

Stop Cervical Cancer: Accelerating Global Access to HPV Vaccines

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HPV Vaccines: Regulatory Issues

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Abstract

More than 90 percent of all countries have established legislative and regulatory frameworks covering all aspects of pharmaceutical product commerce and use.¹ Regulated products, such as human papillomavirus (HPV) vaccines, cannot be legally promoted or sold in a country until they have been approved by the government regulatory authorities. This paper explains the common national regulatory frameworks that will impact availability of HPV vaccines. Also clarified is how these national regulatory frameworks closely interact with the international immunization policy and vaccine procurement frameworks that are critical to global affordability and accessibility of vaccines. Given the World Health Organization's (WHO) critical role in the entire global system, the WHO's roles in each framework, with emphasis on policy and procurement, are discussed. Finally, the current status, prospects, and challenges facing HPV vaccines within these interdependent frameworks are reviewed. Priority areas for action include tracking national regulatory approval in developing countries, ensuring that HPV vaccine is prioritized by the WHO Strategic Advisory Group of Experts (SAGE) in 2007, supporting the WHO prequalification process to alleviate product backlog, and helping countries decide among the several newly available vaccines that will be available before the end of the decade.

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Meeting organized by Global Health Strategies

1. Background: Key Frameworks for Vaccines

Global access to new human papillomavirus (HPV) vaccines will only be achieved when the vaccines have been successfully shepherded through three key frameworks (see Figure 1):

1. National drug and vaccine regulatory framework
2. International immunization policy framework
3. International vaccine procurement framework

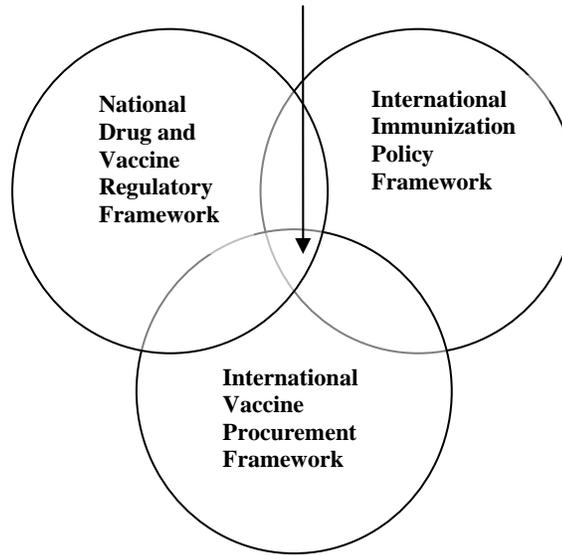
National Drug and Vaccine Regulatory Framework

Almost all countries have some form of national drug and biologic product regulatory system in place. For instance, in the United States, the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) is responsible for regulating vaccines. It is important to clarify the distinction between vaccines, which are biological products, and drugs. Biological products, or biologics, include a wide range of products, such as blood and blood components, gene therapy, tissues, and

Figure 1: Three Critical Frameworks in International Vaccine Access

Access achieved when HPV vaccines have national regulatory approval in all countries where they will be used, an international policy recommendation for use in national immunization programs, and are available through UN procurement agencies. At the current time, all these conditions could be first met in the 2009—2010 timeframe.

National Drug & Vaccine Regulatory Framework involves the country-level legislative and regulatory systems covering pharmaceutical product commerce and use. Every vaccine manufacturer must apply for and receive separate national regulatory approval in every country where a vaccine will be sold and/or used. This is the case for both developed and developing countries.
Merck and GSK are both moving forward with national registration of their HPV vaccines in developed and developing countries. Registration in developing countries for these HPV vaccines can likely be completed more quickly than the other framework processes.



International Immunization Policy Framework involves the WHO-led processes that determine whether a new type of vaccine will be recommended as a priority for global or regional incorporation into national immunization programs.
The WHO's SAGE plays a key role in immunization policy, and has not made a recommendation on HPV vaccines. The earliest this could happen will be the April 2007 SAGE meeting.

International Vaccine Procurement Framework is dominated by UNICEF and PAHO as the major vaccine purchasers and distributors to meet the national immunization program needs of developing countries. WHO provides technical support through the prequalification process to assure the quality of purchased vaccines.

The WHO prequalification process for either Merck or GSK's HPV vaccine could be completed by mid to late 2008, after which PAHO and UNICEF could begin negotiations with each manufacturer. HPV vaccine could become available through one or both of these mechanisms during 2009—2010.

recombinant therapeutic proteins. While drugs are chemically synthesized and have a known structure, biologics are complex mixtures that are not as easy to completely characterize. Since all biologics are in some way “grown,” they are subject to natural variability in the production process. Additionally, biologics are often sensitive to heat and are susceptible to microbial contamination to a much greater extent than drugs. Consequently, regulatory authorities have a specialized set of processes for vaccines and other biologics.

The timeline for getting vaccines through regulation varies. Pharmaceutical companies typically spend 8 to 12 years conducting research and development followed by clinical trials before applying for licensure. In this pre-licensure period, manufacturers conduct three phases of clinical trials, each with increasing numbers of subjects. Phase 1 and 2 studies focus on safety, immunogenicity, and dose-ranging. Phase 3 studies usually enroll thousands of subjects and provide critical data for licensing on effectiveness and broader scale safety.

An overview of the FDA’s 6- to 12 month vaccine approval process illustrates how governments typically regulate vaccines and the critical standard steps:² First, the manufacturer files a Biological License Application (BLA). Then, FDA and the manufacturer together present findings to a non-FDA expert committee (the Vaccines and Related Biological Products Advisory Committee), which makes a non-binding recommendation to the FDA regarding the product’s safety and efficacy. Once this recommendation is made, an intensive review of the manufacturer’s proposed package insert and labeling for the new vaccine is carried out. This is often a vigorously negotiated process between the FDA and manufacturer, since the approved insert and labeling legally defines the medical claims that the manufacturer will promote to health care providers and the public regarding the vaccine’s efficacy, proper use, dosage, and risks and benefits. Once the labeling issues have been negotiated and the BLA approved, the FDA continues to regulate the vaccine’s manufacturing to ensure ongoing safety. It is common for a vaccine to undergo Phase 4 (post-licensure) trials after it is on the market, as all potential adverse

events cannot be anticipated and known until a vaccine is administered to the general public. Merck received FDA approval for its HPV vaccine, Gardasil®,³ on June 7, 2006. GlaxoSmithKline (GSK) expects to receive its FDA approval for its HPV vaccine, Cervarix®,⁴ during 2007.

In the European Union (EU), licensing under a centralized procedure (applicable to drugs or vaccines utilizing recombinant technology) allows vaccine sponsors to submit a single application to the EMEA for marketing approval in the 25 EU member states. The application is then referred to the EMEA’s scientific committee, the European Committee for Medicinal Products for Human Use (CHMP), which recommends granting or denying a marketing authorization, and is responsible for preparing the agency’s opinions on all questions concerning medicinal products for human use. The European Commission generally follows the CHMP recommendation and grants a final marketing authorization within a few months following a positive recommendation. Early in 2006, Merck and GSK submitted marketing applications for their HPV vaccines to EMEA. On July 26, 2006, CHMP recommended approval of the Merck HPV vaccine Gardasil; recommended approval of GSK’s Cervarix is expected in early 2007.

Primary Versus Secondary National Approval

In most cases, the first regulatory approval for any new vaccine comes from the National Regulatory Authority (NRA) in the country of the manufacturer. This is a result of both practical considerations (the manufacturer will be most familiar with the NRA processes in its own country) and market perception considerations (many NRA’s will not even consider approving a product unless it is already approved in the manufacturers “home” country). For this discussion, “**primary** regulatory approval” refers to approval in the country of the manufacturer, and “**secondary** regulatory approvals” refers to approvals in any other country. In the case of Merck’s Gardasil®, the United States (US) FDA approval is the primary regulatory approval. For GSK’s Cervarix®, EMEA approval will serve as the primary approval.

Large, multinational vaccine manufacturers usually apply simultaneously for their primary and secondary regulatory approvals in countries they view as top priority markets. If multinational manufacturers plan to eventually sell a new vaccine globally, they will apply for secondary approvals in remaining countries within the first few years after primary approval. Smaller vaccine manufacturers outside the US and Europe are more likely to first apply for primary approval, and later seek registration in additional countries if export market opportunities arise.

Although each country has its own regulatory processes, common patterns emerge. For example, if the manufacturer's primary approval has been granted by a highly respected regulatory authority known for rigorous review, such as the FDA and the EMEA, then many NRA's will grant (secondary) approval on an expedited basis without requiring specific in-country clinical studies. Another group of NRAs will grant secondary approval while only requiring small scale in-country clinical studies. For example, in India, the Indian Council of Medical Research, an autonomous body under the Ministry of Health & Family Welfare, recently began a small immunogenicity study of Gardasil® in the Indian population where cervical cancer is the most common cancer among women. This study is required for national registration by the Drugs Controller of India which oversees the regulation of drugs and biologicals in India. GSK has also initiated the required immunogenicity study in India.

The Role of the WHO in the National Framework

The World Health Organization (WHO) has no direct role in regulatory approval of individual drugs or vaccines for any country, as all legal regulatory processes can only be functions of sovereign governments. However, the WHO is quite active in promulgating guidelines for the formation of national drug and vaccine regulatory agencies, providing technical assistance to strengthen NRA's, and assessing whether a country's NRA has sufficient capacity to properly monitor vaccine manufacturing activities.

International Immunization Policy Framework

The WHO leads the process of technical analysis, consensus-building, and decision-making regarding specific vaccines that should be incorporated into regional and national immunization programs to achieve critical global public health goals. By bringing together groups of experts, WHO facilitates international recommendations for immunization programs, particularly for developing countries not always capable of state-of-the-art epidemiological analysis or immunization program planning. WHO has long been *the* global advisor on vaccines and immunizations and has achieved remarkable success through the Expanded Program on Immunization (EPI), which increased global uptake of basic childhood vaccines from 20% in 1980 to over 78% in 2004.

The WHO currently convenes a Strategic Advisory Group of Experts (SAGE) to serve as the principal advisory group for vaccines and immunization. SAGE is charged with advising WHO on overall global policies and strategies, including vaccine research and development, vaccine delivery, and linkages between vaccine and other programs.⁵

Receiving a positive SAGE recommendation for incorporation of a new vaccine into global public health immunization program policy is a critical prerequisite before the United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO) will initiate the process of procuring and distributing the new vaccine. As noted in Figure 1, both UNICEF and PAHO only procure and distribute vaccines formally identified as necessary or recommended components of national immunization programs. Likewise, individual country government immunization policymakers, especially in developing countries, often will not consider adding a new vaccine to their national program unless WHO's SAGE makes a clear recommendation. After regulatory approval, the SAGE process is the next critical "go/no go" step for any new vaccine to become globally accessible. As of September 2006, SAGE had not made a recommendation on the role and priority of HPV vaccines within the global public health immunization policy framework.

International Vaccine Procurement Framework

Key Procurement Agencies: UNICEF Supply Division and PAHO Revolving Fund

The WHO SAGE process described above provides the necessary global policy endorsement to place a new vaccine onto a global public immunization program priority list. It does not, however, assure a new vaccine will become widely distributed. While most middle- and high-income countries have their own national vaccine procurement entities, low-income countries rely heavily on UN institutions to guide and support their national immunization programs. For example, the UNICEF Supply Division has been supplying vaccines for over 50 years. It purchases and distributes the majority of basic EPI vaccines to serve immunization program needs of almost all low-income countries outside of Latin America. In fact, the UNICEF Supply Division is the single largest global purchaser of vaccines when; in 2003 alone, UNICEF procured 2.5 billion doses of vaccine and distributed these to nearly 100 developing countries.⁶ In addition to basic EPI vaccines, UNICEF also procures vaccines on behalf of initiatives, such as the Global Alliance for Vaccine and Immunizations (GAVI). Within Latin America, PAHO manages a vaccine procurement entity, the PAHO Revolving Fund, which makes vaccines available to the governments of all Latin American countries for their national immunization programs.

Therefore, after receiving a SAGE endorsement, the producer(s) of a new vaccine must navigate the process of first qualifying to sell the vaccine to agencies in the UN system and then successfully participating in a tender and bid cycle. All UN vaccine procurement agencies, including the UNICEF supply division and PAHO's revolving fund, rely on a particular technical assessment group within WHO to "prequalify" each producer of each vaccine, including new vaccines, before the procurement

agencies will accept a bid for that vaccine from any producer.

The WHO Prequalification Process

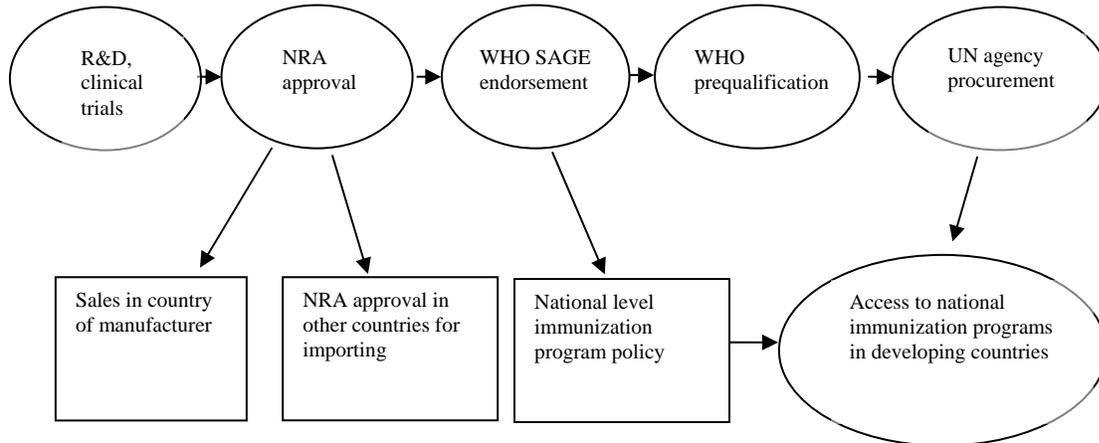
WHO prequalification is a crucial component of the international procurement framework. In commercial terms, WHO prequalification is the "vendor quality screening and monitoring" component of vaccine procurement by UNICEF, PAHO, and any other UN agency and they will only accept bids for prequalified vaccines. The WHO prequalification process verifies that a manufacturer's vaccine (a) meets the specifications of the relevant UN agency and (b) is produced and overseen in accordance with the principles and specifications recommended by the WHO for Good Manufacturing Practices (GMP) and for Good Clinical Practices (GCP).⁷ The process includes steps similar to those of NRA's, such as that of the FDA's outlined above. There are three general steps to this process:⁸

1. Review of general production process and quality control procedures.
2. Testing of consistency of lots.
3. Joint WHO/NRA site visit to manufacturing facilities.

While assessing a vaccine manufacturer, the WHO audits the competence of the NRA overseeing that manufacturer. If the WHO finds the NRA does not meet international standards, then WHO cannot prequalify that producer's vaccines regardless of their manufacturing sophistication and GMP compliance. While there are many companies around the world producing vaccines, there are just over twenty that the WHO has pre-qualified.⁹

WHO prequalification typically takes about 18 months from the time a manufacturer submits a complete prequalification application package, and cannot begin before SAGE has endorsed a new vaccine. However, the WHO's Department of Immunization, Vaccines and Biologicals (IVB)

Figure 2. Linear Progression of the Vaccine Regulatory, Policy, and Procurement Process



has set a new goal in its 2006-2009 strategic plan to streamline the process to a 12-month timeframe for application review of vaccines that the SAGE has identified as high priority.¹⁰ Given the current limited capacity of the WHO's prequalification team, prequalification review is restricted to manufacturers' applications for SAGE-endorsed "high priority" vaccines.

To assure countries a continued, secure supply of quality vaccines at affordable prices, IVB conducts ongoing dialogue with prequalified vaccine manufacturers and procurement agencies. Thus, the process continues after prequalification and procurement in the following manner:⁹

- Reassessments at requested intervals.
- Random check testing for compliance with specifications.
- Monitoring for failure to meet specifications.
- Follow up of complaints and reports of adverse events following immunization (AEFI)

Viewing the Framework Processes in Linear Progression

After considering the three frameworks as they overlap and interrelate, it is also helpful to

view a more linear timeline of the process. Figure 2 provides a timeline from a manufacturer's research and development and clinical trials to access in national immunization programs in developing countries. Also indicated is the separate function of national regulatory approval for sale in individual countries.

2. Analysis: HPV Vaccines

Because of the complexities of the numerous processes and governing bodies involved in vaccine regulation and distribution, HPV vaccines will encounter challenges common to all vaccines as well as new challenges unique to its characteristics and purpose. This analysis outlines the current status (as of summer 2006) of the HPV vaccines in each of the three frameworks and discusses strengths and challenges that the vaccine may face in each.

National Regulatory Status

Two HPV vaccines will soon be available, both protecting against HPV types 16 and 18, which cause 70% of cervical cancer cases globally.¹¹ Merck's vaccine, Gardasil®, which also protects against genital wart-causing HPV types 6 and 11, was approved for sale by the US FDA on June 7, 2006. This was followed closely by approvals in Mexico, Australia, and Canada.

The US FDA approval was for administration to females age 9 to 26, while the Mexican and Australian approvals were for administration to both females and males in this age range. Merck has applied for Gardasil® regulatory approval in 25 or more countries and will continue to add more countries, including most developing countries, during the next few years. Actual sales of the Merck vaccine began in the US in July 2006, with other approved countries following thereafter.

GSK has already submitted an application for Cervarix to EMEA, and registration for Europe is expected by March 2007. GSK also simultaneously applied for licensure in more than 25 additional countries and will work to expand national licensure around the globe, including most developing countries. GSK sales are expected to begin in Europe in the spring of 2007, with other countries following.

Analysis: National regulatory approvals in either developed or developing countries are not likely to pose significant challenges to achieving global access of either Merck's Gardasil® or GSK's Cervarix®.

Both Merck and GSK have the experience, motivation, resources, and commitment to gain national regulatory approval for their HPV vaccines in all countries, and they are both well into this process. For example, both companies are initiating small scale, 12-month clinical immunogenicity trials required by India's NRA for licensure in India, and immunogenicity trials are likely to be initiated in sub-Saharan Africa for GSK's vaccine before the end of 2006. Merck and GSK should be able to complete national registration of their HPV vaccines in developing countries, including the poorest countries of Africa and Asia, within the timeframe for the other key framework processes.

It is always possible for challenges to occur at the individual developing country level if a national regulatory agency restricts the approved use of either the Merck or GSK vaccine in a way inconsistent with global immunization policy recommendations.

International Immunization Policy Status

As of September 2006, the WHO SAGE has not made a formal recommendation regarding HPV vaccines, although it has noted its interest in their development.

The next SAGE meeting is scheduled for November 2006. Discussions with key WHO staff suggest that the HPV vaccine will not be on the agenda for the November meeting, as consideration of pneumococcal vaccines and other emerging issues have already filled the schedule. The first opportunity for consideration of HPV vaccines will be at the April 2007 SAGE meeting; it is key that the SAGE secretariat place HPV vaccines on this meeting agenda.

Analysis: The WHO SAGE process must recommend HPV vaccines as a high priority in order to 1) set a positive stage for national government immunization policy consideration of HPV vaccines and 2) to trigger priority attention to key steps in the international procurement process such as WHO prequalification of Gardasil® and Cervarix® so that UN agencies can then begin purchase and distribution.

As of summer 2006, this is the most critical next milestone in the pathway toward global access; preliminary discussion suggests SAGE will consider HPV vaccine at the April 2007 meeting.

International Vaccine Procurement Status

Although most experts feel the SAGE will recommend HPV vaccines as a priority, SAGE has not yet begun its consideration of the new vaccine and until this recommendation occurs, UN procurement processes, including the necessary WHO prequalification of HPV vaccine suppliers, cannot begin. In the meantime, WHO has already begun developing the necessary HPV vaccine technical standards that will be used in the prequalification process, and these should be completed by the time SAGE recommends the new vaccine.

Analysis: The international procurement process, particularly the WHO prequalification of vendor's vaccines for participation in the UN procurement system, will become the critical path for broad-scale HPV vaccine access once SAGE recommends HPV vaccines as high priority.

The requirements of the WHO prequalification process, as well as expected backlog of applications could delay broad-scale access to an HPV vaccine. Despite such obstacles, it is promising that WHO has proactively started to develop the HPV vaccine technical standards that will underpin a portion of the prequalification process. In previous cases, the lack of such standards at the beginning of the prequalification process caused significant delays for other vaccines, such as GSK's rotavirus vaccine, which is still not pre-qualified.

Also on a positive note, the two initial HPV vaccine producers, Merck and GSK, should have little difficulty meeting the technical requirements of the prequalification process. Any delays in the process will more likely be due to delayed start (awaiting SAGE recommendation) or slower than planned progress due to WHO staff or resource shortages.

Projections suggest that the prequalification process could begin with the May 2007 application period, and will be completed between 12 and 18 months after that, e.g. between mid- and end-2008.

3. Conclusion

The following are key steps that need to take place for broad scale access to HPV vaccines:

- Merck and GSK need to pursue national country-specific regulatory approvals. Both manufacturers are moving forward to achieve regulatory approval of their vaccines in countries around the world. Therefore, this step is unlikely to be a major barrier to HPV vaccine access.
- While Merck and GSK continue to pursue national regulatory approvals, the next critical step is to receive the WHO's SAGE recommendation of the vaccine as a high priority (expected April 2007).

- Once that milestone has been achieved, the WHO prequalification process - a 1-year or longer manufacturer-specific process - can begin. WHO prequalification allows for UN agency procurement of vaccine and GAVI funding.
- Once either or both Merck and GSK succeed in prequalifying their HPV vaccines, they will work through the final key requirement: negotiation with the procurement systems of key UN agencies, including UNICEF and PAHO, to supply vaccines to developing country government programs. Success in this area will likely depend upon external funding for HPV vaccine purchases (see financing paper).

Given that the SAGE process is not likely to take place until April 2007 and prequalification will then require at least 12 months, *HPV vaccines will not become part of the key international procurement and distribution mechanisms until sometime in 2009.*

One of the most significant threats to this timeline is the rapidly increasing number of new vaccines becoming available in the next few years which could overwhelm the capability of WHO and other UN agencies—as well as government health programs. This suggests that all groups interested in rapid global uptake of HPV vaccines should advocate not only for the vaccines themselves, but also for sufficient funding from WHO donor nations and others so that these critical agencies can effectively lead the coordinated efforts to place HPV vaccines squarely in the middle of global immunization efforts.

Lastly – and very importantly – countries likely will need assistance in making evidence-based decisions about when and how to make a range of new vaccines available to the men, women, and children who need them. Ultimately, it is their decision as to how to prioritize, fund, and deliver vaccines to improve the overall health of their citizens.

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