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Quick Pulse

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FDA Panel Recommends Another HPV Vaccine for Females and One for Males

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The FDA's Vaccines and Related Biological Products Advisory Committee recommended approval of GlaxoSmithKline's (GSK's) Cervarix vaccine against human papilloma virus (HPV) in females aged 10-25, and it recommended approval for the use of Merck's Gardasil HPV vaccine to prevent genital warts (condyloma acuminate) in males aged 9-26.

Gardasil, which was approved in June 2006 for females 9-26 years old to protect against cervical, vulvar, and vaginal cancers caused by HPV types 16 and 18 – the two HPV strains associated with 70% of cervical cancers. It was also approved to protect against genital warts caused by HPV types 6 and 11. HPV types 6 and 11 are associated with 90% of genital warts. The Centers for Disease Control and Prevention (CDC) recommends a routine three-dose vaccination series for girls 11 and 12 years of age. The vaccine is also recommended for girls and women ages 13 through 26 years who have not yet been vaccinated or who have not received all three doses.

Although **GSK's Cervarix** is marketed in 97 countries, approval in the U.S. has been difficult because of concerns that it might cause more muscular and neurological problems than Gardasil. In 2007, the FDA asked the company for more data, including final data from a Phase III, 18,600-patient trial called HPV-008. The data include total follow-up of 129,454 person-years and a maximum individual follow-up of 7.4 years. As of May 2009, ~7 million doses of Cervarix had been distributed worldwide, and the FDA said that "no safety concerns have been detected in postmarketing surveillance."

Cervarix is a non-infectious, recombinant vaccine containing Virus Like Particles (VLPs) of the L1 capsid proteins of HPV 16 and 18. It is adjuvanted with aluminum hydroxide and monophosphoryl lipid A (MPL). If approved, it would be the first vaccine licensed in the U.S. containing MPL as a component of the adjuvant. It would also be Gardasil's first rival in the U.S. The panel recommended approval of Cervarix but also suggested a warning against the vaccine's use in pregnant women. Cervarix protects against the same HPV strains associated with cervical cancer, but it does not protect against the strains associated with genital warts.

The panel recommended approval of **Merck's Gardasil** for protection against genital warts in males aged 9-26, saying that it is safe. However, the panel noted that HPV-related penile and anal cancers are extremely rare. Critics of the vaccine's use for males have argued that, although it has health benefits for

females, its cost doesn't justify its use – $400 for a three-dose regimen. There have been questions about how long protection against the HPV strains last and at what age patients should be inoculated. Critics also have questioned whether vaccinating males would be useful, again saying that penile and anal cancers affect <1% of the population. Proponents of the vaccine for males have argued that vaccinating them would help protect females from contracting HPV.

Genital HPV is the most common sexually transmitted disease in the U.S., and the Centers for Disease Control and Prevention (CDC) estimates that more than 6 million people are infected every year. More than 100 HPV types have been identified, and ~40 of them infect the human genital tract. Most are self-limiting, but certain high-risk HPV types are carcinogenic: HPV 16 and 18 are classified as cervical carcinogens, and HPV 31 and 33 are probably carcinogenic. The American Cancer Society (ACS) estimates that although most HPV infections go away on their own, ~11,270 cases of invasive cervical cancer will be diagnosed in the U.S. in 2009, and ~4,070 women will die from the disease. HPV is associated with anal and penile cancer in men; ~2,000 men get anal cancer every year, and penile cancer is even rarer.

Cervical cancer is the second most common cancer in the world. In the U.S., more than 11,000 women are diagnosed yearly with cervical cancer, and it causes >4,000 deaths annually. The average age of diagnosis is 48. Adenocarcinoma, a more aggressive form of the disease, which targets younger women, is increasing.

GSK's Cervarix

The FDA Perspective

The FDA's reviewers gave Cervarix a thumbs up, saying that the vaccine "is expected to provide a significant public health benefit to girls and women between the ages of 10 and 25 years." Reviewers said that the vaccine is effective 93% of the time, about the same as Gardasil. Earlier concerns about possible musculoskeletal and autoimmune problems were resolved, and GSK and the FDA are negotiating a postmarketing study in the U.S. of 44,000 females 10-25 years old to look at that potential problem. Postmarketing studies also will look at spontaneous abortions in women getting the vaccine. Although not statistically significant, there was a higher rate of spontaneous abortions in women getting Cervarix compared to women getting the control vaccine.

The FDA's Center for Biologics Evaluation and Research (CBER) proposed vaccination for girls and women 10-25 years old for the prevention of the following diseases caused by HPV types 16 and 18 included in the vaccine:

- Cervical cancer.
- Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ.*
- CIN grade 1.

GSK wants approval for prevention of cervical cancer (squamous cell carcinoma and adenocarcinoma) by protecting against the following precancerous or dysplastic lesions and infections caused by oncogenic human papilloma viruses (including types 16 and 18 and some non-vaccine HPV types):

- CIN grade 2 and grade 3 or cervical adenocarcinoma *in situ*.
- CIN grade 1.
- Abnormal cytology.
- Persistent infection.
- Incident infection.

FDA reviewers said that 13 studies showed that "immune responses to Cervarix were robust and consistent." They also said that the vaccine is safe. Autoimmune events were comparable in vaccine patients and control patients "with no significant increase in relative risk." Further studies "concluded that there was no increased risk of neuroinflammatory or musculoskeletal autoimmune disorders following vaccination."

The FDA's review chair, Robin Levis, PhD, summarized clinical development:

- Phase I/II safety and immunogenicity (S&I) studies:
  - 002: S&I for monovalent and bivalent vaccine in naïve females 18-20 years old.
  - 003: S&I for bivalent vaccine in non-naïve females 18-30.
  - 004: S&I for adjuvanted and unadjuvanted products in naïve females 18-30.
  - 005: S&I for different VLP doses adjuvanted with AS04 or AI (OH)3 in naïve females 18-30.
- Phase IIb and Phase III pivotal efficacy trials:
  - 001/007: Prevention of incident infection with vaccine HPV types in naïve subjects.
  - 008: Pivotal Phase III efficacy study to prevent CIN2+ associated with vaccine HPV type in naïve individuals.
- Studies in adolescents:
  - 012: Safety and immunogenicity in females 10-14 compared to females 15-25, and lot consistency study.
  - 013: Safety and immunogenicity in females 10-14 (with comparison to immunogenicity in females 15-25 who participated in HPV-001).

One exception in the HPV-008 safety data was the finding of a higher rate of spontaneous abortions in the Cervarix group compared to GSK's hepatitis A vaccine, Havrix, (11.6% vs. 5%). FDA reviewers said, "Although there is no definitive indication that there is an enhanced risk of spontaneous

abortions with use of Cervarix, overall rates of spontaneous abortion are low in the studies, and there may be confounding due to underreporting of pregnancy losses as spontaneous. A postmarketing enhanced pregnancy registry will be conducted to study this issue…The imbalance did not persist in an analysis of the entire study period in the pooled safety dataset. An independent statistical review…concluded that the data do not establish a causal relationship, but they are insufficient to rule out a small effect in pregnancies conceived in the three months immediately after the vaccination."

Dr. Nancy Miller of the FDA's Office of Vaccine Research and Review, CBER, told the panel that Cervarix is safe and effective.

Efficacy against HPV 16/18 related disease:

- The data demonstrated efficacy of Cervarix in females 15-25 years of age naïve to the relevant vaccine HPV type for prevention of HPV 16/18 related cervical cancer, CIN2+ and CIN1+.
- Immunologic bridging provides a basis for inferring effectiveness in females 10-14 years of age.

Efficacy against non-vaccine HPV-related disease:

- In the total vaccinated cohort (TVC) of naïve women, the point estimate of efficacy is ~70% in prevention of CIN2+ irrespective of HPV. This may be predominantly due to prevention of HPV 16/18 related disease, but also possible contribution from prevention of other HPV types when HPV 16 and 18 are excluded from analyses.
- No immunologic bridge available to girls 10-14 years old.

Cervarix Solicited Adverse Events

Adverse event	Cervarix	Placebo
Solicited adverse events 7 days after vaccination		
Local symptoms	91.2%	78.8%
Pain	90.5%	78%
Serious adverse events		
All serious adverse events up to 7 months after vaccination	1.3%	1.3%
All serious events from 7-76 months after vaccination	5.3%	5.9%
Spontaneous abortions	13.7%	9.8%

Cervarix - Safety

Events	Conclusion
Musculoskeletal/ autoimmune	Overall, no statistically significantly increased relative risk in meta-analysis
Neuroinflammatory	Overall, elevated risk, though not statistically significant in meta-analysis
Spontaneous abortions	Imbalance in spontaneous abortions in women 15-25 years old around vaccination in studies 008 and 009, but many limiting factors

Dr. Miller said that Cervarix is effective against:

- HPV 16/18 related CIN2+.
- HPV 16/18 related CIN1+, persistent infection (6- and 12-month definition), abnormal cytology.
- CIN2+ irrespective of HPV type.
- Cervical disease related to non-vaccine HPV types.

She added that longer term efficacy was shown for 6- and 13-month persistent infections and going out to 6 years.

In terms of **side effects**:

- **New onset chronic and new onset autoimmune diseases** in the pooled safety population were similar. The most commonly reported new onset chronic diseases were asthma and hypersensitivity. The most commonly reported autoimmune disease was hypothyroidism.
- An outside panel of expert rheumatologists reviewed **musculoskeletal/autoimmune events**. The overall relative risk for HPV-AS04 containing products in controlled studies over the entire study period was 1.31. The extended analysis found the relative risk for the entire study period was 1.08. The most frequently reported musculoskeletal events were arthritis, fibromyalgia, rheumatoid arthritis, systemic lupus, erythematosus, and arthropathy.
- **Neuroinflammatory** events were few. The meta-analysis for HPV-AS04 products showed the relative risk was 2.33. An external expert neurology panel showed no increased risk of neuroinflammatory disorders following vaccination with MPL-containing vaccines.
- Even though women were advised not to get **pregnant** during the study, almost 20% of study subjects became pregnant over the entire course of the study. For pregnancies with known outcomes around the time of vaccination, the proportions were similar in both groups for known outcomes, including normal birth, premature birth, abnormal infant, and congenital anomaly. However, 13.7% of Cervarix subjects had spontaneous abortions vs. 9.8% in the control group.

Dr. Miller said that the FDA acknowledged limitations in assessment of spontaneous abortions:

- Spontaneous abortion is not a pre-specified outcome.
- Post hoc selection of time window.
- Clinical trials not designed to study spontaneous abortions.
- The rates in treatment groups are within expected background rates (9%-21%).
- In pregnancies around time of vaccination, no difference in mean time to spontaneous abortion in each group.
- Preclinical reproductive toxicology studies without signal.

A National Cancer Institute (NCI) analysis observed, "Among pregnancies with estimated conception date between Day 0 and 89 from nearest vaccination, the miscarriage rate was 15.4% miscarriages in the treatment arm and 9.6% in the control arm…and did not meet the standard threshold for significance. The secondary analysis could neither deny nor confirm an increased discrepancy in spontaneous abortion rates among vaccine recipients."

The reviewers concluded that with regard to **efficacy**:

- Cervarix is effective in preventing genital dysplasias (CIN2+ and CIN1) associated with HPV 16 and/or 18 in 15-25-year-old women who are naïve for the relevant vaccine HPV types.
- Cervarix is ***not*** effective in preventing genital dysplasias (CIN2+ and CIN1) related to vaccine HPV types for which the subject has been exposed.
- Cervarix may have an impact on reducing genital dysplasias (CIN2+) related to HPV 31, but analyses involving multiple HPV types (vaccine and non-vaccine) are complicated.

Immunogenicity:

- Cervarix is immunogenic and elicits anti-HPV 16 Immunoglobulin G (IgG) and HPV 18 IgG as measured by enzyme-linked immunosorbent assay (ELISA). Duration of immune response is at least 76 months. Antibody responses elicited to anti-HPV 16 and 18 appear to follow a similar pattern out to Month 24.
- IgG antibodies to anti-HPV 31 and 45 were demonstrated in a subset of subjects, with a high rate of seroresponse. However, anti-HPV 31 and 45 antibodies are elicited in a smaller percentage of subjects and do not appear to be long lasting.
- Cervarix is immunogenic in females 10-14 years old (in whom genital testing is not possible), and immune responses in this age group are higher in regards to geometric mean titers (GMTs) elicited when anti-HPV 16 and 18 are measured. Immunobridging to females 10-14 has been conducted from subjects 15-25 who participated in study HPV-001 as well as from subjects 15-25 who participated in study HPV-012.
- Lot-to-lot consistency was demonstrated.
- Given the very high effectiveness of Cervarix in preventing CIN2+ related to HPV 16/18, very few breakthrough cases have occurred, and it was not possible to identify an immune correlate of protection.

Overall safety:

- In general, Cervarix elicits solicited adverse events (pain, swelling, redness) and specific solicited general adverse events to a lesser degree (including myalgia and arthralgia) in the seven days after vaccination. The incidences are higher compared to subjects on the active control Havrix. However, compliance rates for completion of the study were high in both treatment groups.
- The number of deaths was similar in both groups.
- The number of serious adverse events was similar in both groups.
- The overall rate of adverse events was somewhat higher in the Cervarix group vs. the Havrix control group (85.4% vs. 74.6%) mostly because of injection site symptoms.
- The number of new onset chronic diseases and new onset autoimmune diseases was similar in both groups. Events related to potential autoimmune etiology will be assessed in postmarketing studies.
- Although there were imbalances in events of potential neuroinflammatory nature in the original Biologics Licensing Application (BLA review), extensive meta-analyses of the events have not demonstrated statistically significant relative risks for such events. A postmarketing study will look at this as well as events of musculoskeletal nature of potential autoimmune etiology.
- An imbalance in the proportion of subjects who experienced a spontaneous abortion was seen in women who received Cervarix in the time period around the estimated date of conception, but not in pregnancies overall. Possible confounding factors include a possible underreporting of elective abortions in countries in which abortions are not approved, but it is difficult to ascertain. An enhanced pregnancy registry will be instituted to follow pregnancies in women who receive Cervarix inadvertently during pregnancy.

Panel Member Questions for FDA Experts about Cervarix

Dr. Bruce Gellin, director of the Department of Health and Human Services' (HHS's) National Vaccine Program Office (NVPO), asked if other countries submit safety reports to the U.S. An FDA official said that if the product is licensed in the U.S., the FDA would receive serious adverse event reports.

*Asked about duration of immunity***,** an FDA reviewer said, "For 16 and 18 we have evidence of immune response out to 76 months."

Dr. Michael Greene, chief of obstetrics at Massachusetts General Hospital in Boston, asked about venous thrombotic events (VTEs), and an FDA official said she didn't remember seeing any such events. GSK said that there was just one case.

Dr. Lauri Markowitz, team leader for epidemiology research at the CDC, asked about spontaneous abortions and whether abortions are illegal in Costa Rica, where Study 009 was conducted. A GSK official said that abortions are illegal there.

Asked about serology data in Phase II trials, an FDA official said that they came from different studies. There was a high seroresponse for HPV 16, 18, and 31. For HPV 33 and 45, she found a 70%-80% rate in several trials. However, there were not much data.

Asked about any adverse events with the hepatitis vaccine (Havrix) used as control, an FDA official said that she was unaware of any specific safety signals.

Panel chair Dr. John Modlin, a pediatrician at Dartmouth-Hitchcock Medical Center in New Hampshire, asked about the secondary endpoints, noting that the efficacy for prevention of incident infection was somewhat lower than for the other secondary endpoints. A GSK executive said that incident infection is a "mixed bag" as a secondary endpoint, "We consistently see lower numbers…It sometimes may not even be considered an infection."

Asked what percent of women in the trial were on birth control pills, a GSK official said a significant percentage of women were on birth control pills, ~60%. He said there was no impact on efficacy due to oral contraceptives.

GSK's Perspective on Cervarix

GSK's proposed indication is for girls and women 10-25 years old for the prevention of cervical cancer HPV types 16, 18, and some non-vaccine types. Cervarix uses a manufacturing process called baculovirus expression vector system (BEVS), which it said is robust. If approved, Cervarix would be the first U.S.-licensed AS04-containing vaccine.

Martine Wettendorff, PhD, vice president for global vaccine development at GSK, presented the vaccine design. She said that HPV evades the immune system, does not induce viremia, stays at the cervix, and takes decades to progress from infection to cancer, so long-lasting protection is needed. More than 80% of sexually active women are infected with HPV by the age of 50. Re-infection is common throughout life. Natural infection antibodies are low and not reliably protective. Most antibodies in the cervix come from blood.

Dr. Wettendorff said there is no evidence of a biological mechanism for autoimmune disease induction in AS04 mechanism of action (MOA). She summarized GSK's design:

- No compromise on HPV 16/18 protection – balance type coverage with risk of immune interference.
- Induce cross-protection against closely phylogenetically related HPV types.
- High and sustained immune response against HPV 16/18.
- No basis for induction/exacerbation of autoimmune disease.
- Improve on natural immunity.
- Optimized combination of antigens/adjuvant.

Dr. Gary Dubin, a GSK vice president, presented the efficacy data from two studies conducted in 15-25-year-old women, HPV-001/007 (1,113 women in a Phase IIb study lasting 6.4 years) and HPV-008 (18,644 women in a 39-month, pivotal Phase III study). The company conducted a total of 11 studies beginning in 1998.

Study HPV-001/007 Efficacy

Measurement	Cervarix cases	Control cases	Vaccine efficacy
Efficacy against HPV 16/18 endpoints (*up to 6.4 years*)			
Primary endpoint: CIN2+	0	9	100%
6-month persistent infection	0	34	100%
12-month persistent infection	0	20	100%
Secondary endpoint: CIN1+	0	15	100%
Efficacy irrespective of HPV DNA in the lesion (*up to 6.4 years*)			
CIN2+	5	17	72%
Efficacy against individual non-vaccine oncogenic types (*up to 6.4 years*)			
HPV 31	13	30	60%
HPV 45	5	21	78%

The primary endpoint in HPV-008 trial was vaccine efficacy in prevention of histopathologically-confirmed CIN2+ associated with HPV 16 or 18 in the cervical lesion (ATP cohort). The total vaccinated cohort (TVC) was 18,644 women. The TVC-1 cohort excluded women with prevalent high grade lesions at baseline.

Study HPV-008: Efficacy Against HPV 16/18 CIN2+
(primary endpoint; seronegative subjects)

HPV types	Cervarix cases	Control cases	Vaccine efficacy
ATP Cohort			
HPV 16/18	4	56	93%
HPV 16	2	46	96%
HPV 18	2	15	87%
TVC-1 Cohort			
HPV 16/18	5	91	95%
HPV 16	4	73	96%
HPV 18	2	24	92%

Panel Member Questions for GSK about Cervarix

The panel chair characterized the panel as "uncharacteristically quiet" when it came time to question GSK.

Vicky Debold, PhD, RN, the consumer representative and director of patient safety at the National Vaccine Information Center, asked about the **study controls**:

- *Debold:* "Were there any saline arms in GSK's studies? In other words, were there any true control groups?" The answer was no.
- *Debold:* "Doesn't that complicate being able to identify safety signals?" A GSK official responded, "The safety profile of the controls that we used are very well established. These (controls) are well known vaccines for which there are no concerns about safety."
- *Debold:* "It's just that when you look at the product insert for the control, there are safety issues there."

Dr. Markowitz of the CDC asked about **postmarketing studies**. She wanted to know if there were any other neuroinflammatory events reported. A GSK executive said that there were two reports of a neuroinflammatory event and one of multiple sclerosis, and the rates are well below the rates of what is expected in the general population.

Asked about ***safety data for children 10-14***, a GSK official said , "In the clinical program we did two studies that enrolled girls 10-14, and ~2,200 girls were randomized to receive Cervarix or Havrix vaccine. In the postmarketing experience …in the U.K., 12-13 year olds have been vaccinated, and the estimated coverage is one million doses, and the majority are 12-13 years old."

Public Witnesses on Cervarix

Amy Allina of the National Women's Health Network said that her organization is not opposed to an HPV vaccine in particular, and it supported approval of Gardasil, "We have some concerns about how that vaccine was promoted…While its effectiveness appears strong, we are concerned about the higher rate of spontaneous abortion in the Cervarix portion of the trial…The FDA couldn't rule out an association (between the vaccine and spontaneous abortions)…The registry that the company proposes may provide data to clarify what we see…but the question we consider beyond that is: Until the findings from those studies are available, what is the most appropriate way to respond to the information that we do have?...We are urging caution." She recommended delaying approval until there is more information.

Deborah Arrindell of the American Social Health Association said that her group applauds the development of a vaccine against cervical cancer. She asked the FDA to mandate that healthcare providers give pap smears and look for larger systemic healthcare concerns in low income groups.

Diana Zuckerman, PhD, president of the National Research Center for Women and Families, told the panel that GSK seemed to have presented safety information exceeding that of Merck's Gardasil. However, she said that if Cervarix is sold at a similar price to Gardasil, "It's essential that we know how long term the product will last. If a booster is going to be needed, we need to know that." Dr. Zuckerman warned that the adjuvant used in Cervarix hasn't been used in the U.S. And she noted, "Most HPV goes away by itself, and cervical cancer is relatively rare in the U.S." She said that a reanalysis of the data persuaded the FDA that the vaccine is safe, "But is that enough? We think it would be very wise to include very clear warnings to anybody using the vaccine about the potential prenatal exposure…Frankly, we are more concerned with the autoimmune disease concerns and, while they were not statistically significant, they could be rare and should receive more attention than they have so far. We ask that the FDA make available to the public all the information about the autoimmune data."

Dr. Mark Einstein of the Society of Gynecologic Oncologists said that cervical cancer is a significant clinical concern, and he applauded the new vaccine.

Dr. Bart Classen, an immunologist and founder of Classen Immunotherapies, said that vaccines can cause diabetes. He said that metabolic syndrome is evidence of inflammatory disease. Metabolic syndrome correlates with cortisol activity, and an epidemic is seen in grass-fed horses. There is also a positive association with a number of vaccines. He said that parents should be warned that immunization can cause flares of Type I diabetes because they can cause insulin resistance.

Roberta Boyce said that her daughter almost died after being vaccinated with Gardasil, and she spoke against approval of Cervarix. She said that vaccines can be life-threatening to people with pyruvate kinase deficiency and asked that doctors be trained to identify people with this deficiency.

Panel Discussion about Cervarix

The FDA asked the panel to discuss:

- The safety data, specifically the pregnancy outcomes and potential autoimmune associated event signaling.
- Data on cross-protection and the potential impact that may accrue from prevention of persistent infection with non-vaccine types.
- Use of persistent infection as a clinical study endpoint.
- Recommendations on the proposed pharmacovigilance plan, particularly the approach to pregnancy outcome surveillance.

Among the issues raised by the panel during the discussion were:

- The CIN1+ and CIN2+ indications
- Spontaneous abortions
- General safety issues

Indications:

- *Dr. Kenneth Noller, an obstetrician/gynecologist at Tufts University*, wondered why CIN1+ was part of the discussion because the trials were originally set up to look at CIN2+: "As I learn more and more about it, I am convinced that I don't know what CIN1+ is. I have no problem with CIN2+ and cancer in AIS (adenocarcinoma *in situ*). But I hate to see that included. I don't think anybody knows what it means…I don't (think that it's relevant)."
- *Dr. Greene, the obstetrician*, said that he was part of the FDA advisory committee which originally considered outcome measures, and CIN1+ was not included.
- *Dr. Elizabeth Unger, a molecular pathologist at the CDC*, asked why AIS was listed separately; in the tables, it was included along with CIN2+. The panel chair responded that AIS was part of the CIN2+ definition, and that the question was about the indications the company is seeking. He said that he thought that the FDA wants the panel to consider the question as it is posed.
- *Dr. Melinda Wharton, deputy director of the CDC's National Center for Immunization and Respiratory Diseases*, asked why AIS was listed as an indication. The panel chair said that the numbers were very small for AIS, adding that the panel would get in trouble if it parsed out the different endpoints.
- *The Boston obstetrician/gynecologist* said that AIS isn't part of CIN2+ and that it probably makes sense to include it, "But you'll never have a study with enough cases… Even though we don't have specific data, I think that it makes sense to include it because of its relationship to 18…CIN1, CIN2, CIN3, and AIS are not cervical cancers, but cervical cancer precursors. Cervical cancer could be any type, but it's probably squamous and adenode."
- *Dr. Markowitz, the CDC epidemiologist*, asked what the label for Gardasil says regarding indications. The FDA expert said that it is included under dysplastic lesions. Another FDA expert said that the Gardasil label includes CIN1.

There were some questions about **the word "any."** Some panel members also said that it didn't seem as if all the data were consistent – types 31, 33, and 45 didn't all show the same thing. One panel member said, "I'm not convinced…I guess I'd like to see it studied a little more, but some of the data are compelling."

Other comments included:

- *Dr. Robert Seder, an immunologist at the National Institutes of Health's (NIH's) National Institute of Allergy and Infectious Diseases' (NIAID's) Vaccine Research Center*, said that type 31 showed the most consistent and compelling data. He asked if this was an adjuvant effect, or if the way DLP is made is different, and it's an antigen effect.
- *Dr. Greene* said that the statistical significance was lost often for type 33, and he was comfortable adding an indication for prevention of type 31 in addition to 16 and 18. The panel chair asked if the members agreed, and they seemed to agree, but Dr. Unger said that it's too early to specify a type, and more data are needed. However, she said that the data look promising.
- *The panel chair* remarked on the divergence of opinion, and she noted that the analyses are very complex, "It is difficult to take one message away from them. They were done in different populations, and the numbers were small. This makes it very difficult to be very precise. I personally was struck by the fact that in the analyses for each individual type, all seemed to go in the same direction, towards some evidence of degree of protection by the vaccine which I thought was striking, suggesting that there probably is a biologic effect here, but I don't think that we can precisely measure that. I don't think that we can be very specific."
- *Dr. Markowitz* agreed that the data looked good, especially for type 31, and she wondered how criteria would be worded for the vaccine. The panel chair said that Merck has data on cross-protection, and if it wants that indication, it will have to go back to the FDA.

An FDA official asked for **more discussion on the composites** specifically. Dr. Theodore Tsai of Novartis, the industry representative, asked about preclinical data for passive protection against non 16/18 types in animal models. A GSK executive said that so far it has not been possible to test human vaccines in animals. However, she said that there is unpublished material that saw cross-protection in rabbits. Another GSK official said that multiple infections are quite common for the less frequently occurring HPV types, and it is difficult to dissect things out when talking about lesions. He said that the company's persistent infection data were consistent.

- *Dr. Wharton of the CDC* said that was "not an insignificant contribution of this bivalent vaccine. It's difficult from the data we've seen to extract a particular HPV type, and I'm not sure that's really what you're asking for. In composite, I think that there is more bang for the buck."
- *Panel chair:* "I think that's exactly what they're looking for."
- *Dr. Greene* said that while there is some contribution, he would not want to see anything that says all non-vaccine HPV types in the indication. The panel chair added that

there is some evidence that some HPV types are not affected at all, based on the very small numbers.

- *The industry rep* said that grouping all the non-vaccine types together is important, but the limitation is that the interpretation will depend on the circulating strains there at the time the vaccine was used.

Comments on spontaneous abortions included:

- *Dr. Greene*, *obstetrician/gynecologist,* said that the HPV control was protective against spontaneous abortions, but Cervarix was less so, "The HPV control was about half of what you'd expect in any population. The highest number in any of these groups was 13% and half in control, and that was considerably less than what you'd expect (in the general population). I think we have to remember that as we discuss this."
- *Dr. Frank DeStefano*, *director of the CDC's Immunization Safety Office*, wanted to know more about GSK's postmarketing effort with regard to the spontaneous abortion question, "It wouldn't make me vote against the vaccine, but women should be aware of it." A GSK official said that the pharmacovigilance will look at pregnancy reports, including spontaneous abortions. A pregnancy registry has run for a year in the U.K., and the company will get the data from that in the next few months. More important than the registry will be the Phase IV trial.
- *Dr. Gellin*, *the NVPO director*, asked what percentage of pregnancies continue.
- *Dr. Greene* said that extremely sensitive techniques that are capable and apply to a relatively large population are able to detect conception within 6 or 7 days – about 15% wind up as spontaneous first trimester abortions, so there is a huge dropout very early in pregnancy.
- *GSK scientist:* "The spontaneous abortion issue is troubling some people. The first thing is that, of all the problems of reproduction, the spontaneous abortion epidemiology is the most difficult to do. First of all, before the woman misses her first menstrual period, she's lost half her pregnancies, and those are mostly due to chromosome abnormalities…We have two studies. The one massive study was completely negative. The incidence of spontaneous abortion in the vaccine group was almost identical to the other three controls. Then, someone said let's look at the months before and after conception. But that is meaningless. So what do you do? You have this confusion in the epidemiology study. So, you go back to the animal studies, which are wonderful. They found no increase in birth defects, no growth retardation, and no pregnancy loss at all over the controls …There is not a spontaneous abortion risk. We don't have any data to indicate that there is a risk for spontaneous abortion."
- *Dr. Greene:* "It seems to make sense…This wasn't a pregnancy trial. It accidentally was. The spontaneous abortion data I don't find compelling at all. This should be marketed with the usual caveat that it should not be used with pregnancy."

General safety questions:

- *The Massachusetts obstetrician/gynecologist* asked about MPL and the word "detoxification." A GSK official said, "The MPL molecule obtained following the purification retains adjuvant effect, but it is non toxic. The immune stimulation is maintained…and we have shown that the activation of antigen presenting cells by MPL compared to LPS (lipopolysaccharide) produced lower cytokine production than LPS…When we look at the cytokine production in the serum after immunization, we see almost no production of cytokines."
- *Consumer rep:* "It's difficult to sort out the effects here. What is the baseline vs. the so-called controls? In this study there were two different strengths of Havrix used, and other vaccines used as control, and that makes it very difficult to sort things out."
- *The industry rep* asked about myalgia and whether GSK thought there was confusion between local muscle pain and myalgia. GSK said that is possible.
- *Dr. Lisa Rider*, *a pediatric rheumatologist at NIH*, said that the data were reassuring. However, she said strong postmarketing studies are needed to capture "these rare neuroinflammatory events and autoimmune events… We're looking at two cases per million, so we need larger studies to see these effects."

PANEL CONSIDERATION OF FDA QUESTIONS ABOUT GSK'S CERVARIX

QUESTION 1a. Do the data support the efficacy of Cervarix for the prevention of HPV 16/18 related cervical cancer, CIN2+, AIS, and CIN1+ in females 15-25 years of age? YES 12, NO 1

Vicky Debold, the consumer rep, was the sole NO vote.

QUESTION 1b. Do the immunogenicity bridging data support effectiveness for prevention of HPV 16/18 related cervical cancer, CIN2+, AIS, and CIN1+ in adolescent females 10-14 years of age? YES 12, NO 1

Consumer rep Vicky Debold again was the sole NO vote.

Panel comments included:

- *Dr. Pamela McInnes*, *DDS, of the National Institute of Dental and Craniofacial Research at NIH* said that it was clear that the vaccine is highly immunogenic, "I am very comfortable with it."

- *Panel chair:* "Even though we don't have absolute proof of efficacy here, and we don't have a precise surrogate, we do have a strong basis for biologic possibility, and built on top of that is a lot of work known about the natural history of HPV in humans and immune response and the importance of measuring antibodies…I would tend to agree. We also have the precedent here that the currently-licensed vaccine was licensed on bridging immunicity data…We'd have to have some good reason to break precedent, and I don't see that we do."

QUESTION 2. Please comment on the strength of the data to support the efficacy of Cervarix for the prevention of any non-vaccine HPV-related CIN2+ in females 10-25 years of age. **No vote**

The panel chair summarized: "There is a good basis for indicating that bivalent vaccine does protect against some non-vaccine serotypes, most likely those to which there has been demonstrated cross-protection in animal models and cross-neutralization, but we are very uncomfortable with the term 'any non-vaccine HPV-related' type, and there is a little difference of opinion on whether we need to be specific on certain types, such as type 31. Some members feel there should be a specification for 31, and others feel less comfortable with that."

QUESTION 3. Do the safety data support the safety of Cervarix for use in females 10-25 years of age?

YES 11, NO 1

a. **Please comment on imbalance noted in spontaneous abortions.**

b. **Please comment on findings for neuroinflammatory events and diseases of potential autoimmune etiology.**

Again, Debold, the consumer rep, voted NO. There was no post-vote discussion.

QUESTION 4. Please comment on other recommendations for postmarketing commitments.

Dr. Greene – who moderated this question because the panel chair, Dr. Modlin, had to leave early – asked when the company expects to get updated data on spontaneous abortions and neuroimmune disorders. A GSK official couldn't say.

The lone holdout on the previous votes, the consumer rep, said that she was concerned that "we make sure we vaccinate people as safely as we possibly can, and maybe there are some people who shouldn't be vaccinated." Dr. Rider, the pediatric rheumatologist, agreed, saying that there were data about the vaccination and people with pre-existing conditions.

MERCK'S GARDASIL FOR MALES

Merck is seeking an indication for Gardasil in boys and men age 9 through 26 for the prevention of genital warts caused by HPV types 6 and 11. Genital warts are a fairly small problem, with ~1% of the sexually active male population getting genital warts and ~0.02% of males getting medically treated for genital warts every year. That means ~200 per 100,000 men are newly diagnosed with genital warts every year. Among males visiting an STD clinic, genital warts is second to nonspecific urethritis as the most common new diagnosis. Treatment is unpleasant, and recurrence is common and causes psychosocial distress. From 70% to 100% of patients are HPV 6 and/or 11 positive. An FDA reviewer said, "The impact of genital warts is significant, both in terms of individual psycho-social distress and in terms of the burden on the U.S. healthcare system. Treatment options, which range from topical immune modifiers to ablative or excisional procedures, can themselves be the source of significant distress and discomfort, and recurrences requiring multiple procedures are common."

THE FDA PERSPECTIVE

FDA reviewers said that Gardasil is effective in preventing condyloma acuminate, or genital warts caused by HPV types 6 and 11, in males aged 16 to 26. Merck wants expanded approval to cover males aged 9-26 years old. Gardasil protects against two strains of cervical-cancer-causing HPVs as well as two other strains that are responsible for 90% of genital warts in males. The two strains have been linked to cancers of the penis and anus. GSK's Cervarix does ***not*** protect against genital warts.

Although the FDA briefing documents for the panel said that "a comprehensive discussion of prevention and treatment of HPV in males would also include estimates of the impact on transmission to females," the documents did not include any such estimates.

FDA review team chair Dr. Jeff Roberts of CBER told the panel that:

- Gardasil is efficacious in the prevention of genital warts caused by HPV 6 and 11 in males 16-26 years old.
- Anti-HPV GMTs (geometric mean titers) against each of the four VLP types in 9-15-year-old males are non-inferior to those in 16-26-year-old males. Immunogenic-ity bridging provides a basis for inferring protection of 9-15-year-old males against genital warts.
- In the safety database, which includes around 5,400 males, no safety signals have been identified. The details of the postmarketing plan are the subject of ongoing discussions with Merck.

The postmarketing experience with Gardasil in women has shown:

- Syncope (a temporary loss of consciousness) is sometimes accompanied by traumatic injury.
- Other adverse events are being monitored, with no evidence of causation.
- The current postmarketing commitment: 44,000 females receiving all three doses. The study was powered to detect a two-fold increase in a risk, with a background rate of 1:10,000 with alpha 0.05 and power of 80%.

An FDA reviewer said that HPV 6/11/16/18-related external genital lesions (EGL) in the per protocol efficacy (PPE) population was 90.4%. The vast majority of cases were condyloma, and efficacy was 89.4%. There were few cases of perineal intraepithelial neoplasia (PIN) 1, 2, or 3. He said that this explains why the indication is mainly for genital warts.

Gardasil Efficacy Against Condyloma

Type	Efficacy
PPE (HPV 6/11 related)	89%
GHN (any HPV type related)	85%
FAS (HPV 6/11 related)	67%
FAS (any HPV type related)	62%

Gardasil Efficacy Against any HPV Type-Related Condyloma

Subject characteristic (*FAS population*)	Gardasil n=2,025	Placebo n=2,030	Efficacy
Any HPV type related	32	83	62%
15-20 years old	17	49	64%
21-27 years old	15	34	59%
Sexual orientation – heterosexual males	22	61	65%
Sexual orientation – MSM	10	22	55%
Circumcised	11	24	56%
Not circumcised	21	59	65%

Gardasil Efficacy Against HPV 6/11/16/18-Related Genital Lesions and Infections

Endpoint	Gardasil n=1,397	Placebo n=1,408	Efficacy
Efficacy in Protocol 016			
External genital lesions (EGL)	3	31	90%
Condyloma acuminatum	3	28	89%
PIN 1	0	2	100%
PIN 2/3	0	1	100%
Penile/perianal/perineal cancer	0	0	N/A
Efficacy in Protocol 018			
	Gardasil n=1,245	**Placebo n=1,244**	**Efficacy**
Condyloma acuminatum (per protocol efficacy population)	3	28	89%
Condyloma acuminatum (full analysis set)	24	71	67%
Efficacy against persistent infection and DNA detection			
	Gardasil n=1,390	**Placebo n=1,400**	**Efficacy**
Persistent infection	15	101	86%
DNA detection	136	241	45%

The FDA official told the panel that, as in females, duration of efficacy/immunogenicity is not known. The correlate of protection is not established in males. He said that the sponsor has proposed a 10-year follow-up extension of efficacy and immunogenicity in the pivotal study, V501-020. Protocol 018 is in the midst of an extension trial.

Looking at pooled data for serious adverse events in days 1-15 following vaccination, a reviewer said that there were 9 in the Gardasil group vs. 1 in the control group. Boys had more adverse events at the injection site compared to men.

An FDA official said that postmarketing studies are needed. Merck is proposing a Phase IV observational study of 27,000 males (9-26 years old) who will get at least one dose of Gardasil.

The Merck Perspective on Gardasil for Males

Dr. Patrick Brill-Edwards, director of regulatory affairs for Merck, told the panel that Gardasil is:

- Efficacious in men 16-26 years old in preventing:
  - HPV 6/11/16/18 related external genital lesions.
  - HPV 6/11 related genital warts.
  - HPV 6/11/16/18 persistent infection and DNA detection.
- Efficacy of Gardasil inferred in 9-15-year-old boys through immunobridging.
- Gardasil has a favorable safety profile in all populations studied.
  - It was well tolerated in boys and men 9-26 years old.
  - No serious adverse events were considered vaccine related.
  - Discontinuations due to adverse experiences were infrequent.
  - More than 95% of adverse experiences reported were of mild to moderate intensity.

Dr. Dalya Guris, director of clinical research at Merck, told the panel that there is an unmet medical and public health need for Gardasil. HPV is one of the most common sexually transmitted diseases, and infection is often asymptomatic or subclinical. There is no standardized screening for HPV infection or early detection in men. She said that HPV 6 and 11 account for 90% of anogenital warts and are a primary cause of recurrent respiratory papillomatosis. HPV 16 and 18 account for 60%-95% of HPV-related anogenital and

oropharyngeal cancers in men. Dr. Guris said that there is an extensive burden of HPV-related diseases in men, with anogenital warts the most prevalent, and ~3.3 million sexually active U.S. men aged 18-59 have a history of a genital warts diagnosis. Symptoms include itching, burning, tenderness, and anal or urethral bleeding or discharge. She said that current therapies, which include topical agents, cryotherapy, and surgical methods are inadequate and have the potential for severe pain and scarring. In addition, from 10%-90% of warts recur after treatment.

Merck conducted one study (Protocol 020) of 4,055 16-26-year-old men and two safety/immunogenicity studies, Protocol 016 (which studied 508 10-15-year-old boys) and Protocol 018 (which studied 839 9-15 year olds).

Dr. Guris said that immunobridging was successfully demonstrated:

- Comparison of antibody response at Month 7 in the PPI (per protocol immunogenicity) populations of adolescent boys (Protocols 016 and 018 combined) vs. men (Protocol 020)
- Non-inferiority criteria:
  - GMTs – statistically less than two-fold decrease
  - Seroconversion rates – statistically less than 5% decrease in the adolescents

She told the panel that Gardasil efficacy is inferred in boys 9-15 years old through demonstrating non-inferiority of immune response compared to men 16-26 years old.

More adverse events were seen in the Gardasil treated subjects than placebo. While no subjects on placebo had any serious adverse events, nine in the Gardasil group (0.3%) had serious adverse events, but none was related to the vaccine. Most adverse events were injection site pain, followed by erythema, swelling, pruritis, and bruising. Most common serious adverse events were headache and pyrexia. There were four deaths in the vaccine group and 10 in the placebo groups, but none was considered vaccine related. New onset medical conditions were similar in both groups (46% in vaccine vs. 52% in placebo), and the most common conditions were upper respiratory tract infections.

Dr. Guris summarized the safety data:

- Gardasil was well tolerated in males aged 9-26.
- No serious adverse experiences were considered vaccine related.
- Discontinuations due to adverse experiences were infrequent.
- >95% of adverse experiences reported were mild to moderate.
- Gardasil safety profile in boys and men is consistent with that observed in girls and women.

Merck said that its plans for long-term assessment of the vaccine include long-term extension of Protocol 018 (started in 2003) and Protocol 020 (started in 2004), a post-licensure safety study, and ongoing assessment of spontaneous safety reports in males. That includes regular follow-up of subjects and 10-year follow-up from Day 1. The post-licensure safety study will include a health maintenance organization (HMO) database of 27,000 men and boys receiving at least one dose of Gardasil. The safety assessment will include all medical events resulting in emergency room visits or hospitalization.

PUBLIC WITNESSES ON MERCK'S GARDASIL FOR MALES

Deborah Arrindell of the American Social Health Association spoke again, saying she supports the vaccination of men and boys against genital warts, "Gardasil is effective in preventing HPV-related diseases in men…Given that this vaccine is proven safe and generally well tolerated in men and may reduce HPV transmission to women, we believe that the health benefits of this vaccine are great."

Dr. Craig Derkay, a pediatric otolaryngologist at Eastern Virginia Medical School in Norfolk VA, said that the vaccine might substantially reduce cases of recurrent respiratory papillomatosis (RRP) or laryngeal papilloma, which is caused by HPV 6 and 11, in children.

Emily Tarcell, whose 20 year old daughter died 13 days after her third shot of Gardasil, said, "We have reason to believe that it was the Gardasil. This was a totally unnecessary risk, and we would have declined the vaccine in a heartbeat if we had known any of the facts…Doctors, patients, and professional medical organizations have been manipulated and misled by Merck's unethical marketing…The biased, one-sided vaccine sales pitch continues…How can we even think of expanding this vaccine to boys when the risks…are still unknown?" She said that there are no checks and balances about the reporting of adverse events. She said that she has not heard from either Merck or the FDA in the year since her daughter died.

Roberta Boyce also spoke again, saying that her daughter received the Gardasil vaccine two years ago, contracted pneumonia shortly afterwards, and has been chronically ill since then. She talked about niacin and vitamin deficiency and their relationship to polysorbates and vaccines. She argued that a true vaccine placebo might help doctors to determine which patients should or should not get vaccinated.

Barbara Loe Fisher of the National Vaccine Information Center, an advocacy group, spoke against the vaccine. She told the panel that a true placebo was not used in Merck's Gardasil studies and asked, "Why are pharmaceutical companies which seek to sell vaccines to millions of children allowed to use (study designs) that would not pass muster in an eighth grade science class?"

PANEL QUESTIONS FOR FDA AND MERCK OFFICIALS ABOUT GARDASIL FOR MALES

The only three questions were about:

1. The difference between heterosexual subjects and men who had sex with men. A substudy in men having sex with men (MSM) looked at anal intraepithelial neoplasia (AIN) or anal cancer, and there were no differences.
2. Adverse events.
3. Circumcised males vs. non-circumcised males. There was no substantial difference. A Merck official said that there were no differences between circumcised and non-circumcised men with regard to efficacy.

PANEL DISCUSSION OF FDA QUESTIONS ABOUT GARDASIL FOR MALES

The FDA asked the panel to discuss efficacy and safety data and the company's postmarketing plans. Among the issues raised by the panel during the discussion were usefulness (or not) of the vaccine; safety, including syncope; and use of the vaccine in men who have sex with men.

Usefulness of the vaccine:

- *Dr. Greene, an obstetrician/gynecologist who was continuing to serve as the acting panel chair*, said that genital warts are ugly, but in men and women with normal immune systems they are self-limiting and will go away in time. He also said that it is impossible to treat genital warts. He said that once you are infected, it is not prophylactic against infection. Asked if the question should be changed to targeting only naïve subjects, he said that would be up to the FDA, and it would be difficult and dramatically more expensive to screen for that. He also said that there is a difficulty of administering the vaccine to people who have been exposed and are still having efficacious titers at the time they receive the vaccine. He asked for thoughts and received none. He asked if that was a fair summary of the tension and received a few nodding heads.
- *The deputy director of the CDC's National Center for Immunization and Respiratory Diseases* said that efficacy has been demonstrated against genital warts in women.

Safety:

- *The consumer rep s*aid that she had the same concern with Gardasil as with Cervarix, but in this case, a very small number of boys received the saline placebo. She also asked about a syncope signal. She said that when she looked into the subject, there were some cases of boys with syncope. She also said that it would be a mistake to go ahead with the vaccine in boys, especially in light of the data with girls, such as syncope and deep vein thrombosis, "There are too many issues going on. The stories are the same. We need to think before we subject boys to this…This has to do with public trust, transparency. If we make a mistake on this, it will set back the national vaccination effort…There are (also) parents reporting motor neuro issues, the ***JAMA*** (***Journal of the American Medical Association***) paper noted 41 cases, of which only 8 ended up in the analysis because of missing data…Four were tossed out because they didn't fit into a particular time period, and the parent community is well aware of this. I'm just saying that the trial we looked at with boys is relatively small."
- *Dr. Markowitz, the CDC epidemiology team leader*, said that Gardasil is licensed for men in some countries, but there are very little data so far. A GSK official said that it is licensed in 40 countries, with a limited licensure for men, "We've seen results fairly consistent with the reports we've seen." Another GSK official said that there is some limited data from postmarketing of spontaneously reported adverse events in boys and men. The most common adverse events are those related to off-label use, wrong drug administered, inappropriate schedule, and other medical mistakes. The most common adverse events are nausea, dizziness, pyrexia, and injection site pain.
- *Dr. Markowitz* also asked about the difference between vaccination and onset in two cases:
  1. A cellulitis of the right leg in a 20-year-old male who received three doses. A GSK official said that on the third day after vaccination, he noted heat and pain in the lower right leg. He did not go to the hospital, and on Day 6 he was fine.
  2. A 13-year-old male who received three doses who had an infected right toe. He was hospitalized and was discharged with no complications. The problem was not vaccine related.

Subgroup: Men who have sex with men

- *The CDC's National Center for Immunization and Respiratory Diseases deputy director* said that people who get vaccinated and their parents need more information about the nuances of the vaccine, i.e., men who have sex with men will have a lower efficacy rate compared to heterosexual men.
- *Dr. Markowitz, CDC epidemiology research team leader*, said that there will be interest in the vaccine in the group of men who have sex with men, and the message to that population will have to be crafted carefully. It is a small study, and even when data are available the company may not be able to address the questions, she said. Dr. Greene agreed, saying that the data are meager on that subset.

PANEL VOTES ON FDA QUESTIONS ABOUT GARDASIL FOR MALES

QUESTION 1. Given the efficacy and safety data…is the overall risk:benefit ratio favorable for the licensure of Gardasil in males for the indication of prevention of genital warts? YES 7, ABSTAIN 1, NO 0

Dr. DeStefano, *director of the CDC's Immunization Safety Office*, was the abstention.

QUESTION 2. Do the data support the safety of Gardasil for use in males 9 to 26 years of age? YES 7, NO 1

Vicky Debold, the consumer rep, said that there was no appropriate control in the study, and she voted NO.

QUESTION 3. Please comment on and make recommendations regarding the postmarketing plan proposed by the sponsor. No vote and no additional comments.

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