

WHO's Key Normative Processes and Institutions for Vaccines: A Primer

Introduction

This brief describes three World Health Organization (WHO) normative institutions and processes pertaining to the issuance of technical guidelines and opinions about the public health value of new vaccines, their quality, and the acceptability of their manufacturing. This primer examines (1) the Strategic Advisory Group of Experts (SAGE) and WHO vaccine “position papers”; (2) the Expert Committee on Biological Standardization (ECBS); and the (3) Global Advisory Committee on Vaccine Safety (GACVS). It highlights ways in which these three processes are related to and can reinforce one another, strengthening the coherence of the existing system. The note also describes the procedures established for the prequalification of vaccines, by which WHO assesses their acceptability for purchase by United Nations agencies on behalf of developing countries.

I. Position Papers and the Strategic Advisory Group of Experts

To help countries determine whether, and under what conditions, to adopt new vaccines or use existing vaccines, the WHO periodically issues “position papers.”

Based upon extensive review by experts, regional bodies, interested parties and industry, these position papers are evidence-based summaries on licensed vaccines of public health interest. They typically include information about the disease epidemiology; the pathogen and course of disease; immune responses; existing and new vaccines against the disease, including their dosing schedule and efficacy; and finally, WHO recommendations on use of the vaccine.¹ Since 1998, WHO has published position papers on 21 different vaccines. Some of the recent papers cover diphtheria, *Haemophilus influenzae* type B (Hib), Japanese encephalitis, mumps, pertussis, pneumococcus, rabies, rotavirus, tetanus, and typhoid.

The Strategic Advisory Group of Experts (SAGE) was set up in 1999 to provide advice to the WHO on issues related to vaccines and immunization. The SAGE consists of 15 international experts from a variety of disciplines related to vaccines and immunizations.

In 2005, SAGE revised its terms of reference to take into account the WHO/UNICEF Global Immunization Vision and Strategy framework,² which focuses on the introduction of new vaccines and vaccination technologies and ensuring that immunization programs are integrated into national health systems and priorities.

Since April 2006, one of the major functions of SAGE has been to review and endorse position papers on vaccines before these are sent to the WHO Director General for a final decision and issuance.

The Expert Committee on Biological Standardization

The WHO Expert Committee on Biological Standardization (ECBS) was established in 1947 to set norms and standards for the manufacturing, licensing and control of biologicals, which are documented in WHO International Biological Reference Preparations. Biologicals include blood products, cell regulators, vaccines and in vitro diagnostic tests. The ECBS consists of expert scientists from various institutions including universities and national control laboratories. The ECBS meets annually and reports to the WHO Executive Board, an arm of the World Health Assembly.

The ECBS provides guidelines on vaccine manufacturing, quality control, product labeling, transportation and storage. It makes recommendations on assays and other tests of vaccine purity and potency. The ECBS also provides national regulatory authorities (NRAs) with recommendations on how and when to release a vaccine for use in the country. These standards allow vaccines from different manufacturers and lots to be compared in laboratory tests. These standards can also be used for WHO prequalification processes (see next page).³

The Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to respond promptly to vaccine safety issues of potential global importance. The GACVS does not determine immunization policies, but expresses its scientific opinion on vaccine safety, which could result in policy changes.

The GACVS evaluates vaccine safety by reviewing the latest developments in basic science, epidemiology and clinical practice. The GACVS works in close cooperation with experts from national authorities, academic institutions, and the pharmaceutical sector. It is at liberty to request, monitor and evaluate specific studies that explore a possible link between vaccines or their components and adverse effects. In addition to reports published in the WHO's *Weekly Epidemiological Record*, the GACVS makes information available via the WHO website (www.who.int) where the GACVS' findings can be consulted.⁴

Putting it all together

As Figure 1 shows, a WHO position paper on a given vaccine only emerges after the SAGE has considered and endorsed the draft paper, using inputs from the relevant expert advisory committee, as well as opinions and information from the ECBS and the GACVS, and possibly other global and regional technical groups.

One vaccine for which a position paper is currently in progress is the human papillomavirus (HPV) vaccine. A background technical document is expected to be presented to SAGE in the second half of 2008, building upon the work of the HPV Vaccine Advisory Committee (HVAC), composed of specialists from government, academia, industry, and NGOs. The SAGE discussion will then likely lead to the development of an HPV vaccine position paper which can be endorsed by SAGE and sent to WHO for approval and publication.

II. Prequalification of vaccines

Prequalification is defined as the “procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies.” The prequalification process was originally put in place in 1989, and revised in 1996 and 2002. In 2005, the WHO

also drew up similar guidelines for the prequalification of injection devices. In addition to UN agencies, many individual countries use the list of prequalified vaccines to select reliable and high quality vaccines.

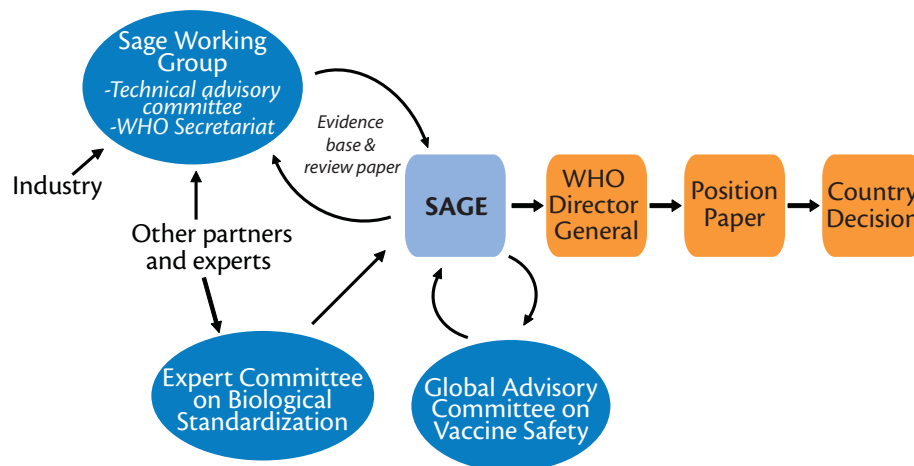
During prequalification, the WHO verifies that manufacturers produce vaccines that meet ECBS standards and any additional UN procurement specifications, and that are produced in accordance with Good Manufacturing Practice (GMP), the widely accepted international standards for production and testing of vaccines.

Manufacturers can apply for prequalification by submitting a request and a technical dossier to WHO. Vaccines are reviewed for prequalification if they are deemed to be priority products by UN purchasing agencies, especially UNICEF and the Pan American Health Organization and vaccine funders such as the GAVI Alliance.⁵ Prequalification is especially important because these two organizations together purchase more than USD\$ 700 million worth of vaccines annually, and this amount is likely to rise in the coming years.

To achieve prequalification, the National Regulatory Agency (NRA) of the country where the vaccines are produced must be fully functional and meet a set of indicators designed to ensure that it can effectively oversee production and release of high quality vaccines. WHO ensures that manufacturers meet quality standards by lot testing and site visits to manufacturing facilities. Prequalification is normally awarded for a period of two years, but can be extended to five years if there have been no significant changes in the product indications and no product recalls.

The cost of the prequalification process is covered by the manufacturers.⁶ Once a vaccine has been accepted for evaluation, the manufacturer must send WHO a

Figure 1. WHO Recommendations on Vaccine Use – Key Steps



Product Summary File (PSF) which is to be reviewed within three months. If the PSF is acceptable, WHO will test 25-200 vaccine samples for potency and toxicity from a minimum of three lots over the next three months. Over the subsequent two months, WHO conducts site visits to manufacturing facilities to ensure that they adhere to GMP. The site visits sometimes lead to follow-up assessments of the country NRA, which can take up to six months. Otherwise, a final decision is made by WHO within 30 days of the site visit by an ad hoc expert committee. In practice, prequalification of a vaccine has typically taken about 18 months to complete.^{7,8}

From 1986-2006, vaccines against 24 diseases, produced by 22 manufacturers, were prequalified by WHO. At the end of 2006, 55% of prequalified manufacturers were based in emerging economies. Pentavalent (diphtheria, tetanus, pertussis-hepatitis B-Hib or DTP-HepB-Hib) vaccine, measles, mumps, and rubella (MMR) vaccine, rotavirus vaccine, Pneumococcal conjugate vaccine (PCV), inactivated polio vaccine (IPV), monovalent oral polio vaccine (mOPV) and seasonal influenza vaccine were all designated high priority for prequalification in 2007 and 2008. The list of prequalified vaccines is regularly updated and available online.⁹

As Figure 2 illustrates, WHO may take into account policy recommendations from the SAGE position paper and from groups such as the ECBS and GACVS, in making its decisions on prequalification.

The pneumococcal conjugate vaccine (PCV), which is currently in the process of being prequalified, is an example of a vaccine that has gone through the various WHO review processes in recent years. In March 2005, the ECBS released its report on the production and control of PCV.¹⁰ In November 2006, SAGE reviewed a technical background paper and developed

recommendations for use of PCV, which led to a revision of an earlier WHO position paper on the vaccine. In March 2007, this new position paper was issued by WHO.¹¹ During 2007, PCV became a high priority vaccine for prequalification, due to interest from developing countries and agreement by GAVI to finance the vaccine for low-income countries. As of March 2008, the prequalification process was nearly completed and a decision on whether to prequalify the vaccine was being finalized.

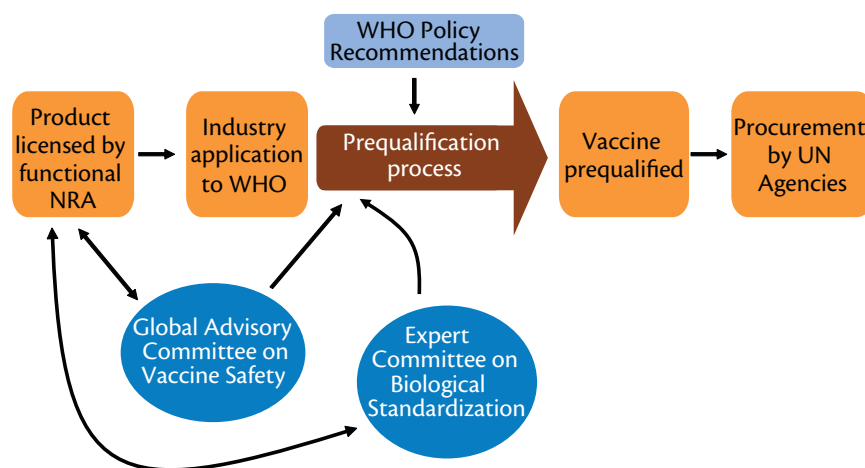
Conclusions

WHO plays a central role in performing a series of normative functions for new and existing vaccines, as well as prequalifying vaccines for purchase by UN agencies on behalf of developing countries. Many organizations involved in improving global immunization performance and delivering life-saving vaccines including developing country health ministries, NRAs, donors, procurement agencies, and manufacturers all look to WHO for its guidance and decisions.

The WHO has strengthened its performance in these normative areas and in prequalification over the past decade. The publication of well-researched and widely accepted vaccine position papers is one example of this progress.

Going forward, it would be useful to look for ways in which WHO can continue to enhance this system. For example, it may be possible to further streamline and speed up some of the SAGE and prequalification processes, while maintaining high standards of quality and safety. It may also be possible to establish better synchronization for these processes, in order to get life-saving vaccines to people who need them faster. Additional work may be helpful to identify remaining bottlenecks and actions to remove them.

Figure 2. WHO Vaccine Prequalification – Key Steps



Annex 1. United Nations Prequalified Vaccine Producers and Vaccines (as of April, 2008)⁹

Producer	Vaccine
Berna Biotech	TT, MR (measles, rubella combination)
Berna Biotech Korea Corp.	Hepatitis B (recombinant), DTP-Hep B-Hib (fully liquid pentavalent) (Quinvaxem)
Bio Farma, Indonesia	DT, DTP, DTP-Hep B, Hepatitis B filled in Uniject ,OPV, TT, TT filled in Uniject, Measles, Measles (20 doses)
Biomanguinhos, Brazil	yellow fever (5, 10 and 50 doses) , polysaccharide meningococcal A and C vaccine (10 doses in glass vials)
Center for Genetic Engineering and Biotechnology, Cuba	Hepatitis B(recombinant)
Novartis Vaccines and Diagnostics GmbH & Co. KG, Germany (formerly Chiron Behring)	DTP, Rabies
Novartis Vaccines and Diagnostics S.r.l, India (formerly Chiron Behring)	Rabies
Novartis Vaccines and Diagnostics S.r.l, Italy (formerly Chiron Vaccines)	OPV, Hib, DTP-Hib
CSL, Australia	DTP, TT
GlaxoSmithKline, Belgium	Hepatitis B (recombinant), Hib, OPV (produced in MRC-5), meningococcal A + C, meningococcal ACW 135; DTP-Hep B (Tritanrix) , DTP-Hep B to be combined with Hib (pentavalent) (Tritanrix-Hib) , DTP-Hep B (Zilbrix) , DTP-Hep B + Hib (Zilbrix-Hib), measles, MMR, Rotavirus (Rotarix)
Haffkine Bio Pharmaceutical Corporation Ltd, India	OPV (from bulk supplied by Biofarma, Indonesia)
Institut Pasteur Dakar, Senegal	yellow fever
Japan BCG	BCG
LG Life Sciences Ltd. , Korea	Hepatitis B (recombinant)
Merck and Co. Inc, USA	Hepatitis B (recombinant), Hib
BB-NCIPD Ltd., Bulgaria, Intervax, Canada	BCG, TT, DT, dT
Panacea Biotec, India	DTP Biofarma - Hib Novartis (1 dose) (EASYFOUR), DTP Biofarma - Hepatitis B PHB (1 dose) (ECOVAC), Hepatitis B (Enivac B), OPV (from bulk supplied by Biofarma, Indonesia), OPV (from bulk supplied from Chiron, Italy)
Sanofi Pasteur, France	DT, dT, DTP, DTP-Hib, IPV, OPV, TT, measles, MMR, Hib, rabies, yellow fever, meningococcal A + C
SBL Vaccin AB, Sweden	Inactivated oral cholera
Serum Institute of India	BCG, DT, dT, DTP, DTP-Hep B, Hep B (recombinant), TT, MR, MMR, measles, rubella
Shantha Biotechnics Private Ltd., India	Hepatitis B (recombinant), DTP-Hep B (Shantetra), TT (Shan TT)
Statens Seruminstitut, Denmark	BCG

Endnotes and Links to WHO Resources

- <http://www.who.int/immunization/documents/positionpapers>
- http://www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf
- <http://www.who.int/biologicals/publications/trs/areas/vaccines>
- http://www.who.int/vaccine_safety
- GAVI Alliance is a global partnership that combines public and private resources to create greater access to immunizations. <http://www.gavialliance.org>
- \$25,000 for conventional vaccines and \$66,500 for combination or novel vaccines.
- http://whqlibdoc.who.int/hq/2006/WHO_IVB_05.19_eng.pdf
- http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.08_eng.pdf
- http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers
- Example: ECBS recommendations for PCV <http://www.who.int/biologicals/publications/trs/areas/vaccines/pneumo/ANNEX%202%20PneumococcalP64-98.pdf>
- http://www.who.int/immunization/SAGE_wg_detail-dreview_pneumoVaccine.pdf

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