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Preventive Human Papillomavirus (HPV) Vaccines-
Regulatory Briefing Document on Endpoints

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Discussion of Possible Endpoints for Licensure of Human Papillomavirus
(HPV) Vaccines^{1,2,3}

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The purpose of this document is to discuss the merits and drawbacks of endpoints proposed for clinical efficacy trials to evaluate preventive HPV vaccines containing "oncogenic" HPV types. The ultimate goal for these vaccines is the prevention of cervical cancer. Since infection with an oncogenic HPV type is thought to be a necessary step in the pathogenesis of most cervical cancer, a number of potential endpoints proceeding from the initial infection are considered.

Endpoints in clinical studies may be defined as measurable outcome variables following an experimental intervention. Primary efficacy endpoints are usually selected to provide an outcome measure of the greatest clinical relevance. In efficacy trials of vaccines, prevention of a disease is commonly used as the primary outcome variable. However, the severity and stages of disease can vary considerably, and endpoints based on preventing disease of greater or lesser severity may be appropriate for vaccine efficacy trials.

Certain federal regulations relate to selection of efficacy endpoints. Under 21 CFR 314.125, FDA may refuse to approve a drug application if there is a lack of substantial evidence of efficacy from adequate and well-controlled investigations demonstrating that the drug product will have the effect it purports or is represented to have in its proposed labeling. Thus, the approved product indication will reflect the endpoint selection in definitive efficacy studies.

Characteristics of adequate and well-controlled studies are described under 21 CFR 314.126. Relevant parts of this regulation state that the purpose of

¹ This is one of two FDA documents. Please refer to the other FDA document (#2) for more background information on HPV, cervical intraepithelial neoplasia (CIN) and cervical cancer.

² The meeting is only addressing preventive HPV vaccines.

³ Summary table in this document, located immediately before references, may help to orient the reader.

conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. Studies are to use a design that permits valid comparison with a control to provide a quantitative assessment of drug effect. The methods of assessment of subjects' responses are to be well defined and reliable.

Potential endpoints for traditional approval

The choice of endpoints in clinical efficacy trials of prophylactic human papillomavirus (HPV) vaccines will affect the sample sizes, trial designs, duration, resources needed, choice of study populations, and the indication in the vaccine label. In the discussion that follows, endpoints based on virologic, cytologic, and histopathologic outcomes are presented, and arguments both favoring and against those endpoint selections are described. Only endpoints for oncogenic HPV types in the context of cervical abnormalities are considered here.

Virologic endpoints

The presence of an HPV infection in a clinical trial would not be established using classical *in vitro* cell culture methods. Identification and typing of HPV infections rely on detection of viral DNA using tools of molecular virology, such as polymerase chain reaction (PCR) or DNA hybridization. Serology appears to be less sensitive than molecular techniques in establishing that a new, or incident, infection has occurred, and would likely not be able to distinguish a persistent infection from an infection that has resolved. Both incident and persistent infections (starting during the trial) have been proposed as endpoints in HPV vaccine trials.

Incident HPV infection due to vaccine HPV types

Based on abundant epidemiologic data, infection by an oncogenic HPV type appears to be a necessary step in the pathogenesis of the vast majority of cervical cancers. Specifically, it appears likely that incident HPV infection begins the process of malignant transformation and invasion of cervical tissue. Therefore, prevention of HPV infection may be expected to preclude all subsequent steps in the pathogenesis of cervical cancer.

Studies assessing incident HPV infection as the primary efficacy endpoint may be easier to conduct than studies using other outcome measures. Cases could accrue relatively quickly and be completed within a relatively short period of time, a few years from study initiation. Sample sizes adequate to demonstrate a treatment effect would likely be relatively small (e.g., a few thousand subjects), and may not require the length of follow-up to ascertain endpoints as would be required for endpoints assessing more advanced disease in the pathogenesis of cervical cancer. Definitive efficacy trials for incident HPV infection could be

completed within a relatively short time frame, e.g., a few years from study initiation. Monitoring would need to be fairly extensive, e.g., regular Pap smears and HPV testing on all trial participants, plus other interventions such as colposcopy and biopsy, based on a protocol specified algorithm.

From a population perspective, prevention of infection among vaccinated individuals may be expected to result in a decrease in circulating HPV within the larger population. However, this effect is difficult to quantify in the context of an efficacy study.

Prevention of infection can be a difficult endpoint to meet. Typically, the efficacy of vaccines is demonstrated by prevention of disease, as symptomatic disease (or its sequelae) is of greater clinical relevance than is infection, which may be transient and asymptomatic. It is usually symptomatic disease that brings patients to clinicians and trial participants to the attention of clinical investigators. In general, it can be quite difficult to determine whether a vaccine prevents the infection of interest, or whether the vaccine induces an immune response that contains and clears an incipient infection, before disease becomes apparent.

Most incident HPV infections are thought to be asymptomatic and transient without intervention and, therefore, lack clinical relevance for the individual. Thus, a vaccine efficacy estimate for prevention of incident infection could substantially overestimate the protective efficacy for the endpoint of greatest clinical relevance, cervical cancer.

Also, hypothetically, women who develop a poor immune response to an HPV vaccine may be those who are less likely to clear infections spontaneously, and more likely to develop high-grade cervical lesions and cervical cancer. For example, a vaccine that is 90-95% effective in preventing incident infection could be much less effective in preventing high-grade cervical lesions and cancer, if those at greatest risk of progression are over-represented among the 5-10% who would not be protected from infection by the vaccine. If an HPV vaccine proves highly efficacious (>95%) in preventing infection across populations, such a scenario may be less likely.

Another consideration in using incident (or persistent) infection as an efficacy endpoint is the reliability of detection of type-specific HPV infection, both at study entry and throughout the trial. Detection of incident or persistent HPV infection relies on detection of DNA from cervical samples or smears. These samples obtain superficial cervical cells more so than basal layer cells. (This type of HPV testing should be distinguished from testing of biopsy samples, e.g., with *in situ* hybridization of actual lesions). Thus, it may not always be possible to distinguish a new infection from a recurrence or reactivation of a previously latent infection. Assuming a sensitive assay, productive HPV infections (i.e., infection resulting in shedding of infectious viral particles) may be detected readily, but there is

uncertainty about detecting “latent” infections, which would be expected to exist predominantly in basal layer cells of the cervical epithelium.

In a randomized study design, inability to detect the presence of HPV infection at study entry would likely be evenly distributed among groups. While this type of uncertainty about the case definition would not result in systematic bias of measures of efficacy, it would result in less case specificity and may result in a less precise estimate of efficacy. Moreover, if an incident infection in a previously uninfected person achieves latency and integration prior to the next scheduled visit, it might be falsely concluded that no infection occurred. Additionally, it is plausible that a vaccine induced immune response might impair detection of HPV DNA, possibly by facilitating clearance of virus from the more superficial epithelium, while infection and integration of cells in the deeper epithelial layers, especially the basal layer, persists.

The benefits of vaccination to prevent asymptomatic HPV infections may not be viewed favorably when compared to risks of adverse events related to vaccination. This risk-to-benefit assessment would more likely favor vaccination if clear evidence for prevention of high-grade cervical lesions were demonstrated.

Finally, although virologic endpoint studies may allow for demonstration of efficacy using relatively small sample sizes, large randomized datasets are preferred to evaluate safety of HPV vaccines. The bulk of safety data supporting licensure of vaccines is usually obtained in trials designed to demonstrate efficacy. If virologic endpoints are chosen based largely on feasibility considerations, it may be necessary to conduct additional randomized trials in order to closely monitor a large cohort of individuals for safety outcomes.

Persistent HPV infection by oncogenic HPV types

Persistent HPV infection can be defined by the presence of type-specific HPV DNA on repeated visits over some period of time. In one large study, detection of HPV type 16 DNA in the last 2 Pap smears before a diagnosis of carcinoma *in situ* (CIS) excluding smears taken less than 1 year before diagnosis, was found to have a higher odds ratio for association with CIS than was a single finding of HPV DNA (Ylitalo N et al., Cancer Res, 2000). In another study, the relative risk for developing squamous intraepithelial lesions (29 of 31 were low grade) was 37 (95% CI: 14.6-95) for women with the same high-risk type HPV detected at two consecutive visits (6 months apart) compared to women who were HPV negative at one or both visits (Ho GYF et al., 1998).

The optimal interval after which an HPV infection would be considered persistent is not readily apparent. Estimates of the median duration of HPV type 16 infection vary from 8 to 12 months (Ho GYF et al., 1998, Franco EL et al., 1999, Woodman CB, et al., 2001). Thus, study designs in which HPV testing is performed every

4-6 months could conclude that an infection is persistent in cases where viral clearance proceeds normally within a typical duration of infection.

Reservations regarding use of incident HPV infection as an endpoint, as discussed above, also apply to persistent infection. Like incident infection, most persistent infections are thought to be asymptomatic, and, therefore, lack clear clinical relevance for the individual. Clinical trials using only virologic endpoints, ignoring cervical pathology, could significantly overestimate the benefit from vaccination for prevention of cervical cancer. Until an efficacy study using clinical endpoints is conducted that clearly validates virologic endpoints as quantitatively predictive of clinical outcomes of interest with HPV vaccine use, the value of virologic endpoints used without cervical pathology will remain uncertain.

If virologic endpoints are not judged to be adequate for demonstrating efficacy in preventing cervical cancer, it is possible that incident or persistent infection might be suitable surrogate endpoints to support accelerated approval, as described in the FDA regulations. Accelerated approval is discussed later in this document.

Endpoints based on cytology

LSIL and/or ASC, or worse, in association with oncogenic HPV types

Low-grade squamous intraepithelial lesion (LSIL) as discussed in this section, and atypical squamous cells (ASC) are cytologic terms used in the interpretation of Pap smear results. Management of such cytology findings may vary. Workup by immediate colposcopy may occur. However, depending on clinical factors such as availability for follow-up and immune status, clinicians may elect to follow-up such cytologic findings with another Pap smear without immediate colposcopy. When incident or persistent LSIL leads to colposcopy and biopsy, abnormal findings could be reflected in a pathologic diagnosis, such as cervical intraepithelial neoplasia (CIN), as discussed in several sections below.

It may be argued that prevention of LSIL or ASC, or prevention of persistent LSIL would translate into fewer repeat Pap smears, colposcopies and biopsies, and thus would provide evidence of clinical benefit. However, there must be histologic evidence (e.g., CIN 1 on biopsy) in order to initiate treatment. In the US, a finding of LSIL cytology by itself is an insufficient basis to treat. Thus, prevention of the pathologic diagnosis (by histology) would more clearly indicate clinical benefit.

Endpoints based on histology

CIN 1 histology, adenocarcinoma *in situ* (AIS) of the cervix, or worse, in association with oncogenic HPV types

Cervical intraepithelial neoplasia (CIN) is a pathologic diagnosis based on tissue obtained at biopsy, e.g., after a Pap screening test finding of ASC or LSIL. CIN 1 histology is considered a low-grade lesion. The histology is characterized by a finding of undifferentiated cells in the lower third of the cervical epithelium. A pathologic diagnosis of CIN I, or worse, by biopsy is considered more definitive than a cytologic finding of LSIL with regard to therapeutic decisions. Biopsy specimens would include the basal epithelium, thus possibly enabling identification of latent or otherwise inapparent HPV infection. The actual lesions can be evaluated for HPV type by *in situ* hybridization.

Because a diagnosis of CIN 1 is based on tissue samples, prevention of CIN 1 or worse would directly reflect prevention of a procedure (biopsy).

In a recent study (ALTS), 26% (298/1149) of subjects with ASC (at entry) who were randomized to immediate colposcopy had CIN (majority are CIN 1), or worse, at biopsy (Solomon D et al., 2001). In addition, studies have found that 52 to 85% of women with LSIL cytology have CIN (majority are CIN 1) or worse on biopsy [Lonky NM et al., 1999; Jones BA, 2000].

Similar to LSIL, about 50% of CIN 1 regressed to normal (Östör AG, 1993). (See Natural History section of the FDA HPV Vaccine Background document for more details.) The risk of CIN 1 progressing to cancer over a period of months or even a few years is thought to be low, at least in those subjects with adequate follow-up [ASCCP (1), 2001; Östör AG, 1993]. Thus, an efficacy estimate for prevention of CIN 1 could substantially overestimate the efficacy in preventing cervical cancer; although the magnitude of an overestimate may be diminished if the efficacy in preventing CIN 1 is high.

Also of interest here, in at least 2 longitudinal studies, some women with normal cytology at baseline had a diagnosis of CIN2/3 (histology) identified on initial workup for an abnormal Pap smear during the study (Koutsky LA et al., 1992; Woodman CD et al., 2001).

If licensure of HPV vaccines were to be based on prevention of predominantly CIN 1, the vaccine indication in the label would reflect that the vaccine prevents CIN 1, not cervical cancer. Additional efficacy studies would be required post-licensure to justify extending the labeled indication to include prevention of cervical cancer.

CIN 2/3 histology, adenocarcinoma *in situ* (AIS) of the cervix, or worse, in association with oncogenic HPV types

Most of the endpoints in this category would be CIN 2 or 3. CIN 2 is defined by moderate dysplasia. CIN 3 includes both severe dysplasia and carcinoma *in situ*. Both CIN 2 and 3 are considered high-grade cervical lesions. In the US, little distinction is made between CIN 2 and CIN 3 in terms of medical management. Thus, it is reasonable to consider CIN 2/3, AIS, or worse as a single entity for the purpose of selection of efficacy endpoints for HPV vaccine trials. If efficacy trials using cervical cancer as the endpoint cannot be conducted, prevention of CIN 2/3, AIS, or worse will most closely approximate the preventive efficacy of HPV vaccines for cervical cancer.

As discussed under the CIN 1 or worse endpoint section, a pathologic diagnosis based on tissue is needed for therapeutic decisions. Prevention of CIN 2/3 would translate into prevention of both the diagnostic biopsy, and a subsequent therapy (excisional or ablative procedure, as appropriate). Thus, in preventing CIN 2/3, substantial clinical benefit will have been realized.

It has been argued that studies examining CIN 2/3 as the primary efficacy endpoint could be prohibitively resource intensive, and of long duration. Concerns expressed regarding use of CIN 2/3 as a primary efficacy endpoint have focused on the following areas:

1. The length of trial considerations as well as sample size projections have been cited as a problem, although little specific information has been presented or published in this regard (WHO meeting, Geneva, Switzerland 1999).
2. Large preventive vaccine efficacy trials, e.g., 10,000 to 40,000 enrollees, are not unusual. However, the type of follow-up (i.e., multiple clinical examinations and laboratory testing) makes this sort of trial more resource intensive and complex than typical preventive vaccine efficacy trials, although similar to virologic endpoint trials with regard to resources per subject per year.
3. In a trial of subjects being followed, e.g., at 4, 6, or 12-month intervals, a certain percentage of incident cervical dysplasia would need to be CIN 2/3 at initial work-up, in order to accrue sufficient cases of CIN 2/3 to demonstrate efficacy. This may be the case whether or not CIN 1 is treated during a trial.

It should be noted that a certain proportion of women with ASC, LSIL and atypical glandular cells (AGC) cytology will have HSIL/CIN 2/3 upon initial work-up. In fact, work-up of such low-grade lesions with colposcopy and biopsy could generate most of the CIN 2/3, AIS, or worse diagnoses in an efficacy trial (Kinney WK et al., 1998; Lonky NM et al., 1999; Woodman CB et al., 2001). Across studies, the proportion of women with CIN 2/3 or worse following the work-up for ASCUS (ASC) has ranged from about 6% to 11% (Solomon D et al., 2001). For LSIL, the proportion with CIN 2/3 or worse at work-up has usually ranged from about 16% to 28% [ASCCP (1) 2001]. However, several European studies have reported rates

as high as 50-70%. For AGUS (AGC), the proportion with CIN 2/3 or worse at work-up has usually ranged from about 9-13%, with a special concern about the percent of frank cancer (as discussed in the other FDA document).

The estimate of the size/duration of a preventive HPV vaccine efficacy trial with a CIN 2/3, AIS, or worse endpoint would come from a prospective cohort of closely monitored subjects who have normal cytology and negative HPV testing results at baseline. Data from one such longitudinal study was recently published (Woodman C et al., 2001, included with FDA briefing materials). In this prospective study conducted in the UK, 1075 women with normal Pap smears and who were negative for HPV at study entry, were followed for a median of 26 months. A diagnosis of CIN 2 or 3 was established for 28 women, 20 of whom were diagnosed with CIN 2 or 3 during work-up of the first episode of abnormal cytology. Median time to diagnosis of CIN 2/3 was 36 months from study entry.

If one assumes the following parameters, *approximately* 12,000 women would need to be enrolled:

A trial with 1:1 randomization, HPV 16 and 18 infection rate similar to the Woodman et al., article, a vaccine efficacy of $\geq 80\%$, trial duration of 3 1/2 years (mean follow-up 3 years), 80% power, 20% loss to follow-up, and about 50% of incident CIN 2/3 cases attributed to vaccine types (HPV type 16 or 18).

If preventive efficacy trials using cervical cancer as the outcome are deemed not feasible or not appropriate, then endpoints based on high-grade CIN pathologic criteria, in the context of HPV infection, appear to be the most clinically relevant and most accurate in predicting and quantifying the preventive efficacy of HPV vaccines for cervical cancer. Should efficacy of an HPV vaccine in preventing high-grade cervical lesions be demonstrated, a labeled indication for prevention of cervical cancer may be considered.

Cervical cancer (invasive)

Prevention of cervical cancer would be the most clinically relevant endpoint for a preventive HPV vaccine comprising oncogenic types. However, there appears to be significant feasibility issues for conducting a vaccine study using cervical cancer as the endpoint. Standard of care in the US dictates that women enrolled in HPV vaccine trials would be followed closely by means of Pap screening and other interventions, as appropriate. Given the relatively protracted duration of carcinogenesis following HPV infection (median time from HPV infection to carcinoma *in situ* has been estimated to be 7-12 years) (Ylitalo N et al., Cancer Res 2000), and the relatively low frequency of cervical cancer in the US due to screening and early treatment, clinical studies using cervical cancer as an endpoint could require a prolonged duration of follow-up to identify sufficient cases to establish efficacy.

The possibility of conducting a long-term, e.g., up to 20 year, population based trial to evaluate the impact of vaccination on ICC (invasive cervical cancer) [with or without CIN 3] in Nordic countries and Estonia has been discussed in the literature. The proposal involved use of cancer registry follow-up. For example, Finland has a country-wide cancer program where practically all invasive cancer cases (>95% histologically confirmed diagnoses) are captured; in addition, CIN 3 and adenocarcinoma *in situ* are captured (Lehtinen M et al., 2000).

It might be considered feasible to conduct HPV vaccine studies using cervical cancer as an endpoint in areas of the world where cervical cancer rates are high, and screening and treatment are not effectively employed. However, in the context of a clinical trial, some would consider it unethical not to provide effective screening and treatment to all participants, even if that level of medical care would not otherwise be available. If effective screening and treatment were made available, then the rates of cervical cancer would be expected to fall, and advantages of conducting trials in those high incidence areas might no longer exist.

Another complex issue for a cervical cancer trial, given the size of such a trial, could be screening for HPV and exclusion at baseline. Without screening and exclusion at baseline, pre-existing HPV infection may substantially dilute vaccine efficacy estimates, as well as increase sample size. The same consideration (although logistically more feasible) applies to the decision of whether or not to HPV test/type the cervical cancer specimens.

Other considerations affecting the selection of endpoints

It should not be assumed that efficacy trials with endpoints such as CIN 2/3 must be conducted in developing countries. HPV infection annual incidence rates that equal or exceed ~ 3% for HPV Type 16 and ~2% for HPV Type 18 have been documented in cohorts in developed countries (Woodman CB et al., 2001; Ho GYF et al., 1998; Thomas KK et al., 2000). If HPV infection is linked to the subsequent development of CIN 2/3 (or worse), then these cohorts would appear to be relatively high-risk populations for the development of high-grade cervical lesions.

The public health community may have difficulty assessing the value of wide implementation (for the US and elsewhere) of an HPV vaccine if the approval is based on endpoints associated with asymptomatic infections, when the effect on the medical conditions of interest, high-grade dysplasia and/or cervical cancer, has not been demonstrated in a well-controlled trial.

When multiple serotypes, etc., of an infectious agent cause disease, the primary endpoint in vaccine efficacy trials has been prevention of disease caused specifically by the ones represented in the vaccine (e.g., pneumococcal conjugate vaccine comprising 7 of the most common serotypes). Cervical cancer has been

associated with multiple oncogenic HPV types, of which HPV type 16 is the most common, found in approximately 50% of cervical cancers. Limiting the primary endpoint to HPV types represented in the vaccine will likely result in a higher vaccine efficacy estimate than if the endpoint reflected disease caused by all HPV types. However, prevention of all cervical cancer associated with HPV is the ultimate goal of an HPV vaccine. Therefore, it will also be important in HPV vaccine trials to conduct pre-specified secondary analyses to assess efficacy of the vaccine for the chosen endpoints (e.g., all CIN 2/3), regardless of the HPV type implicated. Such secondary analyses have the potential to address questions that can be important to the overall risk-benefit assessment, such as “replacement” disease caused by non-vaccine types or other infectious diseases.

Another consideration is that adenocarcinoma accounts for an increasing proportion of cervical cancer in developed countries. HPV Type 18 is the type most commonly associated with cervical adenocarcinoma (Smith HO et al., 2000). Type 18 infections may be fundamentally different from Type 16 infections. Trials using an endpoint other than cervical cancer may not provide sufficient data to make conclusions about the protective efficacy of HPV Type 18 vaccines.

It may not be possible to conduct additional placebo-controlled clinical endpoint studies after licensure of an HPV vaccine, regardless of the efficacy endpoint that provided the basis of licensure. Furthermore, non-inferiority studies comparing a licensed HPV vaccine to another candidate HPV vaccine, using clinical endpoints would need to be larger and even more resource intensive than placebo-controlled studies. Thus, the opportunity to conduct and complete a vaccine study using prevention of high-grade cervical lesions as the primary efficacy outcome, as compared to placebo, may be lost with the licensure of the first HPV vaccine.

Accelerated Approval

[21 CFR 601 Subpart E: Accelerated Approval of New Biologic Products for Serious or Life-Threatening Illnesses]. This subpart of the regulations applies to certain biological products that have been studied for the treatment of serious or life-threatening illnesses, and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy). “FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that a biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity” (Sec. 601.41).

The accelerated approval regulations were intended to make available promising therapies while the definitive confirmatory efficacy studies were completed. Products approved under the accelerated approval regulations must be studied

further, to verify and describe clinical benefit of the product, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Confirmatory post-marketing studies would usually be studies already well underway at the time of accelerated approval; these studies must be carried out with due diligence. Safety of the product will have been demonstrated at the time of accelerated approval. Should the confirmatory studies fail to demonstrate efficacy for clinical endpoints, the product may be withdrawn from the market.

The accelerated approval regulations originated in the setting of rising mortality due to acquired immunodeficiency syndrome (AIDS), prior to availability of highly active antiretroviral agents. The original, and current, intent of accelerated approval regulations is to serve the best interests of the public. Drugs for treatment of HIV infections, drugs and biologics for the treatment of cancer, and other therapeutic products have been approved under accelerated approval. However, the accelerated approval provisions have not previously been invoked for licensure of a prophylactic vaccine.

Accelerated approval and HPV vaccines

Cervical cancer is clearly a serious and life-threatening medical condition. The time from incident infection by oncogenic HPV types to high-grade neoplasia or cancer may be years, and the event rate in a population that has normal cytology and negative HPV status at baseline could be quite low. It has been suggested that studies using CIN 2 and CIN 3 as primary efficacy endpoints could also be resource intensive. Nevertheless, such trials may be feasible, as discussed earlier.

Interest in surrogate endpoints and accelerated approval for HPV vaccines is understandable given the duration of trials that may be required to document unequivocal histologic evidence of high-grade cervical dysplasia or cancer. However, the appropriateness of accelerated approval regulations to prophylactic HPV vaccines is open to interpretation. Available options for preventing cervical cancer include cytologic screening with appropriate interventions, e.g., colposcopy, biopsies, and excisional or ablative procedures as indicated. It may be argued that these prevention modalities are both effective and widely available in the US. It is also expected that continued screening will be necessary, even if HPV vaccines are effective and become available, in order to prevent cervical lesions caused by HPV types not included in the vaccines. On the other hand, a reduction in the number of surgical interventions could be considered a meaningful therapeutic benefit to patients over existing treatments. Of note, cost-effectiveness cannot be used as the basis for FDA regulatory decisions.

To date, the intended populations for products approved under accelerated approval have been limited to those groups of individuals affected by the severe or

life-threatening condition in question. In the case of HPV vaccines, all healthy adolescents and adults could comprise the intended target population. Public health decisions regarding such wide implementation of an HPV vaccine following accelerated approval based on a surrogate endpoint rather than the medical conditions of interest, high-grade dysplasia and/or cervical cancer could be particularly difficult, as was discussed above in the context of traditional approvals based on virologic endpoints or low grade lesions

Should accelerated approval regulations be judged an acceptable pathway for the licensure of HPV vaccines, surrogate and confirmatory endpoints will need to be identified.

Surrogate Endpoints for Accelerated Approvals

FDA regulations state that the surrogate must be “reasonably likely”, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict benefit for the serious or life-threatening condition of interest. Thus, the strength of evidence demonstrating that a surrogate predicts benefit in life-threatening conditions can be broadly interpreted. Arguments can be made that incident HPV infection, persistent HPV infection, LSIL cytology associated with HPV infection, and CIN 1 associated with HPV infection are reasonably likely to predict benefit.

For reasons discussed above, the most informative of these candidate surrogates may be CIN 1 associated with oncogenic HPV.

Confirmatory Trials for Accelerated Approvals

One of the necessary conditions for accelerated approval is that the indication be for treatment or prevention of a serious or life-threatening illness. The confirmatory trial should validate that the surrogate endpoint predicts the outcome of interest. However, because the current practice of screening and treatment of pre-cancerous cervical lesions is largely effective in preventing cervical cancer in the US, the most appropriate confirmatory endpoints would be those most proximal to the endpoint of cervical cancer. It appears that an endpoint combining all cases of CIN 2, CIN 3, AIS, and those cases of cervical cancer not detected through screening and treatment combined is the most appropriate confirmatory endpoint, if the accelerated approval path is followed.

Once a product becomes available through accelerated approval, it may be quite difficult to conduct confirmatory studies because of widespread availability of the product. Sponsors might propose conducting confirmatory studies in countries where the product is not yet approved or available. However, as would be the case following a traditional approval, it may be problematic in the post-licensure setting to conduct trials in which subjects would be randomized to a placebo, even if the product is not otherwise available. Therefore, if a path to accelerated approval is pursued, the confirmatory trials should be fully accrued and well

underway at the time of an accelerated approval in order to assure that the confirmatory trials would yield a definitive result. An efficient approach to past accelerated approvals has been to embed the surrogate endpoint study within a confirmatory endpoint study. Given the long duration of follow-up that may be required to accrue sufficient cases of high-grade lesions, it is also unclear whether completion of the confirmatory trials would be feasible.

Advantages and disadvantages of potential efficacy endpoints for clinical trials of preventive HPV vaccines (cervix)

Endpoint	Advantages	Disadvantages	Other Comments
Incident HPV Infection	<ul style="list-style-type: none"> -Likely to accrue cases quickly. -May predict epidemiologic benefit. 	<ul style="list-style-type: none"> -Traditional endpoints usually for prevention of infectious disease. -Most HPV infections resolve. -Benefit of preventing asymptomatic infection uncertain and difficult to weigh against potential risks (adverse events related to vaccination). -Potential for vaccine-induced immune response to make HPV detection more difficult. -Uncertainty in distinguishing re-infection from new infection. -Uncertainty in existence of, or detection of latent HPV infection. -Non-responders to vaccine may be same as those with greatest risk for high-grade lesions/lesion progression. 	<ul style="list-style-type: none"> -Could be difficult to demonstrate treatment effect for incident endpoint if vaccine promotes viral clearance from superficial cervical cells. -Transient infection may not have consequences for host. Latent infection might have consequences, e.g., if host is subsequently immunosuppressed.
Persistent HPV Infection	<ul style="list-style-type: none"> -Epidemiologic data may indicate that persistent HPV infection is a better predictor of high-grade lesions than a single positive finding. 	<ul style="list-style-type: none"> -No common definition of persistent. -Appropriate time interval between positive HPV DNA test results not defined. -See bullets in above grid. 	<ul style="list-style-type: none"> -HPV type 18 is type most often associated with cervical adenocarcinoma. -Type 18 infections may be fundamentally different from Type 16 infections. -May be insufficient data to conclude anything about HPV 18.
LSIL cytology with HPV		<ul style="list-style-type: none"> -Most LSIL resolves. -See above regarding non-responders to vaccine. 	<ul style="list-style-type: none"> -LSIL cytology (or ASC) is not sufficient for therapy. -Need biopsy result for therapy in US.
CIN 1 (biopsy) with HPV	<ul style="list-style-type: none"> -Pathologic diagnosis, based on tissue, needed for therapy. -Prevention of CIN implies prevention of a procedure (biopsy). 	<ul style="list-style-type: none"> -About half of CIN 1 regresses. -Risk of progression to invasive cancer is low, at least over the short-term. 	<ul style="list-style-type: none"> -Cost-effectiveness cannot be used as basis for FDA regulatory decisions.
HSIL cytology with HPV	<ul style="list-style-type: none"> -High predictive value for a high-grade histology lesion. 	<ul style="list-style-type: none"> -HSIL cytology would be worked up by colposcopy and biopsy, so definitive pathologic diagnosis expected anyway. 	
CIN2/3 (biopsy) with HPV	<ul style="list-style-type: none"> -Most proximal endpoint to cervical cancer. -Always merits treatment in US. 	<ul style="list-style-type: none"> -Studies could take several years to conduct and would be resource intensive. 	<ul style="list-style-type: none"> -Would probably address any issues about vaccine alteration of HPV natural history.
Cervical cancer with HPV	<ul style="list-style-type: none"> -Definitive endpoint. 	<ul style="list-style-type: none"> -View of conducting studies in less developed countries without screening programs is unclear. -Feasibility unclear for both developed and developing countries. 	<ul style="list-style-type: none"> -Would give best understanding of impact on adenocarcinoma, an increasing proportion of cervical cancer in developed countries.

* HPV testing would be used to assign the finding as vaccine serotype or not.

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