific review of vaccine safety issues, assisting countries to establish and improve their systems for monitoring and managing adverse events, and providing support for AEFI investigations.

Reviewing the scientific evidence

For the last ten years, acknowledged experts from around the world meet twice a year as WHO's Global Advisory Committee on Vaccine Safety (GACVS) to consider all available evidence relating to vaccine safety issues of potential global importance. The breadth of topics on which the GACVS has issued conclusions and recommendations — through its multilingual web site — is wide, and includes the safety of HPV vaccines, allegations concerning the measles-mumps-rubella vaccine and autism and hepatitis B and multiple sclerosis, and the vaccine preservative thiomersal.

Improving AEFI management capacity in countries

Activities in this area are carried out largely through networks. Established in 1996, the Global Training Network provides — through its AEFI course — support in vaccine regulation and quality and AEFI monitoring and management to staff of NRAs and control laboratories, public sector manufacturers and national immunization programmes. Four training centres are located in the Russian Federation, South Africa, Sri Lanka and Tunisia, with courses taught in English, French and Russian.

Since 1996, more than 2000 people working for immunization programmes and regulatory authorities at national level have been trained through WHO's Global Training Network on Vaccine Quality and other NRA strengthening activities.

A second network, still in the early stages of development, will focus on helping developing countries ensure high quality post-marketing surveillance of newly introduced vaccines, with a primary focus on monitoring serious AEFIs, and detecting and evaluating signals of potential vaccine reactions. Country-level staff working

in immunization programmes, regulatory authorities, pharmacovigilance centres, WHO, United Nations procurement agencies and independent vaccine safety experts will be involved. Data from the network will be shared among network partners and made available to vaccine manufacturers and other countries.

Investigating serious adverse events

While vaccines can cause reactions, these tend to be minor, such as a sore arm, redness or minor swelling at the injection site, or low-grade fever. Extremely rarely, there are more serious consequences. Thorough investigation of such consequences is a core element of management of vaccine safety issues. WHO provides assistance, through its regional and country offices, to national immunization programmes and regulatory authorities in investigating serious AEFIs. Technical assistance is often provided in collaboration with several partners, including vaccine manufacturers. The level of involvement of WHO is dependent on whether the vaccine is prequalified, the support requested by the country, and implications for immunization programmes across the world. Activities undertaken during investigations primarily include analysis of reported cases and field

investigation of the potential cause(s) of the adverse events. They may also include facilitation of testing of the vaccine or injection

equipment, review of production facilities and processes, and advice on communication strategies.

A sound investment

“We are... in the midst of what experts call the most severe financial crisis and economic downturn seen since the start of the Great Depression in 1929. Work on the prequalification of diagnostics, medicines and vaccines is a prime example of the kind of efficient, joined-up action that helps maintain the delivery of essential health services at a fragile time.

It is this kind of work that helps me argue against cuts in funding for essential public health functions. With programmes such as this one, public health shows that it can indeed achieve greater efficiency without sacrificing quality.”

— Dr Margaret Chan, WHO Director-General, 4th Consultative Stakeholder Meeting for UN Prequalification of Diagnostics, Medicines and Vaccines, Geneva, Switzerland, 3 February 2009.

Protecting the gains and ensuring future progress

Norms and standard work is a core component of WHO’s mandate. Yet, this work is at risk. WHO’s efforts relating to vaccine safety and quality in 2010-11 are projected to be severely underfunded — more than 40% of the budget requirements are

not covered. Failure to address the funding gap of US\$ 13 million will mean scaling down some of the above-mentioned activities, with consequences on the efficient regulation and monitoring of vaccines across the world.



More information

WHO headquarters immunization web site
<http://www.who.int/immunization/en/>

Immunization standards
http://www.who.int/immunization_standards/en/

Prequalified vaccines
http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html

Biologicals (includes information on the Expert Committee on Biological Standardization)
<http://www.who.int/biologicals/en/>

Global Advisory Committee on Vaccine Safety
http://www.who.int/vaccine_safety/en/

Investigations of adverse events following immunization
http://www.who.int/immunization_safety/aefi/investigations/en/index.html



Vaccines of assured quality

This CD contains meeting reports, technical and advocacy documents and audiovisual material relating to WHO's work in the area of vaccines of assured quality. It also contains reports of the meetings of the WHO Strategic Advisory Group of Experts on immunization,

WHO position papers on vaccines, and communications and advocacy material on general immunization issues. Web links for further information are also provided. The CD covers the period May 2006 - April 2009.

