Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Subject: Gardasil 9 Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC)

Sponsor: Merck, Sharp and Dohme

Product: Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant)

STN: 125505

Indication: Girls and women 9 through 26 years of age for the prevention of:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16,18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11
- Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, including Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS), CIN grade 1, Vulvar Intraepithelial Neoplasia (VIN) grade 2 and grade 3, Vaginal Intraepithelial Neoplasia (VaIN) grade 2 and grade 3, and Anal Intraepithelial Neoplasia (AIN) grades 1, 2, and 3

Boys and men 9 through 26 years of age for the prevention of:

- Anal cancer caused by HPV types 16,18, 31, 33, 45, 52, and 58

- Genital warts (condyloma acuminata) caused by HPV types 6 and 11
- AIN grades 1, 2, and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58

1. INTRODUCTION

1.1 Product Description

Gardasil 9 is a recombinant vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The vaccine is indicated in girls and women ages 9 to 26 years for the prevention of:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11
- The following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
    - Cervical intraepithelial neoplasia (CIN) Grade 2 and 3 and Cervical adenocarcinoma *in situ* (AIS)
    - Cervical intraepithelial neoplasia (CIN) Grade 1
    - Vulvar intraepithelial neoplasia (VIN) Grade 2 and 3
    - Vaginal intraepithelial neoplasia (VaIN) Grade 2 and 3
    - Anal intraepithelial neoplasia (AIN) Grades 1, 2 and 3

The vaccine is also indicated in include boys ages 9 to 15 years for the prevention of:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11
- Anal intraepithelial neoplasia (AIN) Grades 1, 2 and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) currently recommends routine vaccination against HPV infection at age 11 or 12 years. Vaccination can be given starting at age 9 years. ACIP also recommends vaccination for females through age 26 years and for males through age 21 years who were not adequately vaccinated previously. Per ACIP, special populations of males, including men who have sex with men and transgendered males, may be vaccinated between the ages of 22 and 26 if not previously vaccinated[1].

1.2 Regulatory History

Gardasil 9 was originally approved in the United States for use in girls and women aged 9-26 years and boys aged 9-15 years on December 10, 2014. This is the vaccine's international birth date. The vaccine has subsequently been approved for use in 22 countries.

On December 15, 2015, the vaccine's indication was expanded to include males aged 16-26 years.

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[1] Meites E, Kempe A, Markowitz LE. Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2016;65:1405–1408

Gardasil 9 was originally approved to be administered as a 3-dose regimen. On October 7, 2016, the Gardasil 9 label was changed to reflect an alternative 2-dose regimen of Gardasil 9 for girls and boys between 9 to 14 years of age.

2. OBJECTIVE

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the original approval and approval of an expanded age range in males, in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The triggers for this pediatric postmarketing safety review are the December 10, 2014 original approval as well as the October 7, 2016 approval of the alternative 2-dose regimen. This review will cover the time period of December 10, 2014 – June 30, 2017.

This memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature. During the surveillance period, no new safety signals were identified, and there were no reports of pediatric deaths that were attributed to Gardasil 9; assessment of the four deaths reported during the review period for which information was available concluded that the deaths were due to alternate causes. The product does not have a requirement for a postmarketing safety study or Risk Evaluation and Mitigation Strategy (REMS), and there were no label changes regarding safety during the PAC review period (December 10, 2014 – June 30, 2017).

3. MATERIALS REVIEWED

Materials/documents evaluated for this review include:

- Vaccine Adverse Events Reporting System (VAERS) – reports of adverse events occurring after Gardasil 9 vaccination received December 10, 2014 – June 30, 2017

- Manufacturer's Submissions
  - Gardasil 9 US package insert, dated January 2017
  - Letter regarding dose distribution data, dated Oct. 26, 2017
  - Risk Management Plan, dated December 2014
  - First Annual Report on Exposure during Pregnancy from the Merck Pregnancy Registry for Gardasil 9, dated Aug. 19, 2016
  - Second Annual Report on Exposure during Pregnancy from the Merck Pregnancy Registry for Gardasil 9, dated Aug. 4, 2017

- FDA Documents
  - Gardasil 9 Approval Letter, dated Dec. 10, 2014

- Review of Gardasil 9 pharmacovigilance plan as part of original approval, dated November 14, 2014
- Gardasil 9 FDAAA Section 915 Safety Review, dated Oct. 4, 2016
- Gardasil 9 pregnancy registry first annual report review, dated Oct. 21, 2016

- Publications (see Literature Search in section 8 and endnotes)

4. SAFETY-RELATED LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns for Gardasil 9 during the review period.

5. PRODUCT UTILIZATION DATA

The manufacturer estimates that from December 10, 2014 through June 30, 2017, approximately [redacted] doses of Gardasil 9 were distributed worldwide. [redacted] of these doses were distributed in the U.S. Note: These estimates were provided by the manufacturer for FDA review. Dose distribution data is protected as confidential commercial information and may require redaction from this review.

6. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

6.1 Sponsor's Pharmacovigilance Plan

Safety specifications from the pharmacovigilance plan (PVP) include important identified risks of hypersensitivity, syncope with fall resulting in injury, and exposure during pregnancy. Hypersensitivity and syncope with fall are listed in the 'Adverse Reaction' section of the package insert, and syncope with fall is also listed in the product insert under 'Warnings and Precautions.' Important potential risks identified in the pharmacovigilance plan included viral type replacement, Guillain-Barre Syndrome (GBS), product confusion, and "mixed regimen" (i.e., a single patient receiving two or more different types of HPV vaccine in a series), and each of these risks are being assessed via a post-market extension study (V503-021 – discussed below) as well as routine pharmacovigilance. The risks associated with exposure during pregnancy are being characterized via the sponsor's ongoing pregnancy registry (discussed below). Additionally, in their pharmacovigilance plan, the sponsor identifies long-term effectiveness/ immunogenicity as areas of important missing information; they are evaluating these areas, in addition to any other potential safety signals not identified in the clinical development studies, through routine monitoring of adverse event reports as well as three postmarket surveillance studies (discussed below).

Ongoing postmarket safety assessments are discussed below.

6.2 Postmarketing Commitment (PMC) V503-002-20: study extension to clinical trial V503-002

Clinical trial V503-002 was conducted prior to Gardasil 9 approval to assess and compare the immunogenicity and safety of Gardasil 9 in young women aged 16-26 years, girls aged 9-15 years, and boys aged 9-15 years. Postmarketing surveillance study V503-002-20 enrolled all patients from V503-002 who had received three doses of the vaccine during the trial (approximately 2500 subjects) to evaluate longer-term immunogenicity, effectiveness, and safety. This observational surveillance study will follow subjects for up to ten years. The first Interim Report is planned for 4th quarter 2017, and the final report is planned for March 31, 2023.

6.3 PMC V503-021: study extension to clinical trial V503-001 (Nordic Region countries of Denmark, Norway and Sweden)

Clinical trial V503-001 was conducted prior to Gardasil 9 approval to assess and compare the efficacy and safety of Gardasil to that of Gardasil 9 in young women aged 16-26 years. Postmarketing surveillance study V503-021 enrolled patients from V503-001 in Nordic Region countries (approximately 4500 subjects) into a registry-based long-term follow up study. This observational surveillance study will follow subjects for up to ten years and evaluate safety, immunogenicity, and effectiveness. The first Interim Report is planned for 4th quarter 2019, and the final report is planned for December 31, 2026.

6.4 PMC – Post Authorization Safety Study

This is an observational study to further characterize the safety profile of Gardasil 9 in approximately 10,000 persons. The objective of this study is to describe the general safety of Gardasil 9 in a population of 10,000 males and females who have received at least one dose of Gardasil 9 by a) estimating the risk of health outcomes resulting in emergency room visits or hospitalizations occurring within a pre-specified risk period and b) comparing this estimate to the risk of such health outcomes in a post-vaccination self-comparison reference period. The study is being conducted within the Kaiser Permanente Northern California health network using vaccination and medical records available in computerized databases. The first Interim Report is planned for December 31, 2018, and the final report is planned for December 31, 2019.

6.5 Pregnancy Safety Postmarketing Commitment

This is a 5-year pregnancy registry to prospectively collect data on spontaneously reported exposures to Gardasil 9 occurring within 30 days prior to the last menstrual period or at any time during pregnancy. Rates of anomalies and other pregnancy outcomes will be compared to baselines established by the Centers for Disease Control Metropolitan Atlanta Congenital Defects Program. As of the most recent interim report, information on 22 evaluable, prospectively enrolled subjects was available. Outcomes were known for 9 of these subjects; 8 reports were of healthy, live births. The outcome of the ninth pregnancy was a spontaneous abortion that occurred during the 10th week of gestation; the subject had been vaccinated 6 weeks into the pregnancy. No retrospective reports of exposure to Gardasil 9 during pregnancy had yet been enrolled as of the most recent interim report, submitted August 22, 2017.

6.6 Additional Safety Studies

Three additional studies planned at approval are underway. CDC is conducting a targeted observational study utilizing the Vaccine Safety Datalink (a computerized database of linked longitudinal medical records) to identify and characterize pregnancy outcomes in women vaccinated with Gardasil (Human Papilloma Virus 4-valent Vaccine, Recombinant) and Gardasil 9 while pregnant. VSD has recently completed a project evaluating spontaneous abortion (SAB) and Gardasil, and is already funding initial SAB data collection on Gardasil 9. Because the vaccine is not recommended in pregnant women, it may take a number of years for cases of vaccinated pregnant women to accumulate so as to provide sufficient data for an adequately sized scientific study.

CDC also conducted near real-time sequential monitoring of Gardasil 9 using the Vaccine Safety Datalink during the period 10/2015-10/2017. Outcomes monitored included anaphylaxis, allergic reaction, appendicitis, Guillain-Barré syndrome, injection site reaction, pancreatitis, seizure, stroke, syncope, and venous thromboembolism. Statistically significant safety findings were further evaluated using medical record review and additional statistical methods. These first two years of this Gardasil 9 safety surveillance in the Vaccine Safety Datalink did not demonstrate any new or serious adverse events associated with Gardasil 9.

FDA is conducting a general safety study which will use healthcare billing claims data in FDA's Sentinel System (a network of large U.S. healthcare provider organizations and other healthcare data partners) to identify and characterize safety outcomes in patients vaccinated with Gardasil 9.

7. ADVERSE EVENT REVIEW

7.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Gardasil 9 between December 14, 2014 and June 30, 2017. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the number of doses administered, and lack of direct and unbiased comparison groups.

7.2 Results

The results of the VAERS search of adverse event reports for Gardasil 9 during the review period are listed in Table 1 below.

Table 1: VAERS Reports for Gardasil 9 (December 10, 2014 – June 30, 2017)

	Serious Non-Fatal		**Deaths**		**Non-serious**		**Total**	
Age	**US**	**Foreign**	**US**	**Foreign**	**US**	**Foreign**	**US**	**Foreign**
<18 years	138	21	4	0	1,907	0	2,049	21

≥18 years	34	8	0	0	449	0	483	8
Unknown	45	20	1	0	2,886	0	2,932	20
Total	217	49	5	0	5,242	0	5,464	49

*Serious adverse events are defined in 21CFR600.80

7.2.1 Deaths

Five death reports from the reporting period are described below:

- 14 year old female, died [redacted] days after vaccination with first dose of Gardasil 9. Vaccinee experienced mild upper respiratory infection symptoms in the 2-3 days immediately following vaccination, but collapsed suddenly at school and was unable to be resuscitated. At autopsy, cardiac hypertrophy was noted, and the cause of death was found to be dissection of the aorta. This case was documented in a second separate VAERS report; in this report, the vaccinee's age was noted as "unknown"
- 16 year old male, awoke [redacted] days after receiving first doses of HPV9 and Hepatitis A vaccine with headache and vomiting. Vaccinee suddenly lost consciousness and died the following day of intracerebellar hemorrhage from ruptured aneurysm
- 12 year old female, died [redacted] day after receiving HPV9; no additional information provided in report
- 11 year old male, received HPV9 10/25/16, died of acute meningoencephalitis; workup demonstrated "positive mycoplasma IgM" but was otherwise negative, including postmortem TB and fungal cultures of basal meningeal tissue.

Review of these cases revealed no information suggestive of a causal relationship between the reported deaths and Gardasil 9 vaccination.

7.2.2 Non-fatal serious reports

During the reporting period, there were 266 non-fatal serious reports in Gardasil 9 recipients; of the 201 reports where age at vaccination was reported, 159 (79%) occurred in patients <18 years old. Table 2 below lists the 20 most frequently reported MedDRA (Medical Dictionary for Regulatory Activities, a standardized and clinically validated international medical terminology dictionary) adverse event terms, known as preferred terms (PTs), in these reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 2. Most Frequently Reported PTs in Serious VAERS Reports for Gardasil 9 (Dec. 10, 2014 - Jun. 30, 2017; <18 years of age)

MedDRA PT	Number of Reports	Label Status	Section of Label
Headache	52	Labeled	AR*
Dizziness	38	Labeled	AR
Nausea	37	Labeled	AR

Fatigue	32	Labeled	AR
Loss of consciousness	31	Labeled	AR; labeled as 'syncope' under W/P**
Syncope	31	Labeled	AR, W/P
Pyrexia	29	Labeled	AR
Seizure	28	Labeled	AR; tonic-clonic movements also labeled in W/P
Asthenia	22	Labeled	AR
Vomiting	22	Labeled	PME***
Fall	21	Labeled	AR, W/P
Abdominal pain	20	Labeled	AR
Anxiety	18	Unlabeled	
Pain	18	Labeled	AR
Confusional State	16	Unlabeled	
Myalgia	16	Labeled	AR, PME
Pallor	16	Unlabeled	
Arthralgia	15	Labeled	PME
Malaise	15	Labeled	PME
Muscular Weakness	15	Unlabeled	

*AR = Adverse Reactions
**W/P = Warnings and Precautions
***PME = Postmarketing Experience; refers to adverse events reported in the postmarketing period for HPV4/Gardasil

In general, the most frequent PTs in serious VAERS reports for Gardasil 9 were known, labeled events and involved few reports. 'Pallor' and 'confusional state' are not individually labeled, however, the majority of cases with these PTs occurred in association with syncopal events immediately post-vaccination. Review of reports of 'muscular weakness' revealed no clustering or discernable patterns. Review of reports of 'anxiety' revealed no clustering or discernable patterns; many of these cases were also associated with post-vaccination syncope. Overall, no unusual frequency, clusters, or other trends for adverse events were identified from review of the serious reports. No new safety concerns were identified.

'Of note, 9 cases of 'head injury' occurring in patients <18 years old and designated as serious were reported; case series review revealed that most occurred after syncope with fall, a labeled AE.

7.2.3 Non-serious reports

During the reporting period, there were 5,242 non-serious reports; of the 2,356 reports where age at vaccination was reported, 1,907 (81%) occurred in patients <18 years old. Table 3 below lists the 20 most frequently reported MedDRA preferred terms (PTs) for these reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3. 20 most frequently reported PTs for non-serious VAERS reports (Dec. 10, 2014 - Jun. 30, 2017; <18 years of age)

MedDRA PT	No. of Reports	Label
No Adverse Event*	381	N/A
Dizziness	323	Labeled
Syncope	261	Labeled
Headache	229	Labeled
Incorrect Product Storage	226	N/A (not an AE)
Injection Site Erythema	202	Labeled
Nausea	186	Labeled
Pyrexia	169	Labeled
Injection Site Swelling	165	Labeled
Injection Site Pain	156	Labeled
Loss of Consciousness	153	Labeled
Pallor	147	Labeled
Vomiting	130	Labeled
Pain	122	Labeled
Erythema	118	Labeled
Fatigue	111	Labeled
Pain in Extremity	111	Labeled
Fall	103	Labeled
Urticaria	97	Labeled
Injection Site Warmth	93	Labeled

*The PT of no adverse event often accompanies a report of an issue related to the vaccine product or vaccine administration procedure (e.g., a vaccine storage issue or administration error) that was not associated with a clinical adverse event even though it resulted in a VAERS report

The non-serious adverse events are consistent with those seen in the pre-licensure studies and are included in the package insert. Many of the most frequently reported non-serious events were related to syncope or near-syncope following vaccination (dizziness, syncope, loss of consciousness, pallor, and fall), as was observed among the serious reports and is discussed above. Injection site reactions (injection site erythema, injection site swelling, injection site pain, erythema) are labelled events and typically resolve quickly. Some of the remaining terms (headache, vomiting, nausea, fatigue) are not specific to a particular condition, and are also labelled and were observed in the pre-licensure studies. The PTs related to incorrect product storage refer to storage and handling errors such as temperature deviations when refrigerating the vaccine.

7.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Gardasil 9 were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with a data lock date of November 1, 2017, identified PTs with a disproportional reporting alert for Gardasil 9 (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean). Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 4. PTs Identified with Data Mining as Disproportionally Reported in VAERS

PT	EB05	Comment
Fall	2.019	Labeled
Head injury	2.356	Review of reports revealed that events occurred after syncope with fall
Inappropriate schedule of drug administration	3.101	N/A (not an AE)
Interchange of vaccine products	7.05	N/A (not an AE)
Pregnancy test urine positive	3.065	N/A (not an AE)
Syncope	2.22	Labeled
Drug administered to patient of inappropriate age	2.403	N/A (not an AE)

PTs included 'Inappropriate schedule of drug administration,' 'Drug administered to patient of inappropriate age' and 'Interchange of vaccine products' which are PTs related to variations in the recommended vaccination schedule/regimen and are not adverse events. 'Pregnancy test urine positive' is a PT reflecting inadvertent vaccination of a pregnant patient and is also not an adverse event. 'Loss of consciousness,' 'Fall,' and 'Syncope' are labeled events. Case series review of reports for the PT 'Head injury' revealed that most of these reports involved head injuries that occurred after syncope with fall and usually included PTs 'syncope,' 'loss of consciousness,' or 'fall.'

7.4 Periodic Adverse Event Report (PAER)

The manufacturer's quarterly postmarket periodic safety reports for Gardasil 9 covering the surveillance period were reviewed. The adverse events reported in the periodic safety reports were consistent with those seen in VAERS. No additional safety issues were identified.

8. LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on 10/30/2017 for peer-reviewed literature published between Dec. 10, 2014, and Jun. 30, 2017, with

the search term “Gardasil 9” and no additional search parameters retrieved 68 articles. The titles and abstracts of these articles were reviewed. Six articles reported results of clinical trials which supported approval of the vaccine:

- Van Damme P, Meijer CJLM, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, Baudin M. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016 Jul 29;34(35):4205-4212
- Van Damme P, Bonanni P, Bosch FX, Joura E, Kjaer SK, Meijer CJ, Petry KU, Soubeyrand B, Verstraeten T, Stanley M. Use of the nonavalent HPV vaccine in individuals previously fully or partially vaccinated with bivalent or quadrivalent HPV vaccines. Vaccine. 2016 Feb 3;34(6):757-61
- Garland SM, Cheung TH, McNeill S, Petersen LK, Romaguera J, Vazquez-Narvaez J, Bautista O, Shields C, Vuocolo S, Luxembourg A. Safety and immunogenicity of a 9-valent HPV vaccine in females 12-26 years of age who previously received the quadrivalent HPV vaccine. Vaccine. 2015 Nov 27;33(48):6855-64
- Schilling A, Parra MM, Gutierrez M, Restrepo J, Ucros S, Herrera T, Engel E, Huicho L, Shew M, Maansson R, Caldwell N, Luxembourg A, Ter Meulen AS. Coadministration of a 9-Valent Human Papillomavirus Vaccine With Meningococcal and Tdap Vaccines. Pediatrics. 2015 Sep;136(3):e563-72
- Vesikari T, Brodszki N, van Damme P, Diez-Domingo J, Icardi G, Petersen LK, Tran C, Thomas S, Luxembourg A, Baudin M. A Randomized, Double-Blind, Phase III Study of the Immunogenicity and Safety of a 9-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine (V503) Versus Gardasil® in 9-15-Year-Old Girls. Pediatr Infect Dis J. 2015 Sep;34(9):992-8
- Einstein MH, Takacs P, Chatterjee A, Sperling RS, Chakhtoura N, Blatter MM, Lalezari J, David MP, Lin L, Struyf F, Dubin G; HPV-010 Study Group. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: end-of-study analysis of a Phase III randomized trial. Hum Vaccin Immunother. 2014;10(12):3435-45

One additional article (Van Damme P, Meijer CJLM, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, Baudin M. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016 Jul 29;34(35):4205-4212) reported clinical trial data that supported expansion of the vaccine’s indication to include men aged 16-26 years.

None of the remaining 61 articles were found to have pertinent safety information; no new safety issues were discerned.

9. CONCLUSION

This postmarketing pediatric safety review of Gardasil 9 was triggered by the December 10, 2014 original approval and the October 7, 2016 approval of the alternative 2-dose

regimen. Review of passive surveillance adverse event reports, periodic safety reports, and the published literature for Gardasil 9 does not indicate any new safety concerns. Most adverse event reports were non-serious and were consistent with the known safety profile of Gardasil 9.

10. RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Gardasil 9. The results of the ongoing postmarket safety studies will be reviewed.