Guidelines to Assure the Quality, Safety, and Efficacy of Recombinant Human Papillomavirus Virus-Like Particle Vaccines

Executive Summary

Biological medical products such as vaccines save lives, reduce suffering and improve health, but only if these products are of good quality, are safe, effective, available, affordable and properly used. The World Health Organization (WHO) works with its Member States towards the goal of using only vaccines of assured quality in national health systems. The WHO Expert Committee on Biological Standardization (ECBS) establishes global norms and standards that help define products of assured quality.

During its latest meeting in Geneva, Switzerland on 23-27 October 2006, ECBS adopted a guidance document establishing new standards for human papillomavirus vaccine, "Guidelines to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines". The document provides background and guidance to national regulatory authorities and vaccine manufacturers on product manufacture and quality assessment and nonclinical and clinical evaluation of recombinant HPV virus-like particle (VLP) vaccines. This written standard also facilitates the prequalification of vaccines needed before large-scale public sector vaccine purchase.

Guideline development was based on experience with the two vaccines developed thus far. Both vaccines contain recombinant protein L1 VLP and adjuvant to stabilize L1 VLP integrity and to enhance immunogenicity. The vaccines have different HPV L1 protein antigens, production substrates, adjuvant properties and final formulation. The two vaccines are:

1) A bivalent vaccine comprised of oncogenic HPV types 16 and 18 VLPs reassembled from L1 protein expressed and purified from insect cells infected with a recombinant baculovirus. This vaccine is formulated with a novel adjuvant, AS04, which contains aluminium hydroxide and monophosphoryl lipid A (MPL); and

2) A tetravalent vaccine made of the low risk HPV types 6 and 11 and the oncogenic HPV types 16 and 18. Type specific L1 proteins for this vaccine are expressed and purified from yeast cells containing L1 expression plasmids. The VLPs are adsorbed to an amorphous aluminium hydroxyphosphate sulfate-containing adjuvant.

Several special considerations need to be addressed in the manufacturing, non-clinical and clinical development of these vaccine products. VLPs are complex biological products and need to be assessed at various levels. With respect to manufacturing and product quality the following items should be considered:

1) The bivalent vaccine expressed from recombinant baculovirus in insect cells is the first vaccine to be developed in this host expression system. Testing of this cell substrate may have some unique requirements;
2) The bivalent vaccine includes a novel adjuvant which has not previously been used on a global scale. The immunostimulant is MPL which is a detoxified form of lipid A derived from the lipopolysaccharide (LPS) isolated from bacterial cell walls of the Gram negative bacterium Salmonella minnesota R595. While detoxified, MPL was shown to retain the capacity of the natural LPS compound to act as an immunostimulant by potentiating cellular and humoral adaptive immune responses;

3) L1 protein in its native form is not glycosylated. HPV L1 VLP vaccines produced in new or different cell substrates should be assessed for glycosylation status;

4) Disassembly and reassembly of the L1 capsomers may contribute to purification of the product and lead to more stable VLPs;

5) Purified L1 VLP preparations will have to be characterized biochemically and immunologically, to determine L1 concentration, purity and assembly state; and

6) Current HPV vaccines are manufactured in single dose presentations without preservative. In the future, the availability of multi-dose vaccine vials would facilitate the adoption of innovative vaccination strategies targeting pre-adolescents and adolescents in developing countries. If these vaccines do not contain preservative, the use of such vaccine vials should be time-restricted as is the case of reconstituted Bacillus Calmette-Guérin (BCG) and measles vaccines. If a preservative were to be added, the effect on antigenicity, immunogenicity, and safety must be assessed.

With respect to the nonclinical studies it is critical that such studies demonstrate immunogenicity and the production of neutralizing antibodies.

Regarding clinical assessment of HPV VLP vaccines, critical considerations include:

1) Since 90% of HPV- related cancers are cervical cancers, the efficacy of the vaccines developed so far has been studied in sexually active women;

2) In order to obtain maximal benefit from these vaccines, young adolescents should be vaccinated before onset of sexual activity. Although rate of HPV acquisition is high in the 5 to 10 years following sexual debut, most women remain naïve to vaccine HPV types during this time, and few have been infected with all vaccine HPV types;

3) Licensure of first generation vaccines requires a definitive demonstration of prophylactic efficacy with respect to cervical intraepithelial neoplasm (CIN) 2/3 and adenocarcinoma in situ (AIS) caused by vaccine HPV types;

4) Persistent infection (e.g., detection of the DNA of the same virion in cervicovaginal specimens collected on consecutive visits over a period of at least 12 months) may be an appropriate endpoint for second generation vaccines, including those with additional HPV types. When these Guidelines were prepared, however, there was no international consensus on how persistent HPV infection can be defined based on detection of HPV DNA by restricted PCR; and

5) Once licensed, evaluations of the long term effectiveness these vaccines should consider how vaccines are integrated into cervical cancer screening and early detection programs.