Chapter 22: Assuring the quality, safety and efficacy of HPV vaccines: The scientific basis of regulatory expectations pre- and post-licensure

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Abstract

The potential of human papillomavirus (HPV) vaccines will only be realized if the vaccine candidates under development prove to be safe and effective and can be consistently produced to define quality standards. Whilst the responsibility for delivering a safe and effective product rests with the vaccine producer, a vaccine requires a license to allow it to be placed on the market. Licensure is based on an evaluation of the safety and efficacy profile of a vaccine candidate by national regulatory authorities, ideally on the basis of internationally agreed, science-based specifications and procedures. For vaccines, these international specifications are developed by the World Health Organization (WHO). The scientific basis for the regulatory evaluation of the safety and efficacy of HPV vaccines is described in this paper. Once a vaccine is licensed, a second set of criteria are evaluated by a different group of experts to provide advice to national health policy decision makers as to whether the vaccine should be introduced into national immunization programmes. Factors, such as evidence of high disease burden and high cost-effectiveness are taken into account in this second decision-making process.

Keywords: HPV; Vaccines; Quality; Safety; Efficacy

1. Introduction

The quality, safety and efficacy of a vaccine product are the prime responsibility of the manufacturer. However, the existence and functioning of a comprehensive national vaccine regulatory system supported by legislation is a prerequisite for an overall assurance of the quality, safety and efficacy of a vaccine. Many countries have established an independent assessment of vaccine quality, safety and efficacy through an agency known as the National Regulatory Authority (NRA), which grants marketing authorization and is responsible for continued post-marketing monitoring.

The World Health Organization (WHO) has identified six key functions which the NRA must exercise in order to guarantee the quality, safety and efficacy of a vaccine, including: (i) a published set of clear requirements for licensing of products and manufacturers, (ii) surveillance of vaccine field performance, (iii) a system of batch release, (iv) the use of a laboratory when needed, (v) regular inspections of manufacturers for compliance with Good Manufacturing Practice (GMP) and (vi) evaluation of clinical performance through authorized clinical trials. In carrying out these activities, the NRA makes use of expert advisory committees and technical advisers.

The application to the NRA for a license to market a vaccine is reviewed first by a team of NRA experts, then by an expert advisory committee comprised of scientists, physicians, biostatisticians, consumer representatives and other
The committee reviews the application and provides advice to the NRA concerning the quality, safety and efficacy of the vaccine. In many countries, the committee plays mainly an advisory role. The NRA makes the final decision based on file review, laboratory testing and GMP inspection as to whether the vaccine under application will be approved, although it considers the advisory committee’s recommendations carefully. After all evaluations and recommendations are complete, the NRA sends the applicant an official letter of approval, disapproval or request for additional data.

The regulatory evaluation of vaccines can be divided into three stages: developmental, licensure and post-licensure [1]. The developmental stage consists of two parts, namely non-clinical research and development, and clinical research and development. Non-clinical research and development is carried out in the laboratory and uses in vitro techniques or, when necessary, in vivo techniques in animals. Non-clinical and laboratory-research data include details of the development and production of a vaccine together with reports of control testing, which should be adequate to justify subsequent clinical studies in humans [2]. Non-clinical and laboratory-research investigations concerning quality and safety measurements of candidate HPV vaccines are elaborated in detail in Sections 2 and 3 below. Clinical trials in humans are classified into three phases: phases I–III [3]. In some countries, formal regulatory approval is required in order to undertake clinical phases I–III studies. This is in addition to the ethical clearance that is required in all countries for clinical trials. All studies of human subjects require ethical consideration and review, in accordance with the Declaration of Helsinki.

In phase I clinical studies, initial testing of a vaccine is carried out in small numbers (e.g. 20) of healthy adults to test the properties of a vaccine, its tolerability and, if appropriate, its clinical laboratory and pharmacological parameters. Phase I studies are primarily concerned with safety. Phase II studies involve larger numbers of subjects and are intended to obtain preliminary information about a vaccine’s ability to produce its desired effect (usually immunogenicity) in the target population and general safety. To fully assess the protective efficacy and safety of a vaccine extensive phase III studies are required. The phase III clinical trial is the pivotal study on which licensing is based, and sufficient data have to be obtained to demonstrate that a new product is safe and effective for the purpose intended.

By the beginning of the phase III stage of development, a vaccine should have been fully characterized and the final manufacturing process, specifications and batch release testing procedures should have been established. An application for a market authorization is usually submitted to a NRA on the basis of the phase III data and, if approved, the vaccine then becomes available on the market in that particular country. Any subsequent change in production methods or scale-up following licensing will necessitate further product characterizations to demonstrate equivalence, although the extent of re-characterization depends on the nature of the changes implemented; these should be documented and the NRA notified of all changes.

The post-marketing period is critical for the collection of safety and effectiveness data in large numbers of recipients. Therefore, following licensing, there is continued surveillance of a product for adverse events, especially for rare events that can only be detected in very large numbers of subjects. Post-marketing studies are pre-planned in study protocols and are referred to as phase IV studies. Although these studies may occasionally use designs as used in pre-licensure trials, in most cases, phase IV studies are set up as observational cohort or case-control studies. Whereas phases I–III studies make every attempt to standardize subjects, immunizations, evaluations and laboratory studies, it is usually impossible to impose the same degree of standardization, especially concerning selection of subjects, in phase IV studies. Post-marketing surveillance and studies may be conducted to investigate:

- The optimal use of a vaccine (age at vaccination, simultaneous administration of other vaccines, changes in the vaccine strains, interchangeability of vaccines, etc.).
- Efficacy in certain risk groups (elderly, immunocompromised patients, patients with certain diseases, etc.).
- Maintenance of long-term efficacy and monitoring of long-term safety.

After licensure, evidence-based decisions are needed to determine whether a vaccine should be included in national immunization programmes and, if so, what is an appropriate schedule. Such decisions may be made by national immunization committees, or countries may be supported through global guidance developed by the WHO [4]. The decision-making process should include considerations not only of immunization policy perspectives but also the technical feasibility of introducing a new vaccine into an immunization programme [5].

In an increasingly interconnected world, national regulatory decisions are often made in the context of knowledge of decisions made at regional and global levels. In terms of quality, safety and efficacy of vaccines, the WHO has long played a role in providing countries with the best available scientific evidence in the form of written technical specifications.

2. Quality specifications for HPV vaccines

The scientific basis of guidelines to assure the quality, safety and efficacy of HPV vaccines was considered at a consultation held at the WHO in March 2006 [6], with the intention of providing the framework for WHO Guidelines to be developed later during the course of 2006. Although a variety of candidate vaccines were reported to be under development, the most advanced at the time of the consultation were based on virus-like particles (VLP) assembled from the L1 protein of the virus, intended for prophylactic use, and thus it was agreed that the scope of the WHO guidance under
HPV is specific for humans but vaccine developers have at least three homologous models in animals for proof-of-concept studies. These are in rabbits (cotton tail rabbit papillomavirus), cows (bovine papillomavirus) and dogs (canine oral papillomavirus). It has been demonstrated in these homologous animal systems that protection can be passively transferred by serum, which indicates that antibody induction is a key desired feature of an HPV vaccine. However, given that the indication for use of an HPV vaccine is to protect from cervico-vaginal infection, and given that serum titres are 10-fold higher than cervical mucus titres (100-fold at ovulation) [8], this raises a concern about relying on measurements of systemic neutralizing antibodies to predict duration of protection.

The HPV vaccine candidate formulations studied to date are not expected to affect physiological functions (CNS, respiratory, cardiovascular, renal), and thus safety pharmacology studies [2] may not be needed. However, developmental toxicity studies, which are not recommended for paediatric vaccines, will be needed for HPV vaccines since women of child-bearing age will be immunized, and guidance will be given in the WHO guidelines currently under development.

The non-clinical evaluation package for a vaccine candidate with a novel adjuvant is extensive [9]. This will include demonstration of an increased immunological response of the adjuvant/antigen combination in a relevant animal model as a justification for use of the adjuvant. If based on the nature of the adjuvant, it can be expected that the adjuvant might be distributed throughout the body, pharmacokinetic studies should be considered. The toxicity of the adjuvant alone will also need to be evaluated. This may require testing in two species (including non-rodent) unless justified. Ideally, the selected species should be the same in which the proof-of-concept has been studied. Toxicity endpoints include local tolerance, dependent on the route of administration; induction of hypersensitivity and anaphylaxis; pyrogenicity; any systemic toxicity. Finally, toxicity testing of the adjuvant and antigen combination will be required. This entails local tolerance, repeated-dose toxicity studies and characterization of the immune response.

4. Clinical evaluation: what endpoints will be used and why?

Basically, endpoints are the agreed-upon measurement yardstck for whatever objectives a vaccine is expected to achieve. The main endpoints for all vaccines are immunogenicity (B- and T-cell responses), reactogenicity (local and systemic reactions), safety (short- and long-term adverse events) and protection (efficacy in clinical trials and effectiveness in population use). To measure if a vaccine protects against a disease, the endpoint often seems obvious at first glance. For example, to test the efficacy of a measles vaccine, one compares the incidence of measles cases in vaccinated and unvaccinated children. In unvaccinated areas, there are

3. Non-clinical testing of HPV vaccine candidates

The aims of any non-clinical testing for a candidate vaccine are to identify possible risks to the vaccinees, ahead of first testing in humans, and to help to plan the clinical trial protocols. These tests are frequently done in animals, but it should be noted that there are certain limitations, such as pathogenesis and immune responses that are frequently species-specific, and potential safety concerns in animals may not necessarily indicate a problem in humans.

As with all vaccines, thorough characterization of the starting materials for freedom from adventitious agents will be required, and the manufacturing processes will need to be validated and conducted under GMP. Also, as with other vaccines, each manufacturing production run will need to be monitored and controlled by tests carried out at each stage of manufacture. This includes tests on the crude antigen harvests, during purification, on the formulated vaccine bulks and on the final product that has been filled into syringes. Key tests will be on the antigenicity and immunogenicity of the vaccine candidates. A test has been developed for one vaccine candidate that the manufacturer claims links antigenicity, as measured by an in vitro method, with immunogenicity in both test animals and also in human clinical trials for at least one of the HPV types in the formulation [7].

In the first vaccine candidate, the VLPs are adsorbed onto alum as an adjuvant whereas in the baculovirus-derived vaccine candidate the VLPs are adsorbed onto a novel adjuvant that contains both alum and also a Lipid A derivative purified from Salmonella Minnesota (see Chapter 12). The use of a novel adjuvant requires additional non-clinical and clinical development to provide adequate data for registration purposes.
numerous cases that are easily diagnosed clinically and confirmed by well-established and standardized tests, therefore a trial can be set up and completed relatively quickly.

Evaluation of HPV vaccines poses a number of problems, some specific and others common to all vaccines. The main disease to be prevented – cervical cancer – appears in a relatively small proportion of women, often after a very long period, which is inconvenient since it is impossible to wait for it to occur within the framework of a clinical trial. Besides cervical cancer, there are a number of other outcomes of interest, like pre-cancerous lesions, benign diseases, genital infections and other cancers.

The selection of a given endpoint will take into consideration a number of factors. An endpoint for efficacy should be a good indicator of disease. Feasibility should be high: it should be frequent to minimize sample size and length of the study, easy to perform and affordable. Its measurement should be valid, easily replicable and with a good positive and negative predictive value. Endpoints will vary for a pre-licensure clinical trial or a post-marketing study of effectiveness. Outcomes that ought not to happen, adverse events, for example, must also be looked at. Endpoints have to be selected according to the interest of the end-user, be it a manufacturer, a regulatory agency, a member of an expert committee, a decision maker, a clinician or a patient. This section will review the pros and cons of various endpoints to measure the efficacy and effectiveness of the HPV vaccines in various circumstances. It will also consider briefly other endpoints related to safety and other possible outcomes of immunization.

4.1. Evaluation of HPV vaccines’ efficacy and effectiveness

Three types of endpoints will be considered: clinical, virological and immunological. Part of this section includes the collective views of a group of experts convened by the WHO in May 2003 [10].

4.1.1. Clinical

Clinical endpoints measure diseases that require medical care. They can be assessed clinically through physical examination, cytologically through Papanicolaou testing or histologically through biopsy sampling. Methods can be combined, for example, in testing for HPV-DNA in cytology or histology samples to assess the presence of genotypes included in the vaccines or not. Histology is the definitive diagnostic procedure to evaluate cervical disease. Pre-cancerous cervical dysplasia lesions are histologically classified as cervical intraepithelial neoplasias (CIN) of mild (CIN-1), moderate (CIN-2) or high grade (CIN-3), which includes carcinoma in situ. CIN-1 is the most common clinical manifestation of cervical HPV infections and it is accompanied by a high rate (60%) of spontaneous clinical regression. Women with CIN-2 also show a high rate of regression but they are at substantial risk of cervical cancer. CIN-3 can regress but more often persists or progresses to cancer.

The group of experts assembled by the WHO did not consider CIN-1 to be an appropriate endpoint for HPV vaccine efficacy trials because its diagnosis can have poor intra-observer reproducibility and because it is not regarded as an obligate precursor to cervical cancer. On the other hand, trials that couple it with viral-DNA analysis as an endpoint could be fairly small, given the high rate of incident CIN-1 in certain populations.

CIN-2 and -3, or worse, accompanied by HPV-DNA detection represent a definitive, clinically relevant endpoint. This has been demonstrated by the success of the Pap test screening program that reduced the incidence of cervical cancer by removing CIN-2 and -3 lesions. CIN-2/3 lesions are identified in a trial by colposcopy with biopsy of suspect lesions and HPV-DNA analysis. This is feasible, although it requires a large number of participants and is resource-intensive. Invasive cancer provides the most valid endpoint but also presents the largest feasibility problems because it is rare and requires a very long time to develop. Further, invasive cancer would be difficult to use as an endpoint for ethical reasons.

Other clinical endpoints may be of interest for other HPV-related diseases. Other cancers are less frequent than cervical cancer and could not be used for trials. Benign lesions, and genital warts in particular, are more frequent, however, and clinical diagnosis is feasible and may be confirmed by histology.

4.1.2. Virological

There are three virological endpoints considered to measure the efficacy of HPV vaccines: incident infection, persistent infection and presence of specific genotypes in a clinical lesion. Incident infection is defined as new detection of HPV-DNA in cervico-vaginal cells in women previously shown to be HPV-DNA negative. Such infections are very common and are usually cleared within a few months without treatment. It is a precursor of disease that is frequent and easy to measure. However, only a small percentage will progress to disease. Persistent infection is defined as detection of the same HPV-DNA in cervico-vaginal specimens obtained in follow-up visits 6–12 months apart in women who were naive at baseline. It is a powerful predictor of CIN-2/3 and cancer (see Chapter 13). The measurement of specific genotypes is important to determine if the vaccines protect against some or all of the genotypes included or even against other non-included genotypes. Studies using this endpoint are quite feasible.

4.1.3. Immunological

The measure of antibodies is not a measure of disease but may turn out to be a measure of protection against disease, provided there is a demonstrable correlation between a given antibody titre and protection. In the case of HPV, it is noteworthy that no universal standard currently exists to measure antibody concentrations, which precludes direct comparison of the results produced by various laboratories (see Chapter 23). Once this seroprotective titre is known, it becomes
easy to conduct clinical trials to assess various schedules and dosages in specific populations. This capacity was extremely useful to define a number of new schedules for the hepatitis B vaccines, for example. Up to now, we still do not know if it is possible to determine a correlate of immunity for HPV. Even if correlation cannot be established, antibody titres will be used as a surrogate of protection. This has been the case for pertussis, for instance, where vaccines for the adult population were licensed on the basis of their immune response even in the absence of correlates of protection with regard to a specific antibody concentration. It would be particularly useful for bridging studies in a number of geographically or immunologically defined populations and also to assess one- or two-dose schedules.

4.2. Other endpoints

Reactogenicity and safety are of paramount consideration. All adverse events and all serious adverse events occurring in the clinical trials with HPV vaccines are registered and their frequency is determined. If a specific disease appears more often than anticipated in the vaccinated population, causality will be assessed. Existing case definitions, such as those proposed by the Brighton collaboration, are often used for this purpose [11].

It will be useful also to define endpoints for other impacts of the vaccines. The most unusual feature of the HPV vaccine is its major impact on another prevention program, the cervical cancer screening program. In order to be able to evaluate this impact, endpoints will have to be agreed upon both for the screening interventions and for the screening programs. The relevant clinical endpoints for efficacy have already been mentioned. The sensitivity and specificity of the screening tests will need to be reassessed in immunized women. With decreasing incidence and prevalence, the positive predictive values (probability that a positive test is really positive after confirmation) will be expected to go down as the absolute number of confirmatory procedures would go down but the proportion of false positives would increase. These endpoints (sensitivity, specificity, predictive values) will be important to measure (see Chapter 20). Based on these, it will become possible to develop new screening protocols (e.g. age at intervention, interval between tests, follow-up investigations) and to minimize unnecessary procedures and costs.

Psycho-social impacts are often neglected. Appropriate indicators of the level of anxiety generated by positive screening test and by cancer could be measured in the vaccinated population. A decrease in anxiety would also be a positive benefit of the vaccine that would require appropriate endpoints in order to be adequately taken into consideration.

5. Post-marketing surveillance

The focus now is on pre-licensure clinical trials that will demonstrate protection against disease. As soon as the vaccines are approved and marketed, other studies will be conducted to extend the knowledge about the impact of these vaccines when co-administered with other vaccines, their impact on various diseases, such as other HPV-related cancers (e.g. anal), for a variety of populations and in a variety of environments. These will all need valid endpoints that can be measured easily. In particular, since some adverse events are very rare, it will not be possible to identify them in clinical trials because the sample size is too limited. In this case, specific studies need to be set up to measure the occurrence of the event when the vaccine is introduced in the general population. The same is true for special populations not included in clinical trials, such as persons with immune deficiencies. In some countries, the impact on other public health interventions, such as screening programmes (as described above), will also need to be evaluated.

All these data will eventually lead to an understanding of whether the available vaccines are safe and effective in a particular population setting. Policy makers will then be in a position, if there is also evidence of high disease burden and high cost-effectiveness, to decide if the introduction of a new HPV vaccine into a national immunization program is a priority on public health grounds. National immunization advisory committees are in place in many countries to provide advice on these immunization policy matters. Issues that are of major importance in making this decision are implications for the national immunization program and, in particular, the financing of the introduction of a new vaccine in a sustainable way [12]. Taking all these factors into account will determine if the potential of HPV vaccines [13] will be realized.

Disclosed potential conflicts of interest

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[6] World Health Organization. Informal consultation on drafting WHO guidelines to assure the quality, safety and efficacy of recom-
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