Meeting on Appropriate Clinical Endpoints for Second Generation HPV Vaccine Trials
19-20 November 2013
Executive Summary

A meeting to establish the appropriate clinical endpoints for second-generation Human Papillomavirus (HPV) trials was held on 19-20 November 2013 in Geneva, Switzerland. This meeting followed an initial scoping meeting held on 27 February 2013 at the World Health Organization (WHO) and a scientific consensus meeting held on 23 and 24 of September at the International Agency for Research on Cancer (IARC) in Lyon, France. Participants at the present meeting included experts in HPV epidemiology, laboratory methods, vaccine trials, and vaccine regulation from IARC, CDC, NCI, regulatory agencies, and the pharmaceutical industry. WHO Secretariat members represented Quality, Safety and Standards; Initiative for Vaccine Research; and Expanded Programme on Immunization. The specific meeting objectives were to review the outcomes of the Lyon scientific meeting, review vaccines in the development pipeline, and assess the regulatory and laboratory needs for a change in clinical trial endpoints/outcomes. Anticipated meeting outcomes were to achieve agreement on establishing an appropriate clinical trial endpoints, based on the current summary of evidence on HPV, taking into account the perspective of vaccine regulators and industry and anticipated outcomes, and create a strategy and plan for next steps. The goal of this discussion was to set the stage for updating the current WHO Technical Review Series (TRS) No. 962, Annex 1, Guidelines to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines, initially published in 2006.

In the Lyon scientific meeting, the group created a series of gender-independent recommendations for HPV-associated cancers, stratified by age group to address L1 or L2 VLP vaccines, or vaccines that generate protective antibodies. In general, persistent HPV infection of 6 months was considered adequate and appropriate for most clinical trials related to cervical outcomes, and among individuals 26 years of age or younger. Immunobridging studies would also be appropriate for HPV types shared by currently licensed vaccines and the vaccine under study. Immunogenicity studies may not be appropriate for L2 and non-VLP vaccines. Non-inferiority trial designs were also considered to be appropriate for evaluation of new vaccine candidates. More specific recommendations are available online (http://www.iarc.fr/en/publications/list/wrk/index.php).

Several companies presented plans early in development for both prophylactic and therapeutic HPV Vaccines. Vaccine candidates more advanced that are in Phase 3 trials included an E. coli-based L1-VLP vaccine against HPV 16/18, developed by Xiamen Innovax Biotech Co. Ltd. (Xiamen, China) and a 9-valent (6/11/16/18/31/33/45/52/58) HPV L1 Virus Like Particle Vaccine, developed by Merck & Co. (USA). A Phase 2 trial is occurring for a yeast (Pichia)-based L1-VLP vaccine against HPV 16/18, developed by Shanghai Zerun Biotechnology Co. Ltd. (Shanghai, China).
In the discussion of regulatory considerations for new vaccine candidates, both US and European regulators commented that endpoints are likely to be evolving based on the copious data becoming available from the Merck 9-valent development program. These data support the use of virologic endpoints, and suggest that histologic endpoints are not likely to be needed. The regulators discussed that, at times, serologic non-inferiority may be appropriate - though the endpoints required will likely be judged on a case by case basis. Placebo controlled trials are no longer appropriate in most settings. Post licensure monitoring will continue to be important, (for instance, if the number of doses were lowered), but this monitoring also may be impacted by herd immunity in areas that have achieved good coverage of the initial HPV vaccines.

A key issue that will be necessary for any endpoint for future vaccine candidates is the importance of proper sample collection and analysis and reporting for serologic and virologic assays. Currently, for virologic endpoints, sample collection, extraction/processing, and assay method are crucial steps but quite variable and not currently standardized. With regard to serology, the sample collection is less variable. However, the lack of commercial reagents and the differing assays used in the various clinical trials create challenges to standardize serologic assays. Standardization is important as these tests are used for immunobridging and non-inferiority testing. Results should be reported in international units when possible.

At the conclusion, based on 1) data from the scientific meeting at Lyon, and 2) vaccine candidates and 3) regulatory perspectives presented, a discussion reviewed what seemed feasible and desirable to update the WHO TRS. There was agreement that persistent HPV infection for 6 months is an appropriate clinical endpoint for HPV vaccine trials. Serologic non-inferiority needs to be demonstrated for currently licensed L1 VLP vaccines for 16/18 in women less or equal to 26 years of age, before adopting new dosing schedules; or, for new L1 VLP vaccines directed against types 16/18. For multivalent L1 VLP vaccines, for the non 16/18 other high-risk HPV types, virologic endpoints need to be used, either as a composite outcome, or for each type. For new, non-L1 VLP vaccines, virologic endpoints are initially needed to document efficacy. Serologic endpoints may ensue in the future. If capsomere vaccines are resulting in L1 antigens, then serologic endpoints may be appropriate.

For methodologic considerations for future trials, exploration of antibody avidity could be investigated in a subset of patients as a secondary outcome, but cannot be a primary outcome as thresholds are not established and assay standardization still needs further refining. For immunobridging studies, it is important to document the plateau titer, not just the peak titer, and it is necessary to establish the proper time-point for measuring these responses. To enhance future trials and comparison of efficacy of vaccines, there is an acute need to develop standard operating procedures for HPV DNA detection and HPV serologic assays. International units should be used so that results between trials can be compared.
Meeting on Appropriate Clinical Endpoints for Second Generation HPV Vaccine Trials

19-20 November 2013
Geneva, Switzerland

A. Background and Introduction

A meeting to establish consensus on the appropriate clinical endpoints clinical trials of second-generation human papillomavirus (HPV) vaccines was held on 19-20 November 2013 in Geneva, Switzerland. This meeting followed an initial scoping meeting held on 27 February 2013 at the World Health Organization (WHO) and a scientific consensus meeting held on 23 and 24 of September, 2013 at the International Agency for Research on Cancer (IARC) in Lyon, France. Participants at the present meeting included experts in HPV epidemiology, laboratory methods, vaccine trials, and vaccine regulation from IARC, CDC, NCI, regulatory agencies, and the pharmaceutical industry. WHO Secretariat members represented Quality, Safety and Standards; Initiative for Vaccine Research; and Expanded Programme on Immunization.

Drs Markowitz and Fruth jointly opened the meeting by reviewing the timeline and key issues of the preceding meetings. They charged the participants to establish an agreement on appropriate clinical endpoints for second generation HPV Vaccine trials given the current level of evidence, taking into consideration the perspective of HPV epidemiologists and immunologists, current vaccines in the development pipeline, and vaccine regulators across the world. The goal of this discussion was to set the stage for updating the current WHO Technical Report Series (TRS) No. 962, Annex 1, Guidelines to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines, initially published in 2006. Following this review, several presentations followed on (1) the IARC scientific meeting conclusions, (2) current second generation vaccine candidates in varying development stages; (3) regulatory considerations in changing vaccine trial endpoints; (4) the process to update the TRS guidelines; (5) the need for laboratory standardization for detection of HPV; and (6) a group discussion on whether persistent HPV infection could serve as an appropriate clinical endpoint.

The specific meeting objectives and anticipated outcomes, reviewed by Drs Markowitz and Fruth, were as follows:

Objectives

- Review and discuss the outcomes of the Lyon scientific meeting on appropriate clinical endpoints
- Review vaccines currently in the development pipeline
- Assess the regulatory and laboratory needs for a change in clinical trial endpoints/outcomes

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1 This meeting was made possible by funding from the Bill & Melinda Gates Foundation.
Expected outcomes

- Achieve agreement on the definitions of appropriate clinical trial endpoints, based on the current state of evidence on vaccine-induced protection against HPV, taking into account the perspective of vaccine regulators and industry
- Create a strategy to disseminate this information and plan next steps

A brief review of the role of WHO and the timeline and brief outcome of the preceding scoping meeting and IARC scientific consensus meeting were presented.

B: Review of Presentations

B. 1 Scientific Consensus meeting (IARC, Lyon, France): Summary of Recommendations

R. Herrero, IARC

Dr. Herrero reviewed the background of HPV epidemiology and pathogenesis regarding cervical cancer, with the key points being as follows: (1) HPV is necessary but not sufficient for cervical cancer; (2) there exists a long latency period between HPV infection and cervical cancer, and most infections are transient; (3) HPV RNA and proteins are expressed in pre-cancer and cancer; (4) similar pathogenesis exists in other anogenital sites; (5) the treatment of cervical pre-cancer has led to decreased cervical cancer incidence.

He also reviewed the currently available bivalent (Cervarix, GlaxoSmithKline, against HPV 16/18) and quadrivalent (Gardasil, Merck, against HPV 6/11/16/18) vaccines, which are both L1 protein virus-like particle (VLP) vaccines. Both vaccines are highly effective and confer some degree of cross-protection to non-16/18 oncogenic HPV types. In addition, geographic regions with high coverage of the quadrivalent vaccine have seen herd immunity demonstrated by decreased wart incidence in non-vaccinated males. Primary endpoints in clinical trials were protection against pre-malignant disease (i.e., CIN2+, VIN2+, ValN2+, AIN), with the caveat that these endpoints may have high inter-pathologist variability. Protection against persistent HPV infection was also reported. While clinical trials for these vaccines were performed in older adolescents and adults, regulatory approval was achieved for young adolescents based on immunobridging trials, which demonstrated non-inferior (and stronger) antibody response in this population versus adults and older adolescents.

Given such highly effective vaccines, the rationale for additional clinical trials is as follows: (1) the difficulty in delivering 3 doses of vaccine, (2) the cost of current vaccines, (3) the need to cover the 30% of cervical cancer attributable to non-16/18 HPV types. Trials could address a different dosing schedule, a vaccine with increased valency, alternative administration routes, equivalence trials with other L1-VLP vaccines, new vaccines, or additional eligible populations (for instance, infants).

The purpose of the September 2013 IARC meeting was to consider whether virologic endpoints (i.e. persistent HPV infection) could accelerate vaccine development, reduce cost
of clinical trials, and lead to faster regulatory approval, while using a more reproducible outcome. The goals of that meeting were to develop recommendations for appropriate clinical trial primary outcomes for HPV-attributable cancers by reviewing the current literature on HPV pathogenesis. The meeting included experts from WHO, NCI, and other non-profit and academic institutions with expertise ranging across biology, epidemiology, pathology, clinical trial design, and regulations. These recommendations were meant to address L1 or L2 VLP vaccines, or vaccines that generate protective antibodies.

The first session addressed whether prevention of persistent HPV 16 and 18 infections would be adequate as related to cervical endpoints. Given agreement that HPV infection is necessary but not sufficient for cervical pre-cancer and cancer, and previously demonstrated equivalent vaccine efficacy against CIN2+ or persistent HPV 16/18 infection, use of persistent HPV infection as the primary endpoint would allow clinical trials to have smaller sample sizes, given higher incidence of HPV infection than CIN2+. Virologic endpoints could also eliminate misattribution of co-infected lesions to the wrong HPV type.

- The group concluded that persistent HPV infection of 6 months or greater would be a high fidelity surrogate endpoint for advanced disease/cervical cancer, for new L1 VLP vaccines.
- Using this endpoint would require standardized methods for tissue sampling and laboratory methods of HPV detection.

The second session addressed whether prevention of persistent non-16/18 infections would be adequate as related to cervical endpoints. For non-16/18 types, clinical trials could evaluate the impact of cross-protection and the efficacy of new multi-valent vaccines. A brief review of the epidemiology and pathogenesis of non-16/18 types demonstrated many similarities, with the exception that while persistence rates may be similar, progression rates may be lower than for HPV16. However, the bivalent vaccine demonstrated similar efficacy rates against CIN2+ or persistent infection (6 month or 12-month) against HPV 31, 33, or 45.

- The group concluded that for non-16/18 types, persistent HPV infection remained an appropriate outcome for VLP vaccines, either for types targeted by a vaccine or for evaluation of cross protection; CIN2+ may not be an appropriate outcome in cross-protection studies.
- Immunobridging studies would also be appropriate for HPV types shared by currently licensed vaccines and the vaccine under study, in order to bridge to younger ages.

The third session addressed the duration of protection. While not a requirement for licensure, this is an important vaccine characteristic for health care providers and policy-makers. To establish duration of protection:

- post-licensure studies are important
- immunologic endpoints may be more appropriate
- standardization of assays is critical.
The fourth session evaluated alternative schedules and target ages. The discussion focused on immune response by age, as prior immunobridging studies have shown higher immune responses in younger age groups. The group considered whether immunobridging studies could be used to assess the efficacy of alternative vaccine schedules (i.e., fewer than 3 doses). Current immunogenicity studies have shown that 2 doses in younger girls (ages 9 to 13 or 14) is non-inferior to 3 doses in older girls and women (ages 15 or 16 to 25 or 26).

- Non-inferiority immunobridging studies with standardized assays would be acceptable to determine alternative target populations and administration schedules, with post-licensure studies on duration of protection.
- If non-inferiority is not demonstrated in the immunogenicity trials, then trials with virologic outcomes would be necessary.

The fifth session addressed vaccine efficacy against HPV-related non-cervical disease. For anal cancer, given highly conserved pathogenesis of HPV leading to disease, the group decided that endpoints could be similar to cervical cancer (i.e., virologic endpoints).

- Trials that study efficacy after prior treatment of HSIL should continue to use disease endpoints.
- For vulvar and vaginal cancer, given limited knowledge of the validity of persistent infection as an endpoint, HPV 16/18-related pre-malignant disease endpoints were recommended.
- For oropharyngeal cancer endpoints, persistent infection was recommended as the only feasible endpoint as no clear pre-malignant disease can be identified or screened for.

The group ultimately created a series of gender-independent recommendations for HPV-associated cancers, stratified by age group: <16 (excluding infants), 16-25, >26 years. These recommendations pertain to VLP vaccines. In general, persistent HPV infection was considered adequate and appropriate for most clinical trials related to cervical outcomes. Histologic outcomes could still be studied but would not be required. For non-cervical outcomes, recommendations are above. Among individuals >26 years, less consensus was achieved, as some believed that disease endpoints were indicated, as the significance of infection acquired late was less clear. Immunogenicity studies may not be appropriate for L2 and non-VLP vaccines. Non-inferiority trial designs were also considered to be appropriate for evaluation of new vaccine candidates. More specific recommendations were summarized in tabular form at the end of the IARC report entitled Primary End-points for Prophylactic HPV Vaccine Trials, IARC Working Group Reports No 7 (available online only: http://www.iarc.fr/en/publications/list/wrk/index.php).

Discussion:
The question was raised whether immunogenicity studies with validated assays should document both neutralization activity as well as avidity (surrogate for memory), especially with dose reduction or non-VLP antigens. Perhaps avidity threshold and antibody concentration could be developed as an immune correlate of protection. Questions were raised regarding the scientific bases for setting a numeric threshold around non-inferiority of antibody geometric mean titers (GMT), particularly given no ICP, as GMT and GMT ratios
can be highly skewed by a few high or low values. In addition, it is unclear when antibody should be measured in relation to dose administration. Although these issues were not resolved, the overarching agreement that immunogenicity studies are relevant will likely serve as impetus for further study in this area. Overall, the group agreed that avidity studies would be important but not necessary for licensure requirements.

The group also re-affirmed that while the sample size needed for a non-inferiority trial between currently licensed vaccines and new candidates may be larger, and placebo-controlled trials would be unethical in many settings. Thus, the use of virologic endpoints would be very helpful in decreasing sample size. However, while composite endpoints are helpful from a public health perspective, and would lower sample size, individual endpoints against HPV 16/18 specifically remain important given the high proportion of cancer attributable to these types.

Persistent infection for oropharyngeal infection was subject to some debate, given limited knowledge regarding natural history and pathogenesis, but some data may be soon available to start to investigate this further.

The group agreed that persistent HPV infection for 6 months would be adequate and appropriate.

### B. 2 Current State of Development for Second Generation HPV Vaccines

#### B. 2.1 Development of Cecolin: An E. coli-expressed HPV-16/18 Bivalent Vaccine in China.

*T. Wu, Xiamen Innovax Biotech Co. Ltd. (Xiamen, China)*

Dr. Wu presented an overview of Xiamen Innovax's HPV vaccine candidate. This is an *E. coli*-based L1-VLP vaccine against HPV 16/18, currently in phase 3 trials. Phase I and II clinical trials versus placebo (as neither Gardasil nor Cervarix are licensed in China) have demonstrated both safety and immunogenicity among women aged 18-25 with a 3 dose schedule (0, 1, 6 months). The current phase 3 trial among 6,000 women has co-primary endpoints of CIN2+ and persistent HPV 16/18 infection. The company's goal is to apply for licensure in 2016, if the Chinese Food and Drug Agency (cFDA) accept persistent HPV infection as a valid outcome, or 2018 if CIN2+ is the required outcome.

Dr. Wu also briefly mentioned that a multivalent vaccine is under development.

#### B. 2.2 Recombinant HPV Bivalent (16/18) Vaccine (Yeast Pichia)

*L. Shi, Shanghai Zerun Biotechnology Co. Ltd. (Shanghai, China)*

Dr. Shi presented an overview of Shanghai Zerun’s HPV vaccine candidate. This is a yeast Pichia-based L1-VLP vaccine against HPV 16/18, currently in phase 2 trials. Phase I trials demonstrated safety and immunogenicity. Phase 2 trials are investigating immunogenicity stratified by age group (9-17 vs 18-45 years) and dose as well as immune durability over 4
years. Phase 3 trials are planned for either 6,000 or 12,000 women aged 18-45, starting in 2014 with planned 4 year follow-up. In 2011, at the time of the company’s application to the Chinese FDA, persistent HPV infection was not recognized as a primary endpoint and premalignant disease was recommended. The vaccine will have an aluminum adjuvant and current dosing schedule is 0, 2, 6 months.

Dr. Shi also briefly mentioned that a therapeutic HPV vaccine is under development.

**B. 2.3 An Overview of the 9-valent HPV L1 Virus Like Particle Vaccine Clinical Development Program**

_A. Saah, Merck & Co. (USA)_

Dr. Saah presented an overview of Merck’s nonavalent next generation HPV vaccine candidate, results of which were presented at EUROGIN (European Research Organisation on Genital Infection and Neoplasia) 2013. This is an L1-VLP vaccine against HPV 6/11/16/18/31/33/45/52/58, which would account for 90% of HPV-mediated cervical cancer. This 3-dose vaccine (0, 2, 6 months) has a higher adjuvant content as well as antigen content for HPV 16/18, vs. Gardasil, in order to achieve serologic equivalence. Current studies have demonstrated non-inferiority immunogenicity vs. Gardasil for HPV 6/11/16/18 and efficacy for the additional HPV types in the vaccine among the 14,000 women aged 16-26 years, with up 54 months of follow-up. Efficacy was unchanged whether CIN2+ or persistent HPV for 6 months was studied (96-97%). Immunobridging studies have shown non-inferior immunogenicity among adolescent boys and girls (9-15) vs women aged 16-26, as well as serologic equivalence for HPV 6/11/16/18 antibodies whether receiving quadrivalent or nonavalent vaccine. Concomitant vaccine administration studies and studies among prior Gardasil recipients are completed and results have been presented. This vaccine was approved by the U.S. FDA in December, 2014.

**B. 2.4 Development of Second Generation HPV Vaccines**

_F. Struyf, GlaxoSmithKline (Rixensart, Belgium)_

Dr. Struyf presented GSK’s plans to increase access to Cervarix, given an unmet need for easier-to-implement and more affordable vaccines. Cervarix demonstrated 93% efficacy against CIN3+, regardless of the causative HPV type, in a four year trial suggesting a high degree of cross-protection. The durability of cross-protection is being studied in a larger Finnish cohort for 15-20 years. Given such high short term efficacy, GSK is focusing on extending indications for Cervarix rather than developing a new vaccine with more L1 VLP types.

Among adolescents ages 9-14, GSK plans to pursue a 2-dose schedule, given non-inferior immunogenicity with 2 doses (0, 6 months) compared with 3 doses (0, 1, 6 months) and higher titers than in adults. Co-administration of 2-dose Cervarix with MMR and DTPa among young children 4-6 in Latin America with 3-year follow-up is also being studied. Longer-term follow-up and possible need for a booster have not yet been determined. Efficacy and immunogenicity of 3-dose schedule are also being studied among women > 25,

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with co-primary endpoints of CIN1+ and persistent HPV infection, with results anticipated in 2014/2015. Efficacy studies are also ongoing in China among women ages 18-25; neither Cervarix nor Gardasil are licensed in China.

**B. 2.5 (HPV Vaccines in Development)**
_ U. Shaligram, Serum Institute of India Limited (Pune, India)_

Dr. Shaligram discussed the Hansenula yeast expression system for a prophylactic L1 VLP vaccine that is in early development. They are also developing a Chimeric Duck Hep B system – which offers much room to present antigens, though it is still to be determined how many antigens can be immunogenic. They plan to place L2, E6, and E7 into the chimeric VLPs. Ultimately, the goal is to develop a combined prophylactic and therapeutic vaccine. Given efficacy of current vaccines, placebo-controlled trials would not be possible in India.

**B. 2.6 (Therapeutic Vaccine)**
_ G. Scheper, Crucell (Leiden, Netherlands)_

Crucell is developing a therapeutic adenovirus-based vaccine to target persistent infection and CIN 1. Adenoviruses are efficient in inducing cellular immune responses. They are starting an HPV 18 manufacturing process. They aim to have a therapeutic vaccine for 16/18 to be tested for persistent infection using two adenoviruses so heterologous type boosting can be employed. They will target 12 month persistent infection, especially HPV 16 infection.

**B. 2.7 (HPV vaccine program)**
_ N. Bachtiar, PT Bio Farma (Bandung, Indonesia)_

Indonesia has a vaccine industry in place and is looking to use that industry to develop a HPV vaccine that can be used for their population, as cost of current vaccines is prohibitive. They are looking not only at developing technology but also for technology transfer.

**B. 3. Clinical Development of HPV Vaccines: Regulatory Perspectives**
_ J. Roberts, Food and Drug Administration (USA)_

Dr. Roberts reviewed that in the United States, the FDA determines whether the product is safe and efficacious and actually achieves its stated endpoint. Neither public health benefits nor cost-effectiveness are the FDA’s mandate. He reviewed the history of the FDA’s consideration of HPV vaccines and the advantages and disadvantages of various endpoints (immunologic, virologic, cytologic, histologic) and prior agreement that CIN2+ was appropriate from its initial discussions in 2001. Because CIN2+ was still required, Merck undertook parallel data collection for CIN2+ and persistent HPV infection as well as immunogenicity as endpoints for its nonavalent vaccine candidate, providing ample data to support a change in primary endpoint.
He also stated that placebo-controlled efficacy trials are infeasible and/or unethical once the pivotal efficacy trial demonstrates efficacy, thus serving as an important benchmark. He reviewed the history of studies and approval for next generation vaccines for different diseases. For instance, once PCV7 (7-valent pneumococcal vaccine) was approved, PCV13 placebo-controlled study was not feasible and the endpoints for additional serotypes were based on a post-vaccination immunogenicity threshold. Similarly, meningococcal serogroup B vaccines will be evaluated based on immunogenicity endpoints.

Ultimately, he stated that appropriate endpoints for future studies of HPV vaccines will be evaluated on a case-by-case basis.

A discussion led by the regulators from various agencies ensued.

P. Neels, Consultant (former member of the Vaccines Working Group of the European Medicines Agency)
M. Powell, Medicines and Healthcare Products Regulatory Agency (London, UK)
J. Roberts, FDA (USA)
I. Uhnoo, Swedish Institute for Communicable Disease Control (Lund, Sweden)

Indications for HPV vaccines in Europe differ slightly from those in the United States. In Europe, vaccine indications state ages 9 years and above. They do not specify gender or upper age limit.

European regulators raised the legal challenge of non-inferiority immunogenicity or immunobridging trials comparing vaccine candidates by different manufacturers, given a 10-year data protection clause in Europe imposed by the regulatory agency European Medicines Agency (EMA). This moratorium prevents obtaining an indication for an outcome if the data supporting that outcome consists solely of bridging immunogenicity data with a trial conducted by a different manufacturer. Dr. Roberts said that this does not pose any significant problems for licensure of a new vaccine candidate at the FDA, as long as the comparator vaccine is licensed in the USA.

Although the EMA previously has stated that non-inferior serologic data was insufficient to establish efficacy, accumulating evidence demonstrating efficacy/effectiveness, as summarized in the IARC report, may change this decision, especially if post-licensure monitoring on effectiveness continues. Data presented from Merck's nonavalent vaccine trial were felt to be very instructive and illustrated some of the challenges in doing trials once a vaccine is available.

Much discussion centered on the AIN1+ endpoint. The number of HPV 16/18 related AIN2/3 cases in the quadrivalent HPV vaccine trial was only 9 (8 in placebo, 1 in study group), and the lower confidence interval reached 0. Hence EMA did not give an indication for anal dysplasia.

Brief discussion also touched on whether HPV vaccine indications should change from prevention of cervical cancer/precancerous lesions to prevention of HPV infection, although regulators stated that, in general, products are not licensed for infection.
prevention but rather for disease prevention. In addition, further study of the natural history/epidemiology/pathogenesis of HPV for non-cervical sites was suggested by some prior to broadening to persistent HPV infection outcomes, particularly for oropharyngeal sites.

The tables from the IARC meeting outlining appropriate primary endpoints, stratified by disease site, vaccine type, and age group were discussed (see above). Age group stratification (<16y, 16-26y, >26y) was determined based on the pivotal efficacy studies performed in women up to 26 years for the bivalent and quadrivalent vaccines. While efficacy studies in older women with placebo would be possible in the USA due to current vaccine licensing, this would not be possible in Europe, given that there is no upper age limit for the vaccine indication. Some suggested that both premalignant disease endpoints and persistent HPV infection were the appropriate endpoints for those older than 26 years.

There was also discussion surrounding the reality of post-licensure monitoring and evaluation for efficacy. For instance, while monitoring efficacy of 2-dose schedules might be most feasible in countries with good registries, these same settings are likely to have herd immunity as a result of their vaccination programs, thus making detection of vaccine failure challenging (regardless of outcome).


*M. Powell, Medicines and Healthcare Products Regulatory Agency (London, UK)*

Dr. Powell reviewed the history behind the current guideline, TRS No. 962, Part C. These guidelines pertain to L1-VLP vaccines against cervical cancer and premalignant disease and were initially adopted in 2006, when Gardasil and Cervarix were licensed in some countries. At this time, very little data existed about non-histologic endpoints (i.e., virologic or serologic endpoints). Briefly, the guidelines cover:

- the documentation of bivalent and quadrivalent vaccine efficacy against histologic endpoints, including bridging efficacy to younger age groups via immunobridging;
- the characterization of immune response and relevant assays;
- persistent HPV infection, although little data on this and lack of a standard definition (i.e., 6 months, 12 months, or 18 months persistence) to correlate to premalignant disease;
- cross protection, although no established definition and challenging to characterize;
- post-approval safety/effectiveness;
- trial design for new L1 VLP vaccines, with the consideration that placebo controls may not be ethical/feasible and using historical data instead;
- new vaccines covering additional oncogenic HPV types; and
- immunobridging to younger age groups, looking at males and females separately.

Overall, the guidelines are still valid, but given advances in the field it may be possible to be more definitive in certain areas and address arising issues for next generation vaccines.

Topics to add to the guidelines could include:
• changing the schedule and/or route of administration and/or indication;
• extending the age range of eligible individuals (including older women);
• addressing non-cervical, anogenital infections and oropharyngeal HPV-associated cancers;
• defining preapproval duration of follow-up and post-approval monitoring expectations;
• non-L1-VLP vaccines; and
• therapeutic vaccines or mixed prophylactic/therapeutic vaccines.

Possible revisions include:
• updating evidence regarding virologic and serologic endpoints
• data supporting multivalent HPV vaccine efficacy and new L1 VLP vaccines;
• data supporting new L1 VLP 16/18 vaccines
• post-approval studies

Discussion addressed several issues, including
• changes in licensed L1 VLP vaccines (i.e., with dosing schedule or route of administration) must demonstrate no change in efficacy against HPV 16/18, likely via serologic non-inferiority although this is not established;
• serologic non-inferiority for new non-VLP vaccines or L2 VLP vaccines may not be appropriate, given different types of antibodies likely to be elicited; virologic endpoints are more likely to be appropriate in a trial with an active control group
• investigating the need for vaccine boosting;
• individualizing recommendations for immunodeficient populations and assuring vaccine safety in this varied population;
• studying cross protection phenomenon further to ensure its durability;
• emphasizing acceptance of persistent HPV infection as an appropriate clinical endpoint. This raised the question of whether histology ought to be collected as a secondary endpoint at all (potentially a small study might find a histologic abnormality in a small sample that is not real)

Further discussion regarding these issues occurred at the end of the meeting and are summarized in section C.

B. 5 The Process to Update TRS Document
T. Zhou, WHO

Dr. Zhou reviewed the purpose and use of WHO’s global written standards for biologicals. Standards are international technical specifications that help define safe and efficacious vaccines, based on scientific consultation and international consensus. They provide guidance for national regulatory authorities and manufacturers to assure quality, safety, and efficacy of the vaccines. They may be used by member states as the basis for national legislation, and by the WHO as the basis for prequalification for vaccines procured by United Nations agencies. WHO global standards aim to facilitate international
harmonization of vaccine evaluation and licensure. They are living documents and may be revised in response to scientific advances in the future.

The process for setting standards has multiple steps. WHO holds consultations of all interested parties including vaccine regulators, manufacturers and academia researchers to review and discuss up-to-date evidence and practice in the subject, exchange views and identify key issues, to reach consensus. These initial steps have occurred with the WHO scoping meeting (27 February 2013), the IARC Scientific Meeting (23-24 September 2013), and this current meeting.

Next, a drafting group will be set up by WHO to prepare draft guidelines. The tentative date for a drafting group meeting is April 2014. These draft guidelines will be reviewed through a series of public consultations. A mature draft will then be reviewed in November 2014 at an informal consultation meeting to be held by WHO. Subsequently, a final draft will be presented to the WHO Expert Committee on Biological Standardization (ECBS) for consideration. This is expected to be submitted by July 1, 2015. Following this submission, the draft will be again open to public consultation. Consideration by ECBS will occur in October 2015.

Upon approval, the document is established as a WHO Technical Report Series (TRS) document.

Discussion regarding the process of updating the guidelines revolved around defining the scope of the update (currently licensed vaccines only or including vaccines in clinical development) and whether to endorse/recommend the IARC publication. The group agreed to focus the update on the most important changes, the most significant being the acceptance of persistent HPV infection for 6 months as an appropriate clinical endpoint.

B. 6 HPV Virology and Serology Tests: Importance of Standardization and Quality Control, Pre-analytic issues

E. Unger, CDC

Dr. Unger reviewed the importance of proper sample collection and analysis for serologic and virologic assays. For serologic assays, sample collection is straightforward, but assays are different and no commercial reagents exist to assist in standardization. Currently used assays include the competitive Luminex immunoassay (cLIA), the direct L1 VLP ELISA assay, and the pseudovirion neutralization assay. The latter two are considered by the WHO LabNet.

For virologic endpoints, especially if they are to serve as primary endpoints, sample collection, extraction/processing, and assay method are very important but very variable and not standardized currently. For sample collection, clinician collected specimens placed in ThinPrep or STM media are better, although there is no clear guideline for the collection instrument for the specimen. Extraction needs to be matched to the sample collection, as the volume extracted and proportion in the assay can affect the results. As an example, she
reviewed the differences in sample collection, extraction/processing, and assay method between the bivalent and quadrivalent vaccines.

Dr. Unger concluded by stating that clear standards need to be written, particularly for pre-analytic components of endpoint evaluation. The WHO HPV Lab Manual serves as a good starting point, as standard operating procedures (SOPs) are detailed and agreed upon by the WHO and Lab Net. However the goal of these SOPs was for epidemiologic monitoring of current HPV vaccines and quality control, and not meant for standardizing the virologic assays to be used in clinical trials.

**B. 7 HPV Virology and Serology Tests: Importance of Standardization of HPV Test Laboratory Methods**

*J. Dillner, Lund University, Sweden*

Briefly, there are 125 commercially available tests to identify HPV DNA. In the WHO HPV DNA Proficiency Study, 19% of labs were consistently proficient in their methods; there occurred larger variability between labs using the same assay than between assays.

He proposed that HPV DNA testing and typing needs to be proficient by international criteria, with the following minimum criteria:

- Ability to detect multiple infections
- High capacity to detect typing error
- Ability to apply to all known high risk HPV DNA types
- Minimum threshold of detection would be 50 IU of HPV 16/18 and 500 gEq (genome equivalents) of other high risk types, with 97% specificity

Echoing Dr. Unger, he urged that a manual with SOP for quality control and quality assurance would be highly beneficial.

With regard to serology, standardization is important as these tests are used for immunobridging and non inferiority testing. The sample collection is less variable in serologic testing. However, the lack of commercial reagents and the differing assays used in the various clinical trials create challenges to standardize serologic assays. Results should be reported in international units when possible.

**B. 8. Availability of international measurement standards for HPV**

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International Standards and WHO Reference Reagents are used in calibration of immune response assays in clinical trials, in quality control testing of vaccines (lot release), in development, evaluation, standardization and control of products in industry by regulatory authorities and also in biological research, academic and scientific organizations. They are tools for the comparison of results from different laboratories globally; they support harmonization of international regulations of biologics and facilitate development of vaccines, diagnostics and therapeutics. They are recognized by other international standards setting bodies.
The ECBS has established international standards of anti-HPV 16/18 serum for serologic use and HPV 16/18 DNA for amplification and detection of HPV types 16 & 18 DNA. Standards for HPV DNA for types 31, 33, 45, 52, 58, 6, 11 are under development and are slated for completion by 2015. WHO Reference Panel for Quality Control of HPV 16/18 VLPs used in immunoassays is also under development.

The question was raised whether clinical trials should also include evidence of laboratory proficiency but this was not resolved.

C. Conclusions

The group agreed that the IARC meeting had provided the scientific evidence base for various possible endpoints (virologic vs. serologic vs. histologic), based on the most up-to-date data on HPV epidemiology and pathogenesis. Thus, the purpose of this group’s meeting was to establish what seemed feasible and desirable to update the WHO TRS document. Other points of discussion, based on the gaps identified in the current TRS document, are as follows:

- There was agreement that persistent HPV infection for 6 months is an appropriate clinical endpoint for HPV vaccine trials. This is based on data from the clinical trials showing the absolute risk of CIN3 being the same for persistent infection for 6 or 12 months.

- With respect to currently licensed L1 VLP vaccines for 16/18 in women less or equal to 26 years of age, demonstration of serologic non-inferiority would be necessary before adopting new dosing schedules or routes of administration.

- For new L1 VLP vaccines directed against types 16, 18, serologic non-inferiority needs to be demonstrated.

- In multivalent L1 VLP vaccines, for the non 16,18 other high-risk HPV types, virologic endpoints need to be used, either as a composite outcome, or for each type. However, given anticipated low case rates per high-risk type, some advocated for post-trial ecological surveys to ensure that controls were exposed to those types to ensure that this was a population at risk of disease.

- For new, non-L1 VLP vaccines, virologic endpoints are initially needed to document efficacy. Serologic endpoints may ensue in the future. If capsomere vaccines are resulting in L1 antigens, then serologic endpoints may be appropriate.

- For non-cervical anogenital infections, virologic endpoints may be appropriate, (though consensus was not reached on this). If histologic endpoints are used, the fact that AIN1 may be transient and may reflect low-risk disease may diminish its appropriateness as an endpoint. (though consensus was not reached on this point, either).
Methodological considerations discussed for future trials:

• Exploration of antibody avidity could be investigated in a subset of patients as a secondary outcome, but cannot be a primary outcome as thresholds are not established and assay standardization still needs further refining.

• Observational data collection on histology would not be required for regulatory consideration of new vaccines. However, histologic endpoints are more important for public health monitoring studies and could be pursued.

• For immunobridging studies, it is important to document the plateau titer, not just the peak titer, and it is necessary to establish the proper time-point for measuring these responses.

• To enhance future trials and comparison of efficacy of vaccines, there is an acute need to develop standard operating procedures for HPV DNA detection and HPV serologic assays.

• International units should be used so that results between trials can be compared.