

STABLE FORMULATION OF HUMAN PAPILLOMAVIRUS VIRUS-LIKE PARTICLE VACCINE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of Chinese patent application 202110049777.7 filed on January 14, 2021, the contents of which are incorporated herein by reference.

FIELD

[0002] The invention relates to the field of biological pharmaceutical formulations, in particular to a stable human papillomavirus virus-like particle vaccine formulation.

BACKGROUND

[0003] Cervical cancer is one of the most common female malignant tumors, with about 500,000 new patients worldwide every year, and the incidence rate is the second among female tumors. More than 95% of cervical cancer is associated with Human Papillomavirus, HPV) infection. In addition to the direct cause of cervical cancer, HPV is also strongly associated with bronchogenic cancer, rectal cancer, oral cancer and skin cancer. In addition, HPV is also the main pathogenic factor causing skin and mucosal warts.

[0004] At present, more than 100 HPV types have been found, and different HPV types can cause different diseases. According to its close relationship with cervical cancer, HPV can be divided into high-risk type, suspected carcinogenic type and low-risk type. High risk type and suspected carcinogenic type can induce cancer such as cervical cancer; the high-risk types included types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. Suspected carcinogenic types include types 26, 53, 66, 68, 73 and 82. The low-risk types are mostly related to genital warts, condyloma acuminatum and other diseases, including types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89. HPV types 6, 11 and 16 were the subtypes with the highest detection rate in patients with genital lesions.

[0005] HPV vaccine is an effective way to block the infection of papillomavirus. Virus-like particle (VLP) vaccine is the most advantageous vaccine form among many vaccine forms. However, the VLP-based HPV vaccine is type specific, i.e., it only shows strong

protection against HPV types in the VLP vaccine. To provide broad protection, the development of multivalent HPV vaccines is necessary.

[0006] However, prior to administration, the human papillomavirus vaccine formulation undergoes a storage and transportation process during which the antigen undergoes physical and chemical degradation, and these instabilities may reduce the immunogenicity and/or safety of the antigen, and thus a stable formulation is needed to ensure that the antigen still maintains the immunogenicity and safety satisfying prevention purpose just prior to administration.

SUMMARY

[0007] In one aspect, the present invention provides a stable formulation of multivalent human papillomavirus virus-like particle vaccine for the prevention of HPV-related diseases or infections comprising a plurality of papillomavirus virus-like particles adsorbed on an adjuvant; a physiologically acceptable concentration of a buffer, an osmotic pressure regulator, and optionally a surfactant.

[0008] Wherein the human papillomavirus virus-like particles are selected from HPV virus-like particles assembled by L1 proteins of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 respectively; and one or more HPV virus-like particles assembled from L1 proteins of other pathogenic HPV types.

[0009] In one embodiment, the buffer is selected from one or more of citric acid buffer, acetic acid buffer or histidine buffer; the osmotic pressure regulator is selected from one or more of sodium chloride, sodium phosphate or sodium sulfate; the surfactant is a polyethoxy ether, preferably polysorbate 80; the adjuvant is selected from one or more of aluminum hydroxyphosphate (AlPO_4), amorphous aluminum hydroxyphosphate sulfate (AAHS), or aluminum hydroxide ($\text{Al}(\text{OH})_3$), preferably aluminum hydroxyphosphate (AlPO_4).

[0010] In one embodiment, (a) the total concentration of papillomavirus virus-like particles of all types is 40 $\mu\text{g/mL}$ to 740 $\mu\text{g/mL}$; (b) the concentration of the buffer is 10mM to 26 mM, preferably 10 mM, 18mM or 26 mM;

- (c) the concentration of the osmotic pressure regulator is 150mM to 320 mM, preferably 150 mM or 320 mM;
- (d) the concentration of the surfactant is 0 to 0.02% by weight;
- (e) the concentration of the adjuvant is about 1.0 mg/mL;
- (f) the pH of the formulation is 5.9-6.5, preferably 5.9, 6.2 or 6.5.

[0011] In one embodiment, the concentration of any single type of papillomavirus virus-like particles included in the multivalent papillomavirus virus-like particles is 40 µg/mL to 120 µg/mL.

[0012] In one embodiment, that formulation comprises a total of 0.74mg/mL of papillomavirus virus-like particles of all types, 1.0mg/mL of aluminum phosphate adjuvant, 18mM histidine buff, 320mM sodium chloride, a pH of the formulation solution of 6.2; optionally, polysorbate 80 at a concentration of not more than 0.3mg/mL.

[0013] In one embodiment, the one or more other pathogenic HPV types are selected from HPV types 35, 39, 51, 56 and 59.

[0014] In one embodiment, wherein at least one of the HPV virus-like particles is a chimeric HPV virus-like particle comprising a chimeric HPV L1 protein; the chimeric HPV L1 protein comprise from that N-terminal to the C-terminal thereof:

- a. an N-terminal fragment derived from a papillomavirus L1 protein of a first type, that N-terminal fragment maintaining the immunogenicity of the L1 protein of that type, wherein the papillomavirus of the first type is selected from HPV type 6, 11, 16, 18, 31, 33, 45, 52 and 58 and one or more other pathogenic HPV types; and
- b. a C-terminal fragment derived from a second type of papillomavirus L1 protein having better characteristics of expression and solubility compared to L1 proteins of other types;

wherein the chimeric HPV L1 protein has immunogenicity of the first type of papillomavirus L1 protein.

[0015] In one embodiment, Said N-terminal fragment is a fragment obtained by truncating the C-terminus of the natural sequence of said L1 protein of the first papilloma virus type at any amino acid position within its α5 region, and a fragment having at least 98% identity therewith; and Said C-terminal fragment is a fragment obtained by truncating the N-terminus of the natural sequence of said L1 protein of the second papilloma virus type at any amino acid position within its α5 region and

functional variants resulting from further mutations, deletions and/or additions to the fragment.

[0016] In one embodiment, the C-terminal fragment comprises one or more nuclear localization sequences.

[0017] In one embodiment, wherein the papilloma L1 protein of the first type is selected from HPV type 6, 11, 16, 18, 31, 35, 39, 45, 51, 52, 56 or 58; preferably, the natural sequence thereof is an amino acid sequence encoded by a coding gene as shown in SEQ ID No: 30, SEQ ID No: 31, SEQ ID No: 32, SEQ ID No: 33, SEQ ID No: 34, SEQ ID No: 35, SEQ ID No: 36, SEQ ID No: 37, SEQ ID No: 38, SEQ ID No: 39, SEQ ID No: 40, or SEQ ID No: 41, respectively;
the papilloma L1 protein of the second type is selected from HPV type 16, 28, 33, 59, or 68 L1 protein;
more preferably, the papilloma L1 protein of the second type is selected from an HPV type 33 or HPV type 59 L1 protein.

[0018] In one embodiment, that C-terminal fragment is SEQ ID No: 1; or a fragment thereof having a length of m1 amino acids, preferably a fragment covering amino acids 1-m1 of SEQ ID No:1; wherein m1 is an integer from 8 to 26; or that C-terminal fragment is SEQ ID No: 2; or a fragment thereof having a length of m2 amino acids, preferably a fragment covering amino acids 1-m2 of SEQ ID No:2; wherein m2 is an integer from 13 to 31.

[0019] In one embodiment, that C-terminal fragment is SEQ ID No: 3; or a fragment thereof having a length of n amino acids, preferably a fragment covering amino acids 1-n of SEQ ID No:3; wherein n is an integer from 16 to 38.

[0020] In one embodiment, the N-terminal fragment of the HPV type 6 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:4 at any amino acid site within the $\alpha 5$ region thereof;

the N-terminal fragment of the HPV type 11 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:5 at any amino acid site within the $\alpha 5$ region thereof;

the N-terminal fragment of the HPV type 16 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:6 at any amino acid site within the $\alpha 5$ region thereof;

the N-terminal fragment of the HPV type 18 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:7 at any amino acid site within the $\alpha 5$ region thereof; the N-terminal fragment of the HPV type 31 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:8 at any amino acid site within the $\alpha 5$ region thereof; the N-terminal fragment of the HPV type 35 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:9 at any amino acid site within the $\alpha 5$ region thereof; the N-terminal fragment of the HPV type 39 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No: 10 at any amino acid site within the $\alpha 5$ region thereof; the N-terminal fragment of the HPV type 45 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:11 at any amino acid site within the $\alpha 5$ region thereof; the N-terminal fragment of the HPV type 51 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:12 at any amino acid site within the $\alpha 5$ region thereof; the N-terminal fragment of the HPV type 52 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:13 at any amino acid site within the $\alpha 5$ region thereof; the N-terminal fragment of the HPV type 56 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:14 at any amino acid site within the $\alpha 5$ region thereof; and

the N-terminal fragment of the HPV type 58 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:15 at any amino acid site within the $\alpha 5$ region thereof.

[0021] In one embodiment, the C-terminal of the N-terminal fragment is connected directly to the N-terminal of the C-terminal fragment or by a linker.

[0022] In one embodiment, when the C-terminus of said N-terminal fragment is connected to the N-terminus of said C-terminal fragment, the continuous amino acid sequence RKFL is present within a range of plus or minus 4 amino acid positions of the splicing site,

Preferably, the continuous amino acid sequence LGRKFL is present within a range of plus or minus 6 amino acid positions of the splicing site.

[0023] In one embodiment, the chimeric HPV type 6, 11, 16, 18, 31, 35, 39, 45, 51, 52, 56, and 58 chimeric HPV L1 proteins have 98%, 98.5%, 99%, 99.5% or 100% identity to SEQ ID No:16, SEQ ID No:17, SEQ ID No:18, SEQ ID No:19, SEQ ID No:20, SEQ ID No:21, SEQ ID No:22, SEQ ID No:23, SEQ ID No:24, SEQ ID No:25, SEQ ID No:26 and SEQ ID No: 27, respectively; and the HPV type 33 L1 protein and the HPV type 59 L1 protein have 98%, 98.5%, 99%, 99.5% or 100% identity to SEQ ID No:28 and SEQ ID No:29, respectively.

[0024] In one embodiment, the formulation comprises HPV types 6, 11, 16, 18, 31, 35, 39, 45, 51, 52, 56 and 58 chimeric HPV L1 protein having the amino acid sequences shown in SEQ ID No:16, SEQ ID No:17, SEQ ID No:18, SEQ ID No:19, SEQ ID No:20, SEQ ID No:21, SEQ ID No:22, SEQ ID No:23, SEQ ID No:24, SEQ ID No:25, SEQ ID No:26 and SEQ ID No: 27, respectively; and HPV type 33 L1 protein and HPV type 59 L1 protein having the amino acid sequences shown in SEQ ID No:28 and SEQ ID No: 29, respectively.

[0025] In one aspect, the present invention provides a method of preventing an HPV-related disease or infection comprising administering to a subject a stable formulation of the multivalent human papillomavirus virus-like particle vaccine formulation. The prevention may be considered as a treatment and the two terms are used interchangeably. In one embodiment, the subject is human.

[0026] In one aspect, the formulation is stable at 2 to 8 °C for at least 24 month and at 25 °C for at least 16 weeks.

[0027] In one aspect, the present invention provides the use of the human papillomavirus virus-like particle vaccine formulation in the preparation of a vaccine for the prevention of HPV-related diseases or infections.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Figure 1 shows the results of the adsorption degree test of each formulation sample in Example 1.

[0029] Figure 2 shows the analysis result of antigen content of each formulation sample in Example 1. T0:37 °C, week 0; 37 °C _1W: 37 °C, week 1; 37 °C _ 2 W: 37 °C, week 2; 37 °C 4 W: 37 °C week 4.

[0030] Figure 3 shows the results of the adsorption degree test of each formulation sample in Example 2.

[0031] Figure 4 shows the analysis results of antigen content of each formulation sample in Example 2. T0:37 °C, week 0; 37 °C _1W: 37 °C, week 1; 37 °C _ 2 W: 37 °C, week 2; 37 °C 4 W: 37 °C week 4.

[0032] Figure 5 shows the results of the adsorption degree test of each formulation sample in Example 3.

[0033] Figure 6 shows the analysis results of antigen content of each formulation sample in Example 3. T0:37 °C, week 0; 37 °C _1W: 37 °C, week 1; 37 °C _ 2 W: 37 °C, week 2; 37 °C 4 W: 37 °C week 4.

[0034] Figure 7 shows the results of the adsorption degree test of each formulation sample in Example 4.

[0035] Figure 8 shows the analysis results of antigen content of each formulation sample in Example 4. T0:37 °C, week 0; 37 °C _1W: 37 °C, week 1; 37 °C _ 2 W: 37 °C, week 2; 37 °C 4 W: 37 °C week 4.

DETAILED DESCRIPTION

[0036] The invention provides a stable formulation of a human papillomavirus vaccine, solves the problem of antibody stability in the processes of storage and transportation, and ensures that the pre-dose antigen still has the immunogenicity and safety satisfying the prevention purpose

[0037] The term "formulation" refers to a composition that maintains the biological activity of the active component in an effective manner and does not contain other components that are unacceptably toxic to the subject. Such formulations are sterile. The term "sterile" refers to the absence of live bacteria or the absence or substantial absence of all live microorganisms and their spores.

[0038] As used herein, a "stable" formulation refers to a formulation in which the active ingredient substantially retains its physical and/or chemical stability and/or biological activity after storage. Preferably, the formulation substantially retains its physical and chemical stability as well as its biological activity after storage.

[0039] The terms "patient" or "subject" are used interchangeably and refer to any mammal suffering from a condition or disease in accordance with the present invention. Preferably, human.

[0040] As used herein, "physiologically acceptable" means a concentration or ionic strength of a buffer, excipient, or salt makes the formulation biologically compatible with the immunized target host, e.g., human.

[0041] The stable formulation of the present invention comprises human papillomavirus virus-like particles, a buffer, an osmotic pressure regulator, and an aluminum adjuvant.

[0042] The terms "comprising" and "containing" mean that additional components may be included in addition to the components mentioned.

[0043] As use herein and in that appended claim, the singular forms "a", "an", "the" and "said" include plural referents unless the context clearly dictates otherwise.

[0044] As used herein, "buffer" refers to a buffer solution that resists pH change by the action of its conjugate acid-base pair. In one embodiment of the present invention, histidine buffer is used and the pH of the formulation solution is preferably about 5.9 to 6.5, more preferably 6.2.

[0045] As used herein, "surfactant" refers to a surface active agent, and in one embodiment, the surfactant herein is polysorbate 80.

[0046] The term "osmotic pressure regulator" means a pharmaceutically acceptable osmotic pressure regulator. Suitable osmotic regulators include, but are not limited to salts, and in one embodiment of the present invention are sodium chloride (NaCl) with a concentration of about 150mM to 320mM.

[0047] The term "adjuvant" refers to a compound or mixture that enhances an immune response. In particular, the vaccine may comprise an adjuvant. Adjuvants used in the present invention are selected from one or more of aluminum hydroxyphosphate (AlPO_4), amorphous aluminum hydroxyphosphate sulfate (AAHS), or aluminum hydroxide ($\text{Al}(\text{OH})_3$), preferably aluminum hydroxyphosphate (AlPO_4).

[0048] The "stability" of protein after storage at a selected temperature for a selected period of time may be assessed qualitatively and/or quantitatively in a number of different ways. In the embodiment of the invention, Enzyme-linked immunosorbent assay (ELISA) was used to measure the content of active antigen binding to the recombinant human papillomavirus neutralizing antibody, and the ratio of the active antigen content at each time point to T0 was used to compare the stability of corresponding formulation; Enzyme-linked immunosorbent assay (ELISA) was used to measure the content of the antigen not adsorbed on aluminum phosphate adjuvant with the aid of centrifugation and then to calculate the absorption degree; Determining the

EC₅₀ of the human papillomavirus vaccine formulation and the positive control to the recombinant human papillomavirus neutralizing antibody respectively , calculating the EC₅₀ ratio of the vaccine formulation to the positive control thereby determining the *in vitro* relative potency of the vaccine.

[0049] The term "immunogenicity" refers to the ability of a substance, such as a protein or polypeptide, to stimulate an immune response, i.e., to stimulate the production of antibodies, particularly responses that generates humoral or stimulated cell-mediated responses.

[0050] The term "HPV" or "HPV virus" refers to a papillomavirus of the family *Papillomaviridae*, which is an uncoated DNA virus having a double-stranded closed-loop DNA genome of about 8kb in size and which can generally be divided into three regions: ① the early region (E) comprising six open reading frames encoding nonstructural proteins related to E1, E2, E4-E7 virus replication, transcription and transformation, as well as E3 and E8 open reading frames; ② the late region (L) comprises a reading frame encoding the major capsid protein L1 and the minor capsid protein L2; ③ long regulatory region (LCR) does not encode any protein, but it has the origin of replication and multiple transcription factor binding sites.

[0051] The terms "HPV L1 protein" and "HPV L2 protein" refer to proteins encoded by the late region (L) of the HPV gene and synthesized in the middle and late period of the HPV infection cycle. L1 protein is the major capsid protein and has a molecular weight of 55-60kDa. L2 protein is the minor capsid protein. Seventy-two L1 pentamers form the shell of icosahedral HPV virus particles, wrapping the closed-loop double-stranded DNA micro-chromosome. L2 protein is located inner lining of the L1 protein.

[0052] The term "virus-like particles" is a hollow particle containing one or more structural proteins of a virus without viral nucleic acid.

[0053] The term "concentration of papillomavirus virus-like particle of any single type" refers to the content of papillomavirus virus-like particle of any single type in the formulation, and the term "total concentration of papillomavirus virus-like particles of all types" is the sum of the concentrations of papillomavirus virus-like particle of each single type included in the formulation.

[0054] In one embodiment of the invention, the human papillomavirus multivalent immunogenic composition described in patent application PCT/CN2020/102601 filed on

July 17, 2020 is adopted, and PCT/CN2020/102601 is incorporated by reference into the present specification and claims.

[0055] In a particularly preferred embodiment of the invention, the formulation comprises 0.74mg/mL of papillomavirus virus-like particles, 1.0mg/mL of aluminum phosphate adjuvant, 18mM histidine buffer, 320mM sodium chloride, and a pH of 6.2. Wherein the vaccine comprises polysorbate 80 at a concentration of not more than 0.3mg/mL due to process residues during preparation. The formulation has good stability, and can be stably stored at 2 to 8 °C for at least 24 months and at 25 °C for at least 16 weeks.

[0056] The formulations of the present invention may be provided in liquid form or may be provided in lyophilized form. The lyophilized formulation may be reconstituted prior to administration.

EXAMPLE

[0057] The present invention will be more fully understood by reference to the following examples. However, they should not be construed as limiting the scope of the invention. All documents, patents and patent applications are incorporated herein by reference.

[0058] In the examples below, the preparation, characterization and performance identification of various types of papillomavirus virus-like particles used are described in patent application PCT/CN2020/102601, filed on July 17, 2020.

[0059] In the following examples, the detection method used was as follows:

[0060] 1) Analysis of antigen content (Enzyme-linked Immunosorbent Assay (ELISA)

[0061] The positive control (human papillomavirus virus-like particle standard, source: SinoCellTech Ltd., chimeric HPV type 6, 16, 18, 31, 35, 30, 45, 51, 52, and 56 chimeric HPV L1 protein and HPV type 33 and HPV type 59 L1 protein, corresponding to the amino acid sequence of SEQ ID NO:16-29 respectively, the same as below) and the analyte were completely dissolved using the desorption buffer, serving as the positive control and the analyte to be detected.

[0062] The recombinant human papillomavirus neutralizing antibody (source: Sino Biological, Inc., the same as below) was combined with a solid-phase carrier to form a solid-phase antibody. Diluting the positive control and the analyte to be detected with the sample diluent, and then combining with the solid phase antibody to form a solid phase antigen antibody complex; enzyme-labeled antibody was then added and the

substrate was added for developing, and the color product was read at a wavelength of 450nm. Performing linear regression on the concentration of a series of positive controls and the corresponding absorbance, substituting the absorbance value of the analyte into a linear regression equation, and obtaining the antigen content of the sample to be detected (M. Shank-Retzlaff, F. Wang, T. Morley et al. Correlation between Mouse Potency and *In Vitro* Relative Potency for Human Papillomavirus Type 16 Virus-Like Particles and Gardasil Vaccine Samples. Human Vaccines, 1:5, 191-197).

[0063] 2) Adsorption degree analysis (enzyme-linked immunosorbent assay (ELISA)

[0064] The recombinant human papillomavirus neutralizing antibody is combined with a solid phase carrier to form a solid phase antibody. Centrifuging the sample to be detected, and taking the supernatant as an analyte. Diluting the positive control and the analyte accordingly with the sample diluent, and then combining with the solid phase antibody to form a solid phase antigen antibody complex; enzyme-labeled antibody was then added and the substrate was added for developing, and the color product was read at a wavelength of 450nm. Performing linear regression on the concentration of a series of positive controls and the corresponding absorbance, substituting the absorbance value measured with the analyte into a linear regression equation to obtain the antigen concentration of the supernatant, and calculating the adsorption degree of the sample to be detected by the following equation (Michael J. Caulfield, Li Shi, Su Wang et al. Effect of Alternative Aluminum Adjuvants on the Absorption and Immunogenicity of HPV16 L1 VLPs in Mice. Human Vaccines 3:4, 139-146).

[0065] Adsorption degree (%) = (1- antigen concentration in supernatant/antigen concentration of sample to be detected) %.

[0066] 3) Determination of *In Vitro* Relative Potency, IVRP (IVRP)

[0067] The positive control (14 valent human papillomavirus vaccine (types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) control product obtained from SinoCellTech Ltd, with the sequence same as the protein sequence in the test sample) and the analyte were completely dissolved using desorption buffer, and used as the positive control and the analyte to be detected. The recombinant human papillomavirus neutralizing antibody was diluted to a final concentration of 2µg/mL, added to 96-well plates at 100µL/ well, the plates were tapped to mix the samples, and the samples were coated overnight at 4 °C; the plates were washed with washing solution at a dose of 200µL/ well once and the ELISA plate was dried. Then the ELISA plate was blocked

with blocking solution at 300μL/ well for one hour at room temperature. The samples were washed twice with washing solution at 300μL/ well, and 100μL treated blank control (buffer solution corresponding to analyte), positive control and analyte to be detected were added into each well and incubated for 1 hour at room temperature. After the plates were washed three times with washing solution at 200μL/ well, diluted enzyme-labeled recombinant human papillomavirus neutralizing antibody was added at 100μL/ well. After incubated at room temperature for 1 h, the plates were washed with washing solution at 200μL/ well for three times, and the developing solution was added at 200μL/ well and placed at room temperature for 20±5min. The reaction was terminated by adding a stop solution at 50μL/well; the absorbance at 450nm was detected by a microplate reader. Processing by using a computer program Origin or a four-parameter fitting method, taking the concentration of the positive control or the analyte as an abscissa and the average absorbance as an ordinate to obtain the EC₅₀ of the analyte and the positive control, and dividing the EC₅₀ of the analyte by the EC₅₀ of the positive control to obtain the *in vitro* relative potency of the analyte(M. Shank-Retzlaff, F. Wang, T. Morley et al. Correlation between Mouse Potency and *In Vitro* Relative Potency for Human Papillomavirus Type 16 Virus-Like Particles and Gardasil Vaccine Samples. Human Vaccines, 1:5, 191-197).

[0068] Example 1: Screening study of surfactant concentration

[0069] The composition of the papillomavirus virus-like particle vaccine formulation of this example is shown in the following table:

Table 1 Formulations of different surfactant concentrations

Composition number	Papillomavirus virus-like particle	Aluminum phosphate adjuvant	Histidine buffer	NaCl	Polysorbate 80	pH
F1	0.74mg/mL	1.0mg/mL	18mM	320mM	0.00wt%	6.5
F2	0.74mg/mL	1.0mg/mL	18mM	320mM	0.02wt%	6.5

[0070] Preparation method of papillomavirus virus-like particle vaccine formulation:

[0071] Took a certain amount of HPV 18 virus-like particles appropriate to the formulation, and then mixed it with aluminum phosphate adjuvant, and adsorbed it overnight at 4 °C, so that the pH, the corresponding concentrations of

papillomavirus virus-like particles, aluminum phosphate adjuvant, histidine, sodium chloride, and polysorbate 80 in the papillomavirus virus-like particle vaccine formulation respective met the requirements of Table 1, dispensed it in aliquot. Marked it with the corresponding numbers, placed the samples in a 37 °C incubator, and took it out for analysis of adsorption degree and antigen content at week 0, and for antigen content analysis at weeks 1, 2, and 4.

[0072] Analytical test method:

[0073] Adsorption degree analysis: the detection principle is that antigens not adsorbed onto aluminum phosphate adjuvant are obtained by centrifugation and the content is analyzed to calculate the adsorption degree.

[0074] Antigen content analysis: the detection principle is that the active antigen content capable of binding to the recombinant human papillomavirus neutralizing antibody is measured by ELISA, and the stability of each formulation is compared by comparing the ratio of the active antigen content at each time point with that of T0. The higher the ratio, the higher the active antigen content in the formulation and the better the activity maintained.

[0075] The test results are shown in tables 2-3 and figures 1-2.

Table 2 Adsorption degree of HPV18 virus-like particle formulation

Num	%HPV18 VLPs binding to aluminum adjuvant
F1	99.8
F2	99.9

Table 3 Antigen content of HPV18 virus-like particle formulation

Time point	HPV18VLP content (percentage with T ₀ , %)	
	F1	F2
T ₀	100	100
37°C_1W	87.9	88.2
37 °C_2W	84.8	85.3
37 °C_4W	54.5	55.9

[0076] The test results showed that the adsorption degrees of both two papillomavirus virus-like particle vaccine formulations were above 99%, and there was no significant difference in the changes of antigen content between F1 and F2, that is, the stability of F1 and F2 was comparable.

[0077] Example 2: Screening study of pH

[0078] The composition of the papillomavirus virus-like particle vaccine formulation of this example is shown in the following table:

Table 4 Formulations with different pH

Composition number	Papillomavirus virus-like particle	Aluminum phosphate adjuvant	Histidine buffer	NaCl	Polysorbate 80	pH
F1	0.74mg/mL	1.0mg/mL	18mM	320mM	0.00wt%	5.9
F2	0.74mg/mL	1.0mg/mL	18mM	320mM	0.00wt%	6.2
F3	0.74mg/mL	1.0mg/mL	18mM	320mM	0.00wt%	6.5

[0079] Preparation method of papillomavirus virus-like particle vaccine formulation:

[0080] Took a certain amount of HPV 18 virus-like particles appropriate to the formulation, and then mixed it with aluminum phosphate adjuvant, and adsorbed it overnight at 4 °C, so that the pH, the corresponding concentrations of papillomavirus virus-like particles, aluminum phosphate adjuvant, histidine, sodium chloride, and polysorbate 80 in the papillomavirus virus-like particle vaccine formulation respective met the requirements of Table 4, dispensed it in aliquot. Marked it with the corresponding numbers, placed the samples in a 37 °C incubator, and took it out for analysis of adsorption degree and antigen content at week 0, and for antigen content analysis at weeks 1, 2, and 4.

[0081] Analytical test method:

[0082] Adsorption degree analysis: the detection principle is that antigens not adsorbed onto aluminum phosphate adjuvant are obtained by centrifugation and the content is analyzed to calculate the adsorption degree.

[0083] Antigen content analysis: the detection principle is that the active antigen content capable of binding to the recombinant human papillomavirus neutralizing antibody is measured by ELISA, and the stability of each formulation is compared by comparing the ratio of the active antigen content at each time point with that of T0. The higher the ratio, the higher the active antigen content in the formulation and the better the activity maintained.

[0084] The test results are shown in tables 5-6 and figures 3-4.

Table 5 Adsorption degree of HPV18 virus-like particle formulation

Num	%HPV18 VLPs binding to aluminum adjuvant
F1	99.4
F2	99.4
F3	99.8

Table 6 Antigen content of HPV18 virus-like particle formulation

Time point	HPV18VLP content (percentage with T ₀ , %)		
	F1	F2	F3
T ₀	100	100	100
37°C_1W	93.5	100	87.9
37 °C_2W	87.1	96.6	84.8
37 °C_4W	90.3	82.8	54.5

[0085] The test results showed that the adsorption degrees of the three papillomavirus virus-like particle vaccine formulations were above 99%, and the antigen content change trends of the papillomavirus virus-like particle vaccines in F1 and F2 were better

than that of the F3 formulation, that is, the stability of F1 and F2 was better than that of F3.

[0086] Example 3: Screening study of osmotic pressure regulator concentration

[0087] The composition of the papillomavirus virus-like particle vaccine formulation of this example is shown in the following table:

Table 7 Formulations of different osmotic pressure regulator concentrations

Composition number	Papillomavirus virus-like particle	Aluminum phosphate adjuvant	Histidine buffer	NaCl	Polysorbate 80	pH
F1	0.74mg/mL	1.0mg/mL	18mM	320mM	0.00wt%	6.2
F2	0.74mg/mL	1.0mg/mL	18mM	150mM	0.00wt%	6.2

[0088] Preparation method of papillomavirus virus-like particle vaccine formulation:

[0089] Took a certain amount of HPV 18 virus-like particles appropriate to the formulation, and then mixed it with aluminum phosphate adjuvant, and adsorbed it overnight at 4 °C, so that the pH, the corresponding concentrations of papillomavirus virus-like particles, aluminum phosphate adjuvant, histidine, sodium chloride, and polysorbate 80 in the papillomavirus virus-like particle vaccine formulation respective met the requirements of Table 7, dispensed it in aliquot. Marked it with the corresponding numbers, placed the samples in a 37 °C incubator, and took it out for analysis of adsorption degree and antigen content at week 0, and for antigen content analysis at weeks 1, 2, and 4.

[0090] Analytical test method:

[0091] Adsorption degree analysis: the detection principle is that antigens not adsorbed onto aluminum phosphate adjuvant are obtained by centrifugation and the content is analyzed to calculate the adsorption degree.

[0092] Antigen content analysis: the detection principle is that the active antigen content capable of binding to the recombinant human papillomavirus neutralizing antibody is measured by ELISA, and the stability of each formulation is compared by comparing the ratio of the active antigen content at each time point with that of T0. The

higher the ratio, the higher the active antigen content in the formulation and the better the activity maintained.

[0093] The test results are shown in tables 8-9 and figures 5-6.

Table 8 Adsorption degree of HPV18 virus-like particle formulation

Num	%HPV18 VLPs binding to aluminum adjuvant
F1	99.4
F2	99.6

Table 9 Antigen content of HPV18 virus-like particle formulation

Time point	HPV18VLP content (percentage with T₀, %)	
	F1	F2
T ₀	100	100
37°C_1W	87.9	88.2
37 °C_2W	84.8	85.3
37 °C_4W	54.5	55.9

[0094] The test results showed that the adsorption degrees of the two papillomavirus virus-like particle vaccine formulations were above 99%. There was no significant difference in the active antigen content s changes of F1 and F2 formulations at 4 weeks under 37 °C , that is, the stability of F1 and F2 was comparable.

[0095] Example 4: screening study of buffer concentration

[0096] The composition of the papillomavirus virus-like particle vaccine formulation of this example is shown in the following table:

Table 10 Formulations of different buffer concentrations

Composition number	Papillomavirus virus-like particle	Aluminum phosphate adjuvant	Histidine buffer	NaCl	Polysorbate 80	pH
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F1	0.74mg/mL	1.0mg/mL	10mM	320mM	0.00wt%	6.2
F2	0.74mg/mL	1.0mg/mL	18mM	320mM	0.00wt%	6.2
F3	0.74mg/mL	1.0mg/mL	26mM	320mM	0.00wt%	6.2

[0097] Preparation method of papillomavirus virus-like particle vaccine formulation;

[0098] Took a certain amount of HPV 18 virus-like particles appropriate to the formulation, and then mixed it with aluminum phosphate adjuvant, and adsorbed it overnight at 4 °C, so that the pH, the corresponding concentrations of papillomavirus virus-like particles, aluminum phosphate adjuvant, histidine, sodium chloride, and polysorbate 80 in the papillomavirus virus-like particle vaccine formulation respective met the requirements of Table 10, dispensed it in aliquot. Marked it with the corresponding numbers, placed the samples in a 37 °C incubator, and took it out for analysis of adsorption degree and antigen content at week 0, and for antigen content analysis at weeks 1, 2, and 4.

[0099] Analytical test method:

[00100] Adsorption degree analysis: the detection principle is that antigens not adsorbed onto aluminum phosphate adjuvant are obtained by centrifugation and the content is analyzed to calculate the adsorption degree.

[00101] Antigen content analysis: the detection principle is that the active antigen content capable of binding to the recombinant human papillomavirus neutralizing antibody is measured by ELISA, and the stability of each formulation is compared by comparing the ratio of the active antigen content at each time point with that of T0. The higher the ratio, the higher the active antigen content in the formulation and the better the activity maintained.

[00102] The test results are shown in tables 11-12 and figures 7-8.

Table 11 Adsorption degree of HPV18 virus-like particle formulation

Num	%HPV18 VLPs binding to aluminum adjuvant
F1	99.6
F2	99.4
F3	99.6

Table 12 antigen content of HPV18 virus-like particle formulation

Time point	HPV18VLP content (percentage with T ₀ , %)		
	F1	F2	F3
T ₀	100	100	100
37°C_1W	96.6	100	76.5
37 °C_2W	96.6	96.6	70.6
37 °C_4W	89.7	82.8	70.6

[00103] The test results showed that the adsorption degrees of the three papillomavirus virus-like particle vaccine formulations were above 99%, and the antigen content change trends of the papillomavirus virus-like particle vaccines in F1 and F2 were better than those of the F3 formulation, that is, the stability of F1 and F2 was better than that of F3.

[00104] Example 5: Composition confirmation study of each single type (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) papillomavirus virus-like particles vaccine formulation

[00105] Each single type (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) of papillomavirus virus-like particle vaccine formulations (formulation: 0.74mg/mL papillomavirus virus-like particle +1.0mg/mL aluminum phosphate adjuvant +18mM histidine buffer +320mM sodium chloride at pH 6.2) was subjected to stability monitoring at 2–8 °C , respectively. Wherein the vaccine contained polysorbate 80 at a concentration of not more than 0.3mg/mL due to process residues in preparation. The monitoring time points were 3m(3 months), 6m(6 months), 9m(9 months) and 12m(12 months), and the adsorption degree and *in vitro* relative potency were monitored.

[00106] Analytical test method:

[00107] Adsorption degree analysis: the detection principle is that antigens not adsorbed onto aluminum phosphate adjuvant are obtained by centrifugation and the content is analyzed to calculate the adsorption degree.

[00108] *In vitro* relative potency: the detection principle of this method is to detect the EC₅₀ of the analyte and the positive control with the recombinant human

papillomavirus neutralization antibody respectively, then to calculate the percentage ration of EC₅₀ thereof. The higher the value, the higher the *in vitro* relative efficacy and the better quality of the test sample.

[00109] The experimental results are shown in Table 13.

[00110] Experimental results show that each single type of papillomavirus virus-like particle vaccine formulations disclosed by the invention has good stability and can be stably stored for at least 12 months under the condition of 2-8 °C .

Table 13 Stability data of all 14 single types (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) Papillomavirus-like particles adjuvant adsorption liquid composition

Papillomavirus virus-like particle type	Adsorption degree (%)					In vitro relative potency (%)				
	T0	4°C-3m	4°C-6m	4°C-9m	4°C-12m	T0	4°C-3m	4°C-6m	4°C-9m	4°C-12m
6	98	99	99	100	>99	101	117	99	116	113
11	99	100	100	>99	>99	96	113	108	143	113
16	>99	>99	>99	>99	>99	92	116	100	130	97
18	>99	>99	>99	>99	>99	86	110	106	97	109
31	>99	>99	>99	>99	>99	109	108	98	113	92
33	>99	>99	>99	>99	>99	96	113	107	108	103
35	>99	>99	>99	>99	>99	85	86	91	88	97
39	>99	>99	>99	>99	>99	101	110	109	105	102
45	99	>99	>99	>99	>99	88	119	115	107	120
51	>99	>99	>99	>99	>99	94	118	98	110	117
52	>99	>99	>99	>99	>99	90	120	104	103	106
56	>99	>99	>99	>99	>99	90	108	99	92	101
58	>99	>99	>99	>99	>99	97	98	106	113	108
59	>99	>99	>99	>99	>99	96	104	106	114	115

[00111] Example 6 Formulation preparation and composition confirmation of 14 valent human papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59)

[00112] Preparation method of 14 valent human papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59):

[00113] Each single type (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) of papillomavirus virus-like particle vaccine formulation (Composition: 0.74mg/mL papillomavirus virus-like particles +1.0mg/mL aluminum phosphate adjuvant +18mM histidine buffer +320mM sodium chloride, pH value: 6.2) was respectively taken and mixed in a certain volume ratio (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 =1.5:2:3:2:1:1:1:1:1:1:1:1:1:1) to obtain a 14 valent human papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) semi-finished product, corresponding to the concentration of 0.06mg/mL, 0.08mg/mL, 0.12mg/mL, 0.08mg/mL, 0.04mg/mL, 0.04mg/mL, 0.04mg/mL, 0.04mg/mL, 0.04mg/mL, 0.04mg/mL, 0.04mg/mL, 0.04mg/mL, 0.04mg/mL, 0.04mg/mL of each type of virus-like particle, respectively; then filled into Penicillin vials which were then corked, capped, and labeled to prepare recombinant 14 valent human papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59), wherein the vaccine comprised polysorbate 80 in a concentration of not more than 0.3mg/mL due to process residues in the preparation process. The stability monitoring was then conducted at 2–8 °C (time points are 3, 6, 9, 12, 18, and 24 months) and 25±2 °C (time points are 2 weeks, 4 weeks, 8 weeks, and 16 weeks), and the *in vitro* relative potency and adsorption degree were monitored.

[00114] Analytical test method:

[00115] Adsorption degree analysis: the detection principle is that antigens not adsorbed onto aluminum phosphate adjuvant are obtained by centrifugation and the content is analyzed to calculate the adsorption degree.

[00116] Antigen content analysis: the detection principle is that the active antigen content capable of binding to the recombinant human papillomavirus neutralizing antibody is measured by ELISA, and the stability of each formulation is compared by comparing the ratio of the active antigen content at each time point with that of T0. The higher the ratio, the higher the active antigen content in the formulation and the better the activity maintained.

[00117] The experimental results are shown in tables 14-17.

[00118]

Table 14 *In vitro* relative potency (25 °C) of recombinant 14 valent human

papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59)

Lot	Type Time	<i>In vitro</i> relative potency(%)													
		6	11	16	18	31	33	35	39	45	51	52	56	58	59
Lot1	0 weeks	95	97	95	107	97	95	107	95	97	103	106	93	97	89
	2 weeks	90	96	89	85	96	97	91	83	86	88	84	92	87	90
	4 weeks	91	93	87	79	85	101	103	101	99	94	106	95	94	92
	8 weeks	92	92	89	88	88	87	87	105	81	92	88	93	88	91
	16 weeks	89	85	95	82	80	87	85	96	84	94	89	88	90	85
Lot2	0 weeks	103	95	93	114	113	93	118	113	94	88	107	101	113	99
	2 weeks	86	92	84	92	87	88	87	96	84	88	78	93	97	87
	4 weeks	94	89	75	84	82	90	100	92	93	94	96	92	101	96
	8 weeks	97	90	86	93	79	84	84	104	76	100	80	90	93	96
	16 weeks	86	74	90	79	69	87	80	96	78	101	73	68	80	82
Lot3	0 weeks	90	97	98	105	118	91	115	106	95	93	102	92	118	98
	2 weeks	76	94	76	86	81	76	84	97	87	92	78	93	104	84
	4 weeks	85	92	76	78	71	84	94	89	88	88	93	90	95	86
	8 weeks	86	94	90	86	73	80	80	91	72	89	72	84	92	87
	16 weeks	73	82	94	70	72	89	92	85	69	85	64	69	90	80

Table 15 Adsorption degree (25 °C) of recombinant 14 valent human papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59)

Lot	Type Time	Adsorption degree(%)													
		6	11	16	18	31	33	35	39	45	51	52	56	58	59
Lot1	0 weeks	98	99	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	2 weeks	99	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	4 weeks	99	99	>99	>99	>99	99	99	>99	>99	>99	>99	99	>99	>99
	8 weeks	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	16 weeks	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
Lot2	0 weeks	99	100	100	>99	>99	>99	>99	>99	100	>99	>99	>99	>99	>99
	2 weeks	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	4 weeks	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	8 weeks	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	16 weeks	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
Lot3	0 weeks	99	99	99	>99	>99	>99	>99	>99	99	>99	>99	>99	>99	>99
	2 weeks	99	99	99	100	99	99	>99	>99	>99	>99	>99	>99	>99	>99

4 weeks	100	100	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	100	>99	>99
8 weeks	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
16 weeks	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99

Table 16 *In vitro* relative potency (4 °C) of recombinant 14 valent human papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59)

Lot	Type Time	<i>In vitro</i> relative potency(%)													
		6	11	16	18	31	33	35	39	45	51	52	56	58	59
Lot1	0 months	95	97	95	107	97	95	107	95	97	103	106	93	97	89
	3 months	113	115	100	99	109	103	107	113	112	112	110	132	114	127
	6 months	109	102	98	114	114	100	102	105	104	104	100	100	105	102
	9 months	125	119	111	108	118	122	115	107	105	98	95	100	92	94
	12 months	93	97	92	87	97	94	96	96	102	97	97	100	97	99
	18 months	110	102	103	99	100	98	105	100	99	108	99	96	101	104
	24 months	113	101	96	95	98	99	95	98	101	95	97	95	96	100
Lot2	0 months	103	95	93	114	113	93	118	113	94	88	107	101	113	99
	3 months	109	103	94	102	97	86	101	129	106	114	108	116	112	132
	6 months	96	88	81	105	109	94	96	111	105	111	95	100	99	108
	9 months	123	112	103	106	107	114	110	112	96	101	87	95	95	96
	12 months	133	89	92	88	93	92	98	100	89	84	89	86	89	98
	18 months	107	94	103	101	98	82	96	107	99	105	99	100	106	117
	24 months	110	90	90	92	88	96	95	100	97	99	95	94	100	102
Lot3	0 months	90	97	98	105	118	91	115	106	95	93	102	92	118	98
	3 months	100	95	95	103	93	76	107	121	104	115	109	92	121	121
	6 months	96	96	81	96	124	79	90	98	100	115	98	93	101	104
	9 months	113	113	103	99	118	94	103	102	103	97	82	91	93	96
	12 months	115	98	100	89	99	78	92	104	109	95	99	88	104	106
	18 months	93	96	101	87	96	69	96	102	99	94	97	97	104	110
	24 months	103	93	92	89	84	72	91	94	92	80	83	79	97	91

Table 17 Adsorption degree (4 °C) of recombinant 14 valent human papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59)

Lot	Type Time	Adsorption degree(%)													
		6	11	16	18	31	33	35	39	45	51	52	56	58	59
Lot1	0 months	98	99	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99

	3 months	98	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	6 months	99	100	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	9 months	99	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	12 months	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	18 months	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	24 months	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
Lot2	0months	99	100	100	>99	>99	>99	>99	>99	100	>99	>99	>99	>99	>99
	3months	99	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	6months	100	>99	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	9months	100	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	12months	100	>99	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	18months	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	24months	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
Lot3	0months	99	99	99	>99	>99	>99	>99	>99	99	>99	>99	>99	>99	>99
	3months	99	100	100	>99	>99	>99	>99	>99	100	>99	>99	>99	>99	>99
	6months	100	100	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	9months	100	100	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	12months	100	>99	100	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	18months	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
	24months	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99

[00119] Experimental results show that the 14 valent human papillomavirus vaccine (type 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) preparation disclosed by the invention has good stability, and can be stably stored for at least 24 months at the temperature of 2 - 8 °C and at least 16 weeks at the temperature of 25 °C .

SEQUENCE LISTING

SEQ ID NO	Sequence description	Amino acid or nucleic acid sequence
SEQ ID No: 1	Amino acid sequence of aa 474-499 of HPV type 33 L1 protein	KAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 2	Amino acid sequence of aa 469-499 of HPV type 33 L1 protein	LQAGLKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 3	Amino acid sequence of aa 471-508 of HPV type 59 L1 protein	LQLGARPKPTIGPRKRAAPAPTSTPSPKRVKRRKSSRK
SEQ ID No: 4	Amino acid sequence of aa 1-469 of HPV type 6 L1 protein	MWRPSDSTVYVPPPNPVSKVVATDAYVTRTNIFYHASSRLLAVGHPYFSIKRANKTVVPKVS GYQYRVFKVVLDPNKFALPDSSLFDPPTQRLVWACTGLEVGRGQPLGVGVSGHPFLNKYDD VENSGSGGNPGQDNRNVNMGMDYKQTQLCMVGCAPPLGEHWGKGKQCTNTPVQAGDCPP LELITSVIQDGDMDVTGFGAMNFADLQTNKSDVPIDICGTTCKYPDYQLMAADPYGDRLFFFL RKEQMFARHFFNRAGEVGEVPPDTLIIKSGSNRTSVGSSIVNTPSGSLVSSEAQLFNKPYWL QKAQGHNNIGCWGNQLFVTVDTRSTNMTLCASVTTSTYTNSDYKEYMRHVEEYDLQFIF QLCSITLSAEVMAYIHTMNPSVLEDWNFGLSPPPNGTLEDTRYVVSQAITCQKPTPEKEKPD PYKNLSFWEVNLKEKFSSELDQYPLGRKFLLQSGY
SEQ ID No: 5	Amino acid sequence of aa 1-470 of HPV type 11 L1 protein	MWRPSDSTVYVPPPNPVSKVVATDAYVTRTNIFYHASSRLLAVGHPYFSIKKVNKTVPKVS GYQYRVFKVVLDPNKFALPDSSLFDPPTQRLVWACTGLEVGRGQPLGVGVSGHPFLNKYDD VENSGGYGGNPGQDNRNVNMGMDYKQTQLCMVGCAPPLGEHWGKGKQCTNTPVQAGDCPP PPELITSVIQDGDMDVTGFGAMNFADLQTNKSDVPLDICGTVCCKYPDYQLMAADPYGDRLF FYLRKEQMFARHFFNRAGTVGEVPPDLLVKGGNNRSSHVASSIYVHTPSGSLVSSEAQLFNKPY YWLQKAQGHNNIGCWGNHLFVTVDTRSTNMTLCASVSKSATYTNSDYKEYMRHVEEYDLQFIF QFIFQLCSITLSAEVMAYIHTMNPSVLEDWNFGLSPPPNGTLEDTRYVVSQAITCQKPTPEKE KQDPYKDMFWEVNLKEKFSSELDQYPLGRKFLLQSGY
SEQ ID No: 6	Amino acid sequence of aa of aa 1-474 of HPV type 16 L1 protein	MSLWLPSEATVYLPPVPVSKVVSTDEYVARTNIYYHAGTSRLLAVGHPYFPIKPNNNKILVPK VSGLQYRVFRIHLPDNKFGFPDTSFYNPDTQRLVWACVGEVGRGQPLGVGISGHPLLNKL DDTENASAYAANAGVDNRECISMDYKQTQLCLIGCKPPIGEHWGKGSPCTNVAVNPGDCPP LELINTVIQDGDMDVTGFGAMDFTLQANKSEVPLDICTSICKYPDIKVMSEPYGDSLFFYLRR EQMFVRHLFNRAAGAVGENVPDDLIIKSGSGSTANLASSNYFPTPSGSMVTSDAQIFNKPYWLQ RAQGHNNIGCWGNQLFVTVDTRSTNMSLCAAISTSETTYKNTNFKEYLRHGEEDLQFIFQ LCKITLTADVMTYIHSMNSTILEDWNFGLQPPPGGTLEDTRYFVTSQAIACQKHTPPAPKEDPL KKYTFWEVNLKEKFSADLDQYPLGRKFLLQAGL
SEQ ID No: 7	Amino acid sequence of aa 1-470 of	MALWRPSDNTVYLPSPSVARVVNTDDYVTRTSIFYHAGSSRLLTVGNPYFRVPAGGGNKQDI PKVSAYQYRVFRVQLPDNKFGLPDTSIYNPETQRLVWACAGVEIGRGQPLGVGLSGHPFYNK LDDTESSHAATSNVSEVDNRNVSDYKQTQLCILGCAPAIGEHWAKGTACKSRPLSQGDCPPL

	HPV type 18 L1 protein	ELKNTVLEDGDMVDTGYGAMDFSTLQDTKCEVPLDICQSICKYPDYLMQMSADPYGDSMFFCL RREQLFARHFWRNAGTMDGTVPQSLYIKGTGMRASPGSCVSPSPSGSIVTSDSQLFNKPYW LHKAGHNNNGVCWHNQLFVTVVDTTRSTNLTICASTQSPVPGQYDATKFKQYSRHHVEEDL QFIFQLCTITLTADVMSYIHSNMSSILEDWNFGVPPPTTSLVDTYRFVQSVAITCQKDAAPAE NKDPYDKLFKFWNVLDLKEKFSLDLQYPLGRKFL
SEQ ID No: 8	Amino acid sequence of aa 1-475 of HPV type 31 L1 protein	MSLWRPSEATVYLPVPVSKVVSTDEYVTRTNIYYHAGSARLLTVGHPYYSIPKSDNPKKIVVPK VSGLQYRVFRVRLPDNPKFGFDPDTSFYNPETQRLVWACVGLVGRGQPLGVGISGHPLLKNF DDTENSRYAGGPGTDNRECISMDYKQTQLCLLGCKPPIGEHWGKSGPCSNNAITPGDCPPL ELKNSVIQDGDMDVDTGFGAMDFALTQDTKSNVPLDICNSICKYPDYLMVAEYPGDTLFFYL RREQMFVRHFFNRSGTVGESVPTDLYIKSGSTATLANSTYFPTPSGSMVTSDAQIFNKPYWM QRAQGHNNNGICWGNQLFVTVVDTTRSTNMSVCAAIANSDDTFKSSNFKEYLRHGEEFDLQFI FQLCKITLSADIMTYIHSNMNPAILEDWNFGLTTPPSGSLEDTYRFVTSQAITCQKSAPQPKEDP FKDYVFWEVNLEKFSADLDQFPLGRKFLQAGY
SEQ ID No: 9	Amino acid sequence of aa 1-472 of HPV type 35 L1 protein	MSLWRSNEATVYLPVPVSKVVSTDEYVTRTNIYYHAGSSRLAVGHPYIAIKQDSNKIAVPK VSGLQYRVFRVKLPDNPKNFGFDPDTSFYDPASQRLVWACTGVEVGRGQPLGVGISGHPLLK LDDTENSRYVGNSTNRECISMDYKQTQLCLIGCRPPIGEHWGKGTPCNANQVKAGECPP LELLNTVLQDGDMDVDTGFGAMDFTTLQANKSDVPLDICSSICKYPDYLMVSEYPGDMLEFFYL RREQMFVRHFLNRAGTVGETVPADLYIKGTGTLPSTSYFPTPSGSMVTSDAQIFNKPYWLQR AQGHNNNGICWSNQLFVTVVDTTRSTNMSVCSAVSSSDSTYKDNFKEYLRHGEEYDLQFIFQ LCKITLTADVMTYIHSNMNPSILEDWNFGLTTPPSGTLEDTYRYVTSQAVTCQKPSAPKPKDDPL KNYTFWEVDLKEKFSADLDQFPLGRKFLQAGL
SEQ ID No: 10	Amino acid sequence of aa 1-469 of HPV type 39 L1 protein	MAMWRSSDSMVYLPVPVSAKVNTDDYVTRTGIYYAGSSRLTVGHPYFKVGMNGGRKQ DIPKVSAYQYRVFRVRLPDNPKFSIPDASLYNPETQRLVWACVGEVGRGQPLGVGISGHPLY NRQDDTENSFPSTTNKDSRDNSVDYKQTQLCIIGCVPAIGEHWGKKGACKPNNVSTGDCP PLELVNTPIEDGDMIDTGYGAMDFALQETKSEVPLDICQSICKYPDYLMQMSADVYGDMSFFC LRREQLFARHFWRNRRGMVGDAIPAQLYIKGTDIRANPGSSVYCPSPSGSMVTSDSQLFNKPY WLNKAGHNNNGICWHNQLFVTVVDTTRSTNFTLSTSISSIPSTYDPSKFKEYTRHVEEYDLQFI FQLCTVLTDDVMSYIHTMNSSILDNWNFAVAPPSASLVDTYRYLQSAITCQKDAPEKK DPYDGLKFWNVLDLREKFSLELDQFPLGRKFL
SEQ ID No: 11	Amino acid sequence of aa 1-478 of HPV type 45 L1 protein	MALWRPSDSTVYLPVPVSRVNTDDYVSRSTIFYHAGSSRLTVGNPYFRVVPAGAGNKQA VPKVSAYQYRVFRVALPDNPKFGLPDSTIYNPETQRLVWACVGEIGRGQPLGIGLSGHFPYN KLDDTESAHAATAVITQDVRDNVSDYKQTQLCILGCVPAIGEHWAKGTLCQPAQLQPGDCP PLELNTIIEDGDMVDTGYGAMDFSTLQDTKCEVPLDICQSICKYPDYLMQMSADPYGDSMFFC LRREQLFARHFWRNAGVMGDTVPTDLYIKGTSANMRETPGSCVSPSPSGSITSDSQLFNKP YWLHKAQGHNNNGICWHNQLFVTVVDTTRSTNLTCASTQNPVNTYDPTKFKHYSRHHVEEY DLQFIFQLCTITLTAEVMSYIHSNMSSILENWNFGVPPPTTSLVDTYRFVQSVAVTCQKDDTP PEKQDPYDKLFKFWTVDLKEKFSDDLQYPLGRKFLVQAGL
SEQ ID No: 12	Amino acid sequence of aa 1-474 of HPV type 51 L1 protein	MALWRTNDSKVYLPVPVSRVNTTEYITRTGIYYAGSSRLITLGHYPFIPIKTSTRAAIPKVSF QYRVFRVQLPDNPKFGLPDNLYNPDTDRLVWGCVGVEVGRGQPLGVGLSGHPLFNKYDDT ENSRIANGNAQQDVRDNTSDNKTQLCIIGCAPPIGEHWGIGTTCKNTPVPPGDCPPELV SVIQDGDMDTGFAMDFALQATKSDVPLDISQSVCKYPDYLMKMSADTYGNSMFFHLRRE QIFARHYNKLVGVEDIPNDYIYKSGNGRDPYESYIYATPSGSMITSDSQLFNKPYWLHRAQ GHNNNGICWNNQLFITCVDTTRSTNLTISTATAAVSPTFTPSNFKQYIRHGEEYELQFIFQLCKITL TTEVMAYLHTMDPTILEQWNFGLTLPASLEDAYRFVRNAATSCQKDTPPQAKPDLAKYKF WDVDLKERFSLDLQFALGRKFLVQGV
SEQ ID No: 13	Amino acid sequence of aa 1-478 of HPV type 52 L1 protein	MSVWRPSEATVYLPVPVSKVVSTDEYVSRSTIYYAGSSRLTVGHPYFSIKNTSSGNGKKVLV PKVSGLQYRVFRIKLPDNPKNFGFDPDTSFYNPETQRLVWACTGLEIGRGQPLGVGISGHPLLKNF DDTETS NKYAGKPGIDNRECLSMYKQTQLCILGCKPPIGEHWGKGTPCNNNSGNPGDCPPL QLINSVIQDGDMDVDTGFGCMDFTLQASKSDVPIDICSSVCKYPDYLMASEPYGDSLFFFLR RREQMFVRHFFNRAGTLGDPVPGDLYIQGSNSGNTATVQSSAFFPTPSGSMVTSESQLFNKPY WLQRAQGHNNNGICWGNQLFVTVVDTTRSTNMTLCAEVKKESTYKNENFKEYLRHGEEFDLQ FIFQLCKITLTADVMTYIHKMDATILEDWQFGLTPPSASLEDTYRFVTSTAITCQKNTPPKGKE DPLKDYMFWEVDLKEKFSADLDQFPLGRKFLQAGL
SEQ	Amino acid	MATWRPSENKVYLPPTPVSKVATDSYVKRTSIFYHAGSSRLAVGHPYYSVTKDNTKTNIPKV

ID No: 14	sequence of aa 1-467 of HPV type 56 L1 protein	SAYQYRVFRVRLPDPNKFGLPDTNIYNPDQERLVWACVGLVGRGQPLGAGLSGHPFLFNRLD DTESSNLANNNNVIEDSRDNISVDGKQTQLCIVGCTPAMGEHWTKGAVCKSTQVTTGDCPPLA LINTPIEDGDMIDTGFAMDFKVLQESKAEVPLDIVQSTCKYPDYLMKSADAYGDSMWFLYR REQLFARHYFNRAKGVGETIPAELYLKGSNGREPPSSVYVATPSGSMITSEQLFNKPYWLQR AQGHNNNGICWGNQLFVTVVDTRSTNMTISTATEQLSKYDARKINQYLRHVEEYELQFVFQL CKITLSAEVMAYLHNMNANLLEDWNIGLSPPVATSLEDKYRYVRSTAITCQREQPPTEKQDPL AKYKFWVDVNLQDSFSTDLDQFPLGRKFL
SEQ ID No: 15	Amino acid sequence of aa 1-473 of HPV type 58 L1 protein	MSVWRPSEATVYLPVPVSKVSTDEYVSRSTSIYYAGSSRLAVGNPYFSIKSPNNNNKKVLVPK VSGLQYRVFRVRLPDPNKFGLPDTSFYNPDTQRLVWACVGLVGRGQPLGVGVSGHPYLNKF DDTETSNRYPAQPGSDNRECLSMYKQTQLCLIGCKPPTGEHWGKGVCACNNNAATDCPPL ELFNSIIEDGDMVDGTGFGCMDFGLQANKSDVPIDICNSTCKYPDYLMKASEPYGDSLFFFLRR EQMFVRHFFNRAGKLGEAVPDDLYIKGSGNTAVIQSSAFFPTPSGSIVTSESQLFNKPYPWLQR AQGHNNNGICWGNQLFVTVVDTRSTNMTLCTEVTKEGTYKNDNFKEYVRHVEEYDLQFVFQ LCKITLTAEMTYIHTMDSNILEDWQFGLTPPPSASLQDITYRFVTSQAITCQKTAPPEKEDPLN KYTFWEVNLKEKFSADLDQFPLGRKFLQSGSL
SEQ ID No: 16	Amino acid sequence of chimeric HPV type 6 L1 protein	MWRPSDSTVYVPPPNPVSKVATDAYVTRTNIFYHASSRLLAVGHPYFSIKRANKTVVPKVS GYQYRVFKVVLDPDNKFALPDSSLDFTTQRLVWACTGLEVGRGQPLGVGVSGHPFLNKYDD VENSNGSGGNPGQDNRNVNMGMDYKQTQLCMVGCAPPLGEHWGKGKQCTNTPVQAGDCPP LELITSVIQDGDMDVTGFGAMNFADLQTNKSDVPIDICGTTCKYPDYLMQAADPYGDRLFFFL RKEQMFAHFFNRAGEVGEVPTDTHIKGSGNRTSVGSSIVNTPSGSLVSSEAQLFNKPYPWL QKAQGHNNNGICWGNQLFVTVVDTRSTNMTLCASVTTSSYTNDSYKEYMRHVEEYDLQFIF QLCITLSAEVMAYIHTMNPVLEDWNFGLSPPNGTLEDITYRYVQSAITCQKPTPEKEKPD PYKNLSFWEVNLKEKFSSELDQYPLGRKFLQSGYKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 17	Amino acid sequence of chimeric HPV type 11 L1 protein	MWRPSDSTVYVPPPNPVSKVATDAYVTRTNIFYHASSRLLAVGHPYFSIKKVNKTVPKVS GYQYRVFKVVLDPDNKFALPDSSLDFTTQRLVWACTGLEVGRGQPLGVGVSGHPFLNKYDD VENSNGGYGNPGQDNRNVNMGMDYKQTQLCMVGCAPPLGEHWGKGKQCTNTPVQAGDCPP PLELITSVIQDGDMDVTGFGAMNFADLQTNKSDVPLDICGTVCCKYPDYLMQAADPYGDRLF FYLRKEQMFAHFFNRAGTVGEVPTDTHIKGSGNRTSVGSSIVNTPSGSLVSSEAQLFNKP YWLQKAQGHNNNGICWGNQLFVTVVDTRSTNMTLCASVKSATYTNDSYKEYMRHVEEYDL QFIFQLCSITLSAEVMAYIHTMNPVLEDWNFGLSPPNGTLEDITYRYVQSAITCQKPTPEKE KQDPYKDMSFWEVNLKEKFSSELDQYPLGRKFLQSGYKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 18	Amino acid sequence of chimeric HPV type 16 L1 protein	MSLWLPSEATVYLPVPVSKVSTDEYVARTNIYYHAGTSRLLAVGHPYFPIKKPNNNNKILVPK VSGLQYRVFRIHLPDPNKFGLPDTSFYNPDTQRLVWACVGEVGRGQPLGVGVSGHPFLNKL DDTENASAYAANAGVDNRECISMDYKQTQLCLIGCKPPIGEHWGKGSPCTNVAVNPGDCCP LELINTVIQDGDMDVTGFGAMDFTLQANKSEVPLDICTSICKYPDYLMVSEPYGDSLFFFLRR EQMFVRHLFNRAAGVGENVPDDLYIKGSGSTANLASSNYFPTPSGSMVTSDAQIFNKPYPWLQ RAQGHNNNGICWGNQLFVTVVDTRSTNMSLCAAISTETTYKNTNFKEYLRHGEEDLQFIFQ LCKITLTADVMTYIHSNMNSTILEDWNFGLQPPPGTLEDITYRFVTSQAIAQCQKHTPPAPKEDP LKKYTFWEVNLKEKFSADLDQFPLGRKFLQAGLAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 19	Amino acid sequence of chimeric HPV type 18 L1 protein	MALWRPSDNTVYLPSPVARVNTDDYVTRTSIFYHAGSSRLLTVGNPYFRVPAGGGNKQDI PKVSAYQYRVFRVQLPDPNKFGLPDTSIYNPETQRLVWACAGVEIGRGQPLGVGLSGHPFYNK LDDTESSHAATSNVSEEDVRDNVSVDYKQTQLCILGCAPAIGEHWAKGTACKSRPLSQGDCCPL ELKNTVLEDGDMVDGTGFGAMDFTLQDKCEVPLDICSICKYPDYLMQMSADPYGDSMFFCL RREQLFARHFWRNAGTMGDTVPQSLYIKGTGMRASPGSCVYSPSPSGSIVTSDSQLFNKPYPW LHKAQGHNNNGVCWHNQLFVTVVDTRSTNLTICASTQSPVPGQYDATKFKQYSRHVEEYDL QFIFQLCTITLTADVMSYIHSNMNSTILEDWNFGLVPPPTSLVDITYRFVQSAITCQKDAAPAE NKDPYDKLKFVWVDLKEKFSLDLDQYPLGRKFLKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 20	Amino acid sequence of chimeric HPV type 31 L1 protein	MSLWRPSEATVYLPVPVSKVSTDEYVTRTNIIYHAGSARLLTVGHPYFSIKSDNPKKIVVPK VSGLQYRVFRVRLPDPNKFGLPDTSFYNPETQRLVWACVGLVGRGQPLGVGVSGHPFLNKF DDTENSNRYAGGPGTDNRECISMDYKQTQLCLIGCKPPIGEHWGKGSPCSNNAITPGDCPPL ELKNSVIQDGDMDVTGFGAMDFALQDTKSNVPLDICNSICKYPDYLMVAEYPGDTLFFFLR REQMFVRHFFNRSGTVGESVPTDLYIKGSGSTATLANSTYFPTPSGSMVTSDAQIFNKPYPWM QRAQGHNNNGICWGNQLFVTVVDTRSTNMSVCAAIANSDDTFKSNFKEYLRHGEEDLQFI FQLCKITLSADIMTYIHSNMNPAILEDWNFGLTTPPSGSLDITYRFVTSQAITCQKSAPQKPKEDP

		FKDYVFWENVLKEKFSADLDQFPLGRKFLLQAGYKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 21	Amino acid sequence of chimeric HPV type 35 L1 protein	MSLWRSNEATVYLPVSVSKVSTDEYVTRTNIYYHAGSSRLLAVGHPYIAIKKQDSNKIAVPK VSGLQYRVFRVRLPDPNKFGLPDTSFYDPASQRLVWACTGVEVGRGQPLGVGISGHPLLNKL DDTENS NKYVGN SGT DNRECISMDYKQTQLCLIGCRPPIGEHWGKGTPCNANQVKAGECPP LELLNTVLQDGDMDVTGFGAMDFTTLQANKSDVPLDICSSICKYPDY LKMVSEPYGDM LFFYL RREQMFVRHFLN RAGTVGETVPADLYIKGTTGTL PSTSYFPTPSGSMVTSDAQIFNKPYWLQR AQGHNNGICWSNQLFVTVD TTRSTNMSVCSAVSSSDSTYKDNDFKEYLRHGEEDLQFIFQ LCKITLTADVMTYIHS MNPSILEDWNFGLTPPPSGTLED TYRYVTSQAVTCQKPSAPKPKDDPL KNYTFWEVDLKEKFSADLDQFPLGRKFLLQAGLKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 22	Amino acid sequence of chimeric HPV type 39 L1 protein	MAMWRSSDSMVYLPVPSVAKVNTDDYVTRTGIYYAGSSRLLTVGHPYFKVGMNGGRKQ DIPKVSAYQYRVFRVRLPDPNKFGLPDTNPNPETQRLVWACVGEVGRGQPLGVGISGHPLY NRQDDTENS PFSSTTNKDSRDNVSDYKQTQLCIIGCVPAIGEHWGKGKACKPNNVSTGDPC PLELVNTPIEDGDMIDTGYGAMDFGALQETKSEVPLDICQSICKYPDY LQMSADVYGD SMFFC LRREQLFARHFWNRGGMVGDAIPAQLYIKGTDIRANPGSSVYCPSPSGSMVTSDS QLFNKP YWLHKAQGHNNGICW HNLFTVVD TTRSTNFTLSTSISSIPSTYDPSKFKEYTRHVEEYDLQFI FQLCTVLT TTDVMSYIHTMNSSILDNWNFAVAPPSASLVDTYRYLQSAAITCQKDAPAPEKK DPYDGLKFWNVDLREKFSLELDQFPLGRKFLLQAGLARPPTIGPRKRAAPAPTSTPSKRVKRR KSSRK
SEQ ID No: 23	Amino acid sequence of chimeric HPV type 45 L1 protein	MALWRPSDSTVYLPVPSVARVNTDDYVSRTSIFYHAGSSRLLTVGNPYFRVVP SGAGNKQA VPKVSAYQYRVFRVALPDPNKFGLPDTIYNPETQRLVWACVGM EIGRGQPLGIGLSGHPFY N KLDDTESAHAATAVITQDVRDNVSDYKQTQLCILGCVPAIGEHWAGT LCKPAQLQPGDCP PLELKN TIIEDGDMIDTGYGAMDFSTLQDTKCEVPLDICQSICKYPDY LQMSADPYGDS MFFC LRREQLFARHFWNRAGVMGDTVPTDLYIKGTSANMRETPGSCVSPSPSGSITSDS QLFNKP YWLHKAQGHNNGICW HNLFTVVD TTRSTNLTLCASTQNPVPNTYDPTKFHYSRHVEEY DLQFIFQLCTITLTAEVMSYIHS MNSSILENWNFGVPPPTTSLVD TYRFVQSVAVTCQKDTTP PEKQDPYDKLKFWTVDLKEKFSDDLQYPLGRKFLVQAGLKAKPKLKRAAPTSTRTSSAKRKKV KK
SEQ ID No: 24	Amino acid sequence of chimeric HPV type 51 L1 protein	MALWRTNDSKVYLPAPVSRIVNTEEYITRTGIYYAGSSRLLTGHYPFIPIKTSTRAAIPKVS AF QYRVFRVQLPDPNKFGLPDPNLNPD TRLVWGCVGVEVGRGQPLGVGLSGHPLFNKYDDT ENSRIANGNAQQDVRDNTSVDNKQTQLCIIGCAPPIGEHWGIGTTCKNTPVPPGDCPPELV S SVIQDGD MIDTGF GAMDFAALQATKSDVPLDISQSVCKYPDY LKMSADTYGNSMFFHLRRE QIFARHYYNKLVGVGEDIPNDYIYKSGNGRDPYESYIYSATPSGSMITSDS QIFNKPYWLHRAQ GHNNGICWNNQLFITCVDTTRSTNLTISTATAAVSPTFTPSNFKQYIRHGEYELOQFIFQLCKITL TTEVMAYLHTMDPTILEQWNFGLTLPPSASLEDAYRFVRNAATSCQKDTPPQAKPDPLAKYKF WDVDLKERFSLDLQFALGRKFLLQVGVKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 25	Amino acid sequence of chimeric HPV type 52 L1 protein	MSVWRPSEATVYLPVSVSKVSTDEYVSRTSIYYAGSSRLLTVGHPYFSIKNTSSGNGKKVLV PKVSGLQYRVFRVRLPDPNKFGLPDTSFYNPETQRLVWACTGLEIGRGQPLGVGISGHPLLNKF DDTETS NKYAGKPGIDNRECLSM DYKQTQLCILGCKPPIGEHWGKGTPC NNNSGNPGDCPPL QLINSVIQDGDMDVTGFGCMD FNTLQASKSDVPIDICSSVCKYPDY LQMASEPYGDSLFFFLR REQMFVRHFFNRAGTLGDPVPGDLYIQGSNSGNTATVQSSAFFPTPSGSMVTSES QLFNKP YWLQRAQGHNNGICWGNQLFVTVD TTRSTNMTLCAEVKKESTYKNENFKEYLRHGEEDLQ FIFQLCKITLTADVMTYIHKMDATILEDWQFGLTPPPSASLED TYRFVTSTAITCQKNTPPKGKE DPLKDYMFWEVDLKEKFSADLDQFPLGRKFLLQAGLKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 26	Amino acid sequence of chimeric HPV type 56 L1 protein	MATWRPSENKVYLPPTPVSKVATDSYVKRTSIFYHAGSSRLLAVGHPYYSVTKDNTKTNIPKV SAYQYRVFRVRLPDPNKFGLPDTNIYNPDQERLVWACVGLLEVGRGQPLGAGLSGHPLFNRLD DTESSNLANN NVIEDSRDNISVDGKQTQLCIVGCTPAMGEHWTKGAVCKSTQVTTGD CPPLA LINTPIEDGDMIDTGF GAMD FVLQESKAEVPLDIVQSTCKYPDY LKMSADAYGDSMW FYLR REQLFARHYFN RAGKVGETIPAELYKGSNGREPPSSVYVATPSGSMITSEAQLFNKP YWLQR AQGHNNGICWGNQLFVTVD TTRSTNMTISTATEQLSKYDARKINQYLRHVEEYELQFV FQL CKITLSAEVMAYLHNMNANLLEDWNIGLSPPVATSLEDKYRYVRSTAITCQREQPPTEKQDPL AKYKFWDVNLQDSFSTDLQFPLGRKFLLQAGLKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No:	Amino acid sequence of chimeric	MSVWRPSEATVYLPVSVSKVSTDEYVSRTSIYYAGSSRLLAVGNPYFSIKSPNNNNKKVLV PK VSGLQYRVFRVRLPDPNKFGLPDTSFYNPD TRLVWACVGL EIGRGQPLGVGVSGHPYLNKF DDTETS NRYP AQPGSDNRECLSM DYKQTQLCLIGCKPPTGEHWGKG VACNNNAATDCPPL

27	HPV type 58 L1 protein	ELFNSIIEDGDMVDTGFGCMDFGTLQANKSDVPIDICNSTCKYPDYLMASEPYGDSLFFFLRR EQMFVRHFFNRAGKLGEAVPDDLYIKSGSNTAVIQSSAFFPTPSGSIVTSESQLFNKPYWLQR AQGHNNGICWGNQLFVTVVDTRSTNMTLCTEVTKEGTYKNDNFKEYVRHVEEYDLQFVFQ LCKITLTAEMTYIHTMDSNILEDWQFGLTPPPSASLQDITYRFVTSQAITCQKTAPPKEKEDPLN KYTFWEVNLKEKFSADLDQFPLGRKFLLQSGLKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 28	Amino acid sequence of HPV type 33 L1 protein	MSVWRPSEATVYLPVPVSKVVSTDEYVSRSTSIYYAGSSRLAVGHPYFSIKNPTNAKLLVPK VSLQYRVFRVRLPDPNKFGLPDTSFYNPDTQRLVWACVGLGIGRGQPLGVGSGHPLLNKFD DTETGNKYPGQPGADNRECLSMYDKQTQLCLLGCKPPTGEHWGKGVACTNAAPANDCPPL ELINTIIEDGDMVDTGFGCMDFKTLQANKSDVPIDICGSTCKYPDYLMKMTSEPYGDSLFFFLRRE QMFVRHFFNRAGTLGEAVPDDLYIKSGTTSIQSSAFFPTPSGSMVTSESQLFNKPYWLQRA QGHNNGICWGNQVFTVVDTRSTNMTLCTQVTSSTYKNENFKEYIRHVEEYDLQFVFQLC KVTLTAEVMTYIHAMNPDILEDWQFGLTPPPSASLQDITYRFVTSQAITCQKTVPPEKEDPLG KYTFWEVDLKEKFSADLDQFPLGRKFLLQAGLKAKPKLKRAAPTSTRTSSAKRKKVKK
SEQ ID No: 29	Amino acid sequence of HPV type 59 L1 protein	MALWRSSDNKVYLPSPVAKVSTDEYVTRTSIFYHAGSSRLTVGHPYFKVPKGGNGRQDVP KVSAYQYRVFRVKLPDPNKFGLPNTVYDPNSQRLVWACVGLGIGRGQPLGVGSLGHPLYNK LDDTENSHVASAVDTKDTRDNVSDYKQTQLCIIGCVPAIGEHWTKGTACKPTTVVQGDCCP LELINTPIEDGDMVDTGYGAMDFKLLQDNKSEVPLDICQSICKYPDYLMQMSADAYGDSMFFCL RREQVFARHFWRNSGMTGDQLPESLYIKGTDIRANPGSYLYSPSPSGSVTSDSQLFNKPYWL HKAQGLNNGICWHLNQLFTVVDTRSTNLSVCASTTSSIPNVYTPSTFKEYARHVEEFDLQFIF QLCKITLTTEVMSYIHNMTTILEDWNFGVTPPPTASLVDITYRFVQSAAVTCQKDTAPPVKQD PYDKLKFVWVLDKERFSADLDQFPLGRKFLLQLGARPKPTIGPRKRAAPAPTSTPSPKRVKRRK SSRK
SEQ ID No: 30	Synthetic HPV6L1 gene	ctgggtaccATGTGGAGACCATCTGACAGCACAGTCTATGTGCCTCCTCCAAACCCTGTGAGC AAGGTGGTGGCTACAGATGCCTATGTGACCAGGACCAACATCTTCTACCATGCCTCCTCCA GCAGACTGCTGGCTGTGGGACACCCATACTTCAGCATCAAGAGGGCTAACAAGACAGTGG TGCCAAAGGTGTCTGGCTACCAATACAGGGTGTTCAGGTGGTGTCTGCCTGACCCAAACA AGTTTGCCCTGCCTGACTCCTCCTGTTTGACCCAACCCAGAGACTGGTGTGGGCTTG TACTGGATTGGAGGTGGGACAGGGGACAACCACTGGGAGTGGGAGTGTCTGGACACCCAT TCCTGAACAAATATGATGATGTGGAGAACTCTGGCTCTGGAGGCAACCCTGGACAAGACA ACAGGGTGAATGTGGGGATGGACTACAAGCAGACCCAACCTTGTATGGTGGGCTGTGCC CCTCCACTGGGAGAACACTGGGGCAAGGGCAAGCAGTGTACCAACACACCTGTCCAGGCT GGAGACTGTCCTCCATTGGAACCTGATTACCTCTGTGATTGAGATGGAGATATGGTGGAC ACAGGCTTTGGAGCTATGAACTTTGCTGACCTCCAAACCAACAAGTCTGATGTGCCAATTG ACATCTGTGGCACCATTGTAATACCTGACTACCTCCAAATGGCTGCTGACCCATATGG AGACAGACTGTTCTTCTTCTGAGGAAGGAACAGATGTTTGCCAGACACTTCTTCAACAGG GCTGGAGAGGTGGGAGAACCTGTGCCTGACACCCTGATTATCAAGGGCTCTGGCAACAG GACCTCTGTGGGCTCCAGCATCTATGTGAACACACCATCTGGCTCCTGGTGTCTCTGAG GCTCAACTTTTCAACAAGCCATACTGGCTCCAAAGGCTCAAGGACACAACAATGGCATCT GTTGGGGCAACCAACTTTTGTGACAGTGGTGGACACCACAGGAGCACCAATATGACCC TGTGTGCCTCTGTGACCACCTCCAGCACCTACACCAACTCTGACTACAAGGAATATATGAG GCATGTGGAGGAATATGACCTCCAATTCATCTTCCAACCTTGTAGCATCACCTGTCTGCTG AGGTGATGGCTTACATCCACACAATGAACCCATCTGTGTTGGAGGACTGGAACCTTGGAC TGAGCCCTCCTCCAAATGGCACCTTGGAGGACACCTACAGATATGTCCAGAGCCAGGCTAT CACTTGTGAGAAGCCAACACCTGAGAAGGAGAAGCTGACCCATAACAAGAACCTGTCTT CTGGGAGGTGAACCTGAAAGAGAAGTTCTCCTCTGAACCTGGACCAATACCCACTGGGAG GAAGTTCCTGCTCCAATCTGGCTACAGGGGAGGTCCAGCATCAGGACAGGAGTGAAGA GACCTGCTGTGAGCAAGGCATCTGCTGCCCCAAGAGGAAGAGGGCTAAGACCAAGAGG TAAActcgagctc
SEQ ID No: 31	Synthetic HPV11L1 gene Synthetic HPV 11 L1 gene	ctgggtaccATGTGGAGACCATCTGACAGCACAGTCTATGTGCCTCCTCCAAACCCTGTGAGC AAGGTGGTGGCTACAGATGCCTATGTGAAGAGGACCAACATCTTCTACCATGCCTCCTCCA GCAGACTGCTGGCTGTGGGACACCCATACTACAGCATCAAGAAGGTGAACAAGACAGTGT GTGCCAAAGGTGTCTGGCTACCAATACAGGGTGTTCAGGTGGTGTCTGCCTGACCCAAAC AAGTTTGCCCTGCCTGACTCCTCCTGTTTGACCCAACCCAGAGACTGGTGTGGGCTT GTACTGGATTGGAGGTGGGACAGGGGACAACCACTGGGAGTGGGAGTGTCTGGACACCCA

		CTGCTGAACAAATATGATGATGTGGAGAACTCTGGAGGCTATGGAGGCAACCTGGACAA GACAACAGGGTGAATGTGGGGATGGACTACAAGCAGACCCAACCTTTGTATGGTGGGCTG TGCCCTCCACTGGGAGAACACTGGGGCAAGGGCACCCAGTGTAGCAACACCTCTGTCCA GAATGGAGACTGTCCTCCATTGGAAGTATTACCTCTGTGATTGAGGATGGAGATATGGT GGACACAGGCTTTGGAGCTATGAACTTTGCTGACCTCCAAACCAACAAGTCTGATGTGCCA CTGGACATCTGTGGCAGTGTGTAAATACCCTGACTACCTCCAAATGGCTGCTGACCCAT ATGGAGACAGACTGTTCTTCTACCTGAGGAAGGAACAGATGTTTGCCAGACACTTCTTCAA CAGGGCTGGCAGTGGGAGAACCTGTGCCTGATGACCTGCTGGTGAAGGGAGGCAACA ACAGGTCCTCTGTGGCATCCAGCATCTATGTGCATACACCATCTGGCTCCCTGGTGTCTCT GAGGCTCAACTTTTCAACAAGCCATACTGGCTCCAAAAGGCTCAAGGACACAACAATGGC ATCTGTTGGGGCAACCACCTGTTTGTGACAGTGGTGGACACCACAGGAGACCAATATG ACCCTGTGTGCCTCTGTGAGCAAGTCTGCCACCTACACCAACTCTGACTACAAGGAATATA TGAGGCATGTGGAGGAGTTTGACCTCCAATTCATCTTCCAACCTTTGAGCATCACCTGTCT GCTGAGGTGATGGCTTACATCCACACAATGAACCCATCTGTGTTGGAGGACTGGAACCTT GGACTGAGCCCTCTCCAAATGGCACCTTGAGGACACCTACAGATATGTCCAGAGCCAG GCTATCACTTGTGAGAAGCCAACACCTGAGAAGGAGAAGCAGGACCCATACAAGGATATG AGTTTCTGGGAGGTGAACCTGAAAGAGAAGTTCTCTGAACTGGACAGTTTCCACTG GGCAGGAAGTTCTGCTCCAATCTGGCTACAGGGGCAGGACCTCTGCCAGGACAGGCATC AAGAGACCTGCTGTGAGCAAGCCAAGCACAGCCCCAAAGAGGAAGAGGACCAAGACCAA GAAGTAAActcgagctc
SEQ ID No: 32	Synthetic HPV16L1 gene	ctgggtaccATGAGTCTGTGGCTGCCATCTGAGGCTACAGTCTACCTGCCTCTGTGCCTGTG AGCAAGGTGGTGAGCACAGATGAATATGTGGCAAGGACCAACATCTACTACCATGCTGGC ACCAGCAGACTGCTGGCTGTGGGACACCCATACTTTCCAATCAAGAAGCCAAACAACAAC AAGATTCTGGTGCCAAAGGTGTCTGGACTCCAATACAGGGTGTTCAGGATTCACCTGCCT GACCCAAACAAGTTTGGCTTCTCTGACACCTCCTTCTACAACCTGACACCCAGAGACTGG TGTGGGCTTGTGTGGGAGTGGAGGTGGGCAGGGGACAACCACTGGGAGTGGGCATCTCT GGACACCCACTGCTGAACAAACTGGATGACACAGAGAATGCCTCTGCCTATGCTGCCAAT GCTGGAGTGGACAACAGGGAGTGTATCAGTATGGACTACAAGCAGACCCAACCTTTGTCTG ATTGGCTGTAAGCCTCCAATTGGAGAACACTGGGGCAAGGGCAGCCCATGTACCAATGTG GCTGTGAACCTGGAGACTGTCCTCCATTGGAAGTATAAACACAGTGATTGAGGATGGA GATATGGTGGACACAGGCTTTGGAGCTATGGACTTCACCACCTCCAAGCCAACAAGTCT GAGGTGCCACTGGACATCTGTACCAGCATCTGTAAATACCCTGACTACATCAAGATGGTGT CTGAACCATATGGAGACTCCCTGTTCTTCTACCTGAGGAGGGAACAGATGTTTGTGAGAC ACCTGTTCAACAGGGCTGGAGCAGTGGGAGAGAATGTGCCTGATGACCTCTACATCAAGG GCTCTGGCAGCACAGCCAACCTGGCATCCAGCAACTACTTTCCAACACCATCTGGCAGTAT GGTGACCTCTGATGCCAGATTTTCAACAAGCCATACTGGCTCCAAAGGGCTCAAGGACA CAACAATGGCATCTGTTGGGGCAACCAACTTTTTGTGACAGTGGTGGACACCACAGGAG CACCAATATGAGTCTGTGTGCTGCCATCAGCACCTCTGAGACCACCTACAAGAACACCAAC TTCAAGGAATACCTGAGACATGGAGAGGAATATGACCTCCAATTCATCTTCCAACCTTTGTA AGATTACCCTGACAGCAGATGTGATGACCTACATCCACAGTATGAACAGCACCATCTTGGA GGACTGGAACCTTTGGACTCCAACCTCCTCTGGAGGCACCTTGAGGACACCTACAGGTTT GTGACCAGCCAGGCTATTGCCTGTCAGAAACACACACCTCCTGCCCCAAAGGAGGACCCA CTGAAAAAATACACCTTCTGGGAGGTGAACCTGAAAGAGAAGTTCTCTGCTGACCTGGAC CAGTTTCCACTGGGCAGGAAGTTCTGCTCCAAGCAGGACTGAAAGCCAAGCCAAAGTTT ACCCTGGGCAAGAGGAAGGCTACACCAACCACCTCCAGCACCAGCACCACAGCCAAGAG GAAGAAGAGGAAACTGTAAActcgagctc
SEQ ID No: 33	Synthetic HPV18L1 gene	ctgggtaccATGGCCCTCTGGAGACCATCCGATAACACAGTGTACTTGCCCCACCCAGCGTC GCCCCGGTGGTGAACACAGACGACTACGTACCAAGAACCTCAATCTTCTACCACGCCGGG TCCAGCCGGCTGCTGACCGTGGGCAACCCCTACTTCCGCGTGCCCCGCCGGCGGCGAAAC AAACAAGACATCCCCAAAGTCAGCGCCTATCAGTACCGGGTGTTCGCGTCCAACCTGCCCG ATCCCAACAAGTTCGGCCTGCCGACACCTCCATCTACAACCCCGAGACCCAGAGGCTGGT CTGGGCTTGCGCCGGCTCGAGATCGGGAGGGGCCAACCCCTGGGCGTGGGGTTGTCCG GCCACCCCTTCTACAACAAGCTGGACGATACCGAGTCCAGCCACGCAGCAACCAGCAACG TCTCCGAAGATGTGCGCGATAACGTGAGCGTGGACTACAAACAAACCAACTGTGCATCCT

		GGGATGCGCACCCGCCATCGGCGAGCATTGGGCCAAGGGGACCGCTGCAAGAGCAGGC CCCTGAGCCAAGGGGACTGTCCACCCCTGGAGTTGAAGAATACCGTGCTCGAGGACGGC GACATGGTGGACACCGGCTACGGCGCTATGGATTTCTCCACCTCCAGGACACCAAGTGC GAAGTGCCCTCGACATCTGCCAAAGCATCTGCAAGTACCCGACTACCTCCAGATGAGCG CCGACCCCTACGGCGACAGCATGTTCTTCTGTCTCAGAAGGGAACAATTGTTGCCCCGCA CTTCTGGAACCGGGCCGGCACAATGGGAGATACAGTCCCCAGAGCCTGTACATCAAGGG GACCGGAATGAGGGCCAGCCCCGGGTCTGCGTCTACAGCCCAAGCCCTCCGGGAGCAT CGTCACAAGCGATAGCCAACTCTTCAACAAGCCCTACTGGCTCCACAAAGCCCAAGGCCAC AATAACGGGGTGTGTTGGCACAACCAGCTGTTCTGACCGTCTGGACACAACCAGGTCC ACAAACCTGACCATCTGCGCCAGCACCCAAAGCCCCGTGCCGGCCAGTACGACGCCACA AAGTTCAAACAATACTCTCGGCACGTGGAAGAGTACGACCTCCAATTCATCTTCAACTCT GCACCATCACCTCACCGCCGACGTGATGAGCTACATCCACTCCATGAACTCCTCCATCCTG GAAGACTGGAATTTGCGCGTGCCACCACCCCTACCACCTCCCTCGTCGACACCTACAGAT TCGTGCAGAGCGTGCCATCACATGCCAGAAAGACGCCGCCCGCCGAGAACAAGAC CCATACGACAACTGAAATTCTGGAACGTGACCTGAAAGAGAAATTGAGCCTGGATCTG GACCAGTACCCATTGGGCAGGAAGTTCTCTGTGCAAGCCGGCCTCAGGAGAAAAACCAACA ATCGGGCCCAGGAAGAGGAGCGCCCCAGCGCAACCACAGCAGCAAGCCCGCAAAAAG GGTCAGAGTGAGGGCACGCAATAAAActcgagctc
SEQ ID No: 34	Synthetic HPV31L1 gene	ctgggtaccATGAGCCTGTGGAGGCCAGCGAGGCCACCGTGACCTGCCCCCGTGCCCGT GAGCAAGGTGGTGAGCACCGACGAGTACGTGACCAGGACCAACATCTACTACCACGCCG GCAGCGCCAGGCTGCTGACCGTGGGCCACCCCTACTACAGCATCCCCAAGAGCGACAACC CCAAGAAGATCGTGGTGCCAAAGGTGAGCGGCCTGCAGTACAGGGTGTTGAGGGTGAGG CTGCCCCGACCCCAACAAGTTGCGCTTCCCCGACACCAGTTCTACAACCCCGAGACCAGA GGCTGGTGTTGGGCTGCGTGGGCTGGAGGTGGGCAGGGGCCAGCCCTGGGCGTGGG CATCAGCGGCCACCCCTGCTGAACAAGTTCGACGACACCGAGAACAGCAACAGGTACGC CGGCGGCCCGGCACCGACAACAGGGAGTGATCAGCATGGACTACAAGCAGACCAGC TGTGCTGCTGGGCTGCAAGCCCCCATCGGCGAGCACTGGGGCAAGGGCAGCCCTGC AGCAACAACGCCATACCCCCGGCGACTGCCCCCCTGGAGCTGAAGAACAGCGTGATC CAGGACGGCGACATGGTGACACCGGCTTCGGCGCCATGGACTTCACCGCCTGCAGGA CACCAAGAGCAACGTGCCCTGGACATCTGCAACAGCATCTGCAAGTACCCGACTACCTG AAGATGGTGGCCGAGCCCTACGGCGACACCCTGTTCTTCTACCTGAGGAGGGAGCAGATG TTCGTGAGGCATTTCTTCAACAGGAGCGGCACCGTGGGCGAGAGCGTGCCACCGACCTG TACATCAAGGGCAGCGGCAGCACCGCCACCCTGGCCAACAGCACCTACTTCCCCACCCCA GCGGCAGCATGGTGACCAGCGACGCCAGATCTTCAACAAGCCCTACTGGATGCAGAGG GCCAGGGCCACAACAACGGCATCTGCTGGGGCAACCAGCTGTTCTGTGACCGTGGTGGA CACCACCAGGAGCACCAACATGAGCGTGTGCGCCGCCATCGCCAACAGCGACACCACCT CAAGAGCAGCAACTTCAAGGAGTACCTGAGGCACGGCGAGGAGTTCGACCTGCAGTTCAT CTTCAGCTGTGCAAGATCACCTGAGCGCCGACATCATGACCTACATCCACAGCATGAAC CCCGCCATCTGGAGGACTGGAACCTTCGGCCTGACCACCCCCCAGCGGCAGCCTGGAG GACACCTACAGGTTCTGTGACCAGCCAGGCCATCACCTGCCAGAAAGTCCGCCCCCAGAAG CCCAAGGAGGACCCCTTCAAGGACTACGTGTTCTGGGAGGTGAACCTGAAGGAGAAGTTC AGCGCCGACCTGGACCAAGTTCCCCCTGGGCAAGGAGTTCCTGTGCAAGGCCGGCTACAGG GCCAGGCCCAAGTTCAAGGCCGCAAGAGGAGCGCCCCAGCGCCAGCACCACCACCCC CGCCAAGAGGAAGAAGACCAAGAAGTAAActcgagctc
SEQ ID No: 35	Synthetic HPV35L1 gene	ctgggtaccATGAGTCTGTGGAGGAGCAATGAGGCTACAGTCTACCTGCCTCCTGTGTCTGTG AGCAAGGTGGTGAGCACAGATGAATATGTGACCAGGACCAACATCTACTACCATGCTGGC TCCAGCAGACTGCTGGCTGTGGGACACCATACTATGCCATCAAGAAGCAGGACAGCAAC AAGATTGCTGTGCCAAAGGTGTCTGGACTCCAATACAGGGTGTTGAGGGTGAACTGCCT GACCCAAACAAGTTTGGCTTTCCTGACACCTCCTTCTATGACCCTGCCAGCCAGAGACTGG TGTGGGCTTGTACTGGAGTGGAGGTGGGCAGGGGACAACCACTGGGAGTGGGCATCTCT GGACACCCACTGCTGAACAACTGGATGACACAGAGAACAGCAACAAATATGTGGGCAA CTCTGGCACAGACAACAGGGAGTGTATCAGTATGGACTACAAGCAGACCCAACCTTGTCT GATTGGCTGTAGACCTCCAATTGGAGAACACTGGGGCAAGGGCACACCATGTAATGCCAA CCAGGTGAAGGCTGGAGAGTGTCTCCATTGGAAGTCTGAACACAGTGTCTCAAGATGG

		AGATATGGTGGACACAGGCTTTGGAGCTATGGACTTCACCACCCTCCAAGCCAACAAGTCT GATGTGCCACTGGACATCTGTTCCAGCATCTGTAAATACCCTGACTACCTGAAAATGGTGT CTGAACCATATGGAGATATGCTGTTCTTCTACCTGAGGAGGGAACAGATGTTTGTGAGAC ACCTGTTCAACAGGGCTGGCACAGTGGGAGAGACAGTGCCTGCTGACCTCTACATCAAGG GCACCACAGGCACCCTGCCAAGCACCTCCTACTTTCCAACACCATCTGGCAGTATGGTGAC CTCTGATGCCAGATTTTCAACAAGCCATACTGGCTCCAAGGGCTCAAGGACACAACAAT GGCATCTGTTGGAGCAACCACTTTTGTGACAGTGGTGGACACCACCAGGAGACCAAT ATGAGTGTGTGTTCTGCTGTGCTCCTCTGACAGCACCTACAAGAATGACAACCTCAAGG AATACCTGAGACATGGAGAGGAATATGACCTCCAATTCATCTTCCAACCTTTGTAAGATTAC CCTGACAGCAGATGTGATGACCTACATCCACAGTATGAACCAAGCATCTTGAGGAGCTG GAACTTTGGAAGTACACCTCCTCCATCTGGCACCTTGAGGACACCTACAGATATGTGACC AGCCAGGCTGTGACTTGTGAGAAGCCATCTGCCCCAAAGCCAAAGGATGACCCACTGAAA AACTACACCTTCTGGGAGGTGGACCTGAAAGAGAAGTTCTCTGCTGACCTGGACCACTTT CCTGAGGAGGCTGCCCCCTGCCAGCACCAAGATCCAGCACCAAGAGGAGGAAGGT GAAGAGCTAAActcgagctc
SEQ ID No: 36	Synthetic HPV39L1 gene	ctgggtaccATGGCTATGTGGAGGTCTCTGACAGTATGGTCTACCTGCCTCCTCCATCTGTG GCTAAGGTGGTGAACACAGATGACTATGTGACCAGGACAGGCATCTACTACTATGCTGGC TCCAGCAGACTGCTGACAGTGGGACACCCATACTTCAAGGTGGGGATGAATGGAGGCAG GAAGCAGGACATCCCAAAGGTGTCTGCCTACCAATACAGGGTGTTCAGGGTGACCTGCC TGACCCAAACAAGTTCAGCATCCCTGATGCCTCCTCTACAACCCTGAGACCCAGAGACTG GTGTGGGCTTGTGTGGGAGTGGAGGTGGGACAGGGGACAACCACTGGGAGTGGGCATCT CTGGACACCCACTCTACAACAGACAGGATGACACAGAGAACAGCCATTCTCCAGCACCA CCAACAAGGACAGCAGGGACAATGTGTCTGTGGACTACAAGCAGACCCAACTTTGTATCA TTGGCTGTGTGCCTGCCATTGGAGAACACTGGGGCAAGGGCAAGGCTTGTAAAGCCAAAC AATGTGAGCACAGGAGACTGTCTCCATTGGAAGTGGTGAACACCAATTGAGGATGGA GATATGATTGACACAGGCTATGGAGCTATGGACTTTGGAGCCCTCCAAGAGACCAAGTCT GAGGTGCCACTGGACATCTGTGAGAGCATCTGTAAATACCCTGACTACCTCCAAATGAGTG CTGATGTCTATGGAGACAGTATGTTCTTCTGTCTGAGGAGGGAACAACCTTTTGGCAGACA CTTCTGGAACAGGGGAGGGATGGTGGGAGATGCCATCCCTGCCCAACTCTACATCAAGG GCACAGACATCAGGGCTAACCTGGCTCCTCTGTCTACTGTCCAAGCCATCTGGCAGTAT GGTGACCTCTGACAGCCAACCTTTTCAACAAGCCATACTGGCTGCACAAGGCTCAAGGACA CAACAATGGCATCTGTTGGCACAACCACTTTTCTGACAGTGGTGGACACCACCAGGAG CACCAACTTACCCTGAGCACCAGCATTGAGTCCAGCATCCAAGCACCTATGACCCAAAGC AAGTTCAAGGAATACACCAGGCATGTGGAGGAATATGACCTCCAATTCATCTTCCAACCTT GTACTGTGACCCTGACCACAGATGTGATGAGTTACATCCACACAATGAACTCCAGCATCCT GGACAACCTGGAACCTTGTGTGGCTCCTCCTCATCTGCCTCCTGGTGGACACCTACAGA TACCTCCAATCTGCTGCCATCACTTGTGAGAAGGATGCCCTGCCCTGAGAAGAAGGACC CATATGATGGACTGAAGTTCTGGAATGTGGACCTGAGGGAGAAGTTCTCCTTGGAACTGG ACCAGTTTCCACTGGGACAGGAAGTTCTGCTCCAAGCCAGGGTGAGGAGGAGACCAACCA TTGGACCAAGGAAGAGACCTGCTGCCAGCACCTCCTCCTCTGCCACCAAAACACAAGAG GAAGAGGGTGAGCAAGTAAActcgagctc
SEQ ID No: 37	Synthetic HPV45L1 gene	ctgggtaccATGGCTCTGTGGAGACCATCTGACAGCACAGTCTACCTGCCTCCTCCATCTGTG GCAAGGGTGGTGAACACAGATGACTATGTGAGCAGGACCAGCATCTTCTACCATGCTGGC TCCAGCAGACTGCTGACAGTGGGCAACCCATACTTCAAGGTGGTGCCAAGTGGAGCAGG CAACAAGCAGGCTGTGCCAAAGGTGTCTGCCTACCAATACAGGGTGTTCAGGGTGGCTCT GCCTGACCCAAACAAGTTTGGACTGCCTGACAGCACCATCTACAACCTGAGACCCAGAG ACTGGTGTGGGCTTGTGTGGGGATGGAGATTGGCAGGGGACAACCACTGGGCATTGGAC TGTCTGGACACCCATTCTACAACAACTGGATGACACAGAGTCTGCCATGCTGCCACAGC AGTGATTACCCAGGATGTGAGGGACAATGTGTCTGTGGACTACAAGCAGACCCAACTTTG TATCCTGGGCTGTGTGCCTGCCATTGGAGAACACTGGGCTAAGGGCACCTGTGTAAGCC TGCCCAACTCCAACCTGGAGACTGTCCTCATTGGAAGTGAAGAACACCATCATTGAGGAT GGAGATATGGTGGACACAGGCTATGGAGCTATGGACTTCAGCACCTCCAAGACACCAAG TGTGAGGTGCCACTGGACATCTGTGAGAGCATCTGTAAATACCCTGACTACCTCCAAATGA

		GTGCTGACCCATATGGAGACAGTATGTTCTTGTCTGAGGAGGGAACAACCTTTTGGCAG ACACTTCTGGAACAGGGCTGGAGTGATGGGAGACACAGTGCCAACAGACCTCTACATCAA GGGCACCTCTGCCAATATGAGGGAGACACCTGGCTCCTGTGTCTACAGCCCAAGCCCATCT GGCAGCATCACCACCTCTGACAGCCAACCTTTTCAACAAGCCATACTGGCTGCACAAGGCTC AAGGACACAACAATGGCATCTGTTGGCACAACCAACCTTTTGTGACAGTGGTGGACACCA CCAGGAGCACCAACCTGACCCTGTGTGCCAGCACCCAGAACCCTGTGCCAAACACCTATG ACCCAACCAAGTTCAAGCACTACAGCAGGCATGTGGAGGAATATGACCTCCAATTCATCTT CCAACCTTGTACCATCACCTGACAGCAGAGGTGATGAGTTACATCCACAGTATGAACTCC AGCATCTTGGAGAACTGGAACCTTGGAGTGCCTCCTCCTCAACCACCTCCCTGGTGGACA CCTACAGGTTTGTCCAGTCTGTGGCTGTGACTTGTGAGAAGGACACCACCTCCTGAGAA GCAGGACCCATATGACAACTGAAGTTCTGGACAGTGGACCTGAAAGAGAAGTTCTCCTC TGACCTGGACCAATACCACTGGGCAGGAAGTTCTGGTCCAGGCTGGACTGAGGAGGA GACCAACCATTGGACCAAGGAAGAGACCTGCTGCCAGCACCCAGCACAGCCAGCAGACCT GCCAAGAGGGTGAGGATTAGGAGCAAGAAGTAAA ctcgagctc
SEQ ID No: 38	Synthetic HPV51L1 gene	ctgggtaccATGGCTCTGTGGAGGACCAATGACAGCAAGGTCTACCTGCCTCCTGCCCTGTG AGCAGGATTGTGAACACAGAGGAATACATCACCAGGACAGGCATCTACTACTATGCTGGC TCCAGCAGACTGATTACCCTGGGACACCCATACTTTCCAATCCCAAAGACCAGCACCAGGG CTGCCATCCCAAAGGTGTCTGCCTTCCAATACAGGGTGTTCAAGGTCCAACCTCCTGACCC AAACAAGTTTGGACTGCCTGACCCAAACCTCTACAACCTGACACAGACAGACTGGTGTG GGGCTGTGTGGGAGTGGAGGTGGGCAGGGGACAACCACTGGGAGTGGGACTGTCTGGA CAACCACTGTTCAACAAATATGATGACACAGAGAACAGCAGGATTGCCAATGGCAATGCC CAACAGGATGTGAGGGACAACACCTCTGTGGACAACAAGCAGACCCAACCTTTGTATCATT GGCTGTGCCCCTCCAATTGGAGAACACTGGGGCATTGGCACCATTGTAAGAACACACCT GTGCCTCCTGGAGACTGTCCTCATTGGAACCTGGTGTCTCTGTGATTGAGGATGGAGATA TGATTGACACAGGCTTTGGAGCTATGGACTTTGCTGCCCTCCAAGCCCAAGTCTGATGT GCCACTGGACATCAGCCAGTCTGTGTGTAATAACCTGACTACCTGAAAAATGAGTGCTGAC ACCTATGGCAACAGTATGTTCTTCCACCTGAGGAGGGGAACAGATTTTTGCCAGACACTACT ACAACAAACTGGTGGGAGTGGGAGAGGACATCCCAAATGACTACTACATCAAGGGCTCT GGCAATGGCAGGGACCCAATTGAGTCTACATCTACTCTGCCACACCATCTGGCAGTATGA TTACCTCTGACAGCCAGATTTTCAACAAGCCATACTGGCTGCACAGGGCTCAAGGACACAA CAATGGCATCTGTTGGAACAACCAACCTTTTCATCACTTGTGTGGACACCACCAGGAGCACC AACCTGACCATCAGCACAGCCACAGCAGCAGTGAGCCCAACCTTCACACCAAGCAACTTCA AGCAATACATCAGACATGGAGAGGAATATGAACTCCAATTCATCTTCCAACCTTTGTAAGAT TACCCTGACCACAGAGGTGATGGCTTACCTGCACACAATGGACCCAACCATCTTGAACA GTGGAACCTTTGGACTGACCCTGCCTCCATCTGCCTCCTTGGAGGATGCCTACAGGTTTGTG AGGAATGCTGCCACCTCTGTGAGAAGGACACACCTCCACAGGCTAAGCCTGACCCACTG GCTAAATACAAGTTCTGGGATGTGGACCTGAAAGAGAGGTTCTCCTGACCTGGACCG TTTGCCCTGGGCAGGAAGTTCTGCTCCAAGTGGGAGTCCAGAGGAAGCCAAGACCTGG ACTGAAAAGACCTGCCTCCTCTGCCTCCTCCTCCTCCTCCTCTGCCAAGAGGAAGAGG GTGAAGAAGTAAActcgagctc
SEQ ID No: 39	Synthetic HPV52L1 gene	ctgggtaccATGAGCGTGTGGAGGCCAGCGAGGCCACCGTGACCTGCCCCCGTGCCCGT GAGCAAGGTGGTGAGCACCGACGAGTACGTGAGCAGGACCAGCATCTACTACTACGCCG GCAGCAGCAGGCTGCTGACCGTGGGCCACCCCTACTTCAGCATCAAGAACACCAGCAGCG GCAACGGCAAGAAGGTGCTGGTGCCCAAGGTGAGCGGCCTGCAGTACAGGGTGTTGAGG ATCAAGCTGCCCCGACCCCAACAAGTTCGGCTTCCCCGACACCAGCTTCTACAACCCCGAGA CCCAGAGGCTGGTGTGGGCCTGCACCGCCTGGAGATCGGCAGGGGGCCAGCCCCTGGGC GTGGGCATCAGCGGCCACCCCTGCTGAACAAGTTCGACGACACCGAGACCAGCAACAAG TACGCCGGCAAGCCCGGCATCGACAACAGGGAGTGCCTGAGCATGGACTACAAGCAGAC CCAGCTGTGCATCCTGGGCTGCAAGCCCCCATCGGCGAGCACTGGGGCAAGGGCACCCC CTGCAACAACAACAGCGGCAACCCCGGCGACTGCCCCCCCCTGCAGCTGATCAACAGCGT GATCCAGGACGGCGACATGGTGGACACCGGCTTCGGCTGCATGGACTTCAACACCTGCA GGCCAGCAAGAGCGACGTGCCATCGACATCTGCAGCAGCGTGTGCAAGTACCCCGACTA CCTGCAGATGGCCAGCGAGCCCTACGGCGACAGCCTGTTCTTCTTCTGAGGAGGGAGCA GATGTTCTGTGAGGCACTTCTTCAACAGGGCCGGCACCTGGGCGACCCCGTGCCCGGCGA

		CCTGTACATCCAGGGCAGCAACAGCGGCAACACCGCCACCGTGAGAGCAGCGCCTTCTT CCCCACCCAGCGGCAGCATGGTGACCAGCGAGAGCCAGCTGTTCAACAAGCCCTACTG GCTGCAGAGGGCCAGGGCCACAACACGGCATCTGCTGGGGCAACCAGCTGTTCTGTA CCGTGGTGGACACCACCAGGAGCACCACATGACCCTGTGCGCCGAGGTGAAGAAGGAG AGCACCTACAAGAACGAGAACTTCAAGGAGTACCTGAGGCACGGCGAGGAGTTCGACCT GCAGTTCATCTTCCAGCTGTGCAAGATCACCTGACCGCCGACGTGATGACCTACATCCAC AAGATGGACGCCACCATCCTGGAGGACTGGCAGTTCGGCCTGACCCCCCCCCCAGCGCC AGCCTGGAGGACACCTACAGTTCGTGACCAGCACCGCCATCACCTGCCAGAAGAACC CCCCCAAGGGCAAGGAGGACCCCTGAAGGACTACATGTTCTGGGAGGTGGACCTGAA GGAGAAGTTCAGCGCCGACCTGGACCAGTTCCTTGGGAGGAAAGTTCCTGCTGCAGGC CGGCCTGCAGGCCAGGCCAAGCTGAAGAGGCCCGCCAGCAGCGCCCCAGGACCAGCA CCAAGAAGAAGAAGGTGAAGAGGTAAActcgagctc
SEQ ID No: 40	Synthetic HPV56L1 gene	ctgggtaccATGGCTACCTGGAGACCATCTGAGAACAAGGTCTACCTGCCTCCAACACCTGTG AGCAAGGTGGTGGCTACAGACTCCTATGTGAAGAGGACCAGCATCTTCTACCATGCTGGC TCCAGCAGACTGCTGGCTGTGGGACACCCATACTACTCTGTGACCAAGGACAACACCAAG ACCAACATCCCAAAGGTGTCTGCCTACCAATACAGGGTGTTCAGGGTGAGACTGCCTGAC CCAAACAAGTTTGGACTGCCTGACACCAACATCTACAACCCTGACCAGGAGAGACTGGTG TGGGCTTGTGTGGGATTGGAGGTGGGCAGGGGACAACCACTGGGAGCAGGACTGTCTG GACACCCACTGTTCAACAGACTGGATGACACAGAGTCCAGCAACCTGGCTAACAACAATG TGATTGAGGACAGCAGGGACAACATCTCTGTGGATGGCAAGCAGACCCAACCTTTGTATTG TGGGCTGTACTCTGCTATGGGAGAACACTGGACCAAGGGAGCAGTGTGAAGAGCACC CAGGTGACCACAGGAGACTGTCTCCACTGGCTCTGATAAACACACCAATTGAGGATGGA GATATGATTGACACAGGCTTTGGAGCTATGGACTTCAAGGTGCTCCAAGAGAGCAAGGCT GAGGTGCCACTGGACATTGTCCAGAGCACTTGTAATACCTGACTACCTGAAAATGAGT GCTGATGCCTATGGAGACAGTATGTGGTTTACCTGAGGAGGGAACAACCTTTTGGCAGA CACTACTTCAACAGGGCTGGCAAGGTGGGAGAGACCATCCCTGCTGAACCTACCTGAAA GGCAGCAATGGCAGGGAACCTCCTCCATCCTCTGTCTATGTGGCTACCATCTGGCAGTA TGATTACCTCTGAGGCTCAACTTTTCAACAAGCCATACTGGCTCCAAAGGGCTCAAGGACA CAACAATGGCATCTGTTGGGGCAACCAACTTTTGTGACAGTGGTGGACACCACCAGGAG CACCATATGACCATCAGCACAGCCACAGAACAACCTTAGCAATATGATGCCAGGAAGAT AAACCAATACCTGAGGCATGTGGAGGAATATGAACTCCAATTTGTGTTCCAACCTTTGTAAG ATTACCCTGTCTGCTGAGGTGATGGCTTACCTGCACAATATGAATGCCAACCTGTTGGAGG ACTGGAACATTGGACTGAGCCCTCCTGTGGCTACCTCCTTGGAGGACAAATACAGATATGT GAGGAGCACAGCCATCACTTGTGAGAGGAACAACCTCCAACAGAGAAGCAGGACCCAC TGGCTAAATACAAGTTCTGGGATGTGAACCTCCAAGACTCCTTCAACAGACCTGGACCA GTTTCCACTGGGCAGGAAGTTCCTGATGCAACTTGGCACAGGAGCAAGCCTGCTGTGGC TACCAGCAAGAAGAGGTCTGCCCCAACCAGCACACCTGCCAAGAGGAAGAGGA GGTAAActcgagctc
SEQ ID No: 41	Synthetic HPV58L1 gene	ctgggtaccATGAGCGTGTGGAGGCCAGCGAGGCCACCGTGACCTGCCCCCGTGCCCGT GAGCAAGGTGGTGAGCACCGACGAGTACGTGAGCAGGACCAGCATCTACTACTACGCCG GCAGCAGCAGGCTGCTGGCCGTGGGCAACCCCTACTTCAGCATCAAGAGCCCCAACAACA ACAAGAAGGTGCTGGTGCCCAAGGTGAGCGGCCTGCAGTACAGGGTGTTCAGGGTGAGG CTGCCCCGACCCCAACAAGTTCGGCTTCCCCGACACCAGCTTCTACAACCCGACACCCAGA GGCTGGTGTGGGCCTGCGTGGGCCTGGAGATCGGCAGGGGCCAGCCCTGGGCGTGGG CGTGAGCGGCCACCCCTACCTGAACAAGTTCGACGACACCGAGACCAGCAACAGGTACCC CGCCAGCCCGGCAGCGACAACAGGGAGTGCCTGAGCATGGACTACAAGCAGACCCAGC TGTGCCTGATCGGCTGCAAGCCCCCACCAGGAGCACTGGGGCAAGGGCGTGGCCTGC AACAACAACGCCGCCGCCACCGACTGCCCCCCTGGAGCTGTTCAACAGCATCATCGAG GACGGCGACATGGTGGACACCGGCTTCGGCTGCATGGACTTCGGCACCTGCAGGCCAAC AAGAGCGACGTGCCATCGACATCTGCAACAGCACCTGCAAGTACCCGACTACCTGAAG ATGGCCAGCGAGCCCTACGGCGACAGCCTGTTCTTCTCCTGAGGAGGGAGCAGATGTTT GTGAGGCACTTCTTCAACAGGGCCGGCAAGCTGGGCGAGGCGCGTGGCCGACACCTGTA CATCAAGGGCAGCGGCAACACCGCCGTGATCCAGAGCAGCGCCTTCTTCCCCACCCAG CGGCAGCATCGTGACCAGCGAGAGCCAGCTGTTCAACAAGCCCTACTGGCTGCAGAGGG

		CCCAGGGCCACAACAACGGCATCTGCTGGGGCAACCAGCTGTTCTGTGACCGTGGTGGACA CCACCAGGAGCACCAACATGACCCTGTGCACCGAGGTGACCAAGGAGGGCACCTACAAG AACGACAACCTCAAGGAGTACGTGAGGCACGTGGAGGAGTACGACCTGCAGTTCGTGTTT CAGCTGTGCAAGATCACCTGACCGCCGAGATCATGACCTACATCCACACCATGGACAGC AACATCCTGGAGGACTGGCAGTTCGGCCTGACCCCCCCCCCAGCGCCAGCCTGCAGGAC ACCTACAGGTTCTGTGACCAGCCAGGCCATCACCTGCCAGAAGACCGCCCCCCCCAAGGAG AAGGAGGACCCCTGAACAAGTACACCTTCTGGGAGGTGAACCTGAAGGAGAAGTTCAG CGCCGACCTGGACCACTTCCCCCTGGGCAGGAAGTTCCTGCTGCAGAGCGGCCTGAAGGC CAAGCCCAGGCTGAAGAGGAGCGCCCCACCACCAGGGCCCCCAGCACCAAGAGGAAGA AGGTGAAGAAGTAAA ctcgagctc
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Claims

1. A stable formulation of a multivalent human papillomavirus virus-like particle vaccine for the prevention of HPV-related diseases or infections comprising

- (a) a plurality of human papillomavirus virus-like particles;
- (b) an adjuvant;
- (c) a physiologically acceptable concentration of a buffer;
- (d) a physiologically acceptable concentration of an osmotic pressure regulator; and optionally

- (e) a physiologically acceptable concentration of a surfactant,

wherein the human papillomavirus virus-like particles are selected from HPV virus-like particles assembled by L1 proteins of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58; and

one or more HPV virus-like particles assembled from L1 proteins of other pathogenic HPV types,

wherein that human papillomavirus virus-like particle are adsorbed on an adjuvant.

2. The formulation according to claim 1, wherein

the buffer is selected from one or more of citric acid buffer, acetic acid buffer or histidine buffer;

the osmotic pressure regulator is selected from one or more of sodium chloride, sodium phosphate or sodium sulfate;

the surfactant is a polyethoxy ether, preferably polysorbate 80;

the adjuvant is preferably an aluminum adjuvant, more preferably one or more of aluminum hydroxyphosphate (AlPO_4), amorphous aluminum hydroxyphosphate sulfate (AAHS) or aluminum hydroxide ($\text{Al}(\text{OH})_3$), most preferably aluminum hydroxyphosphate (AlPO_4).

3. The formulation according to claim 1 or 2, wherein

(a) the total concentration of papillomavirus virus-like particles of all types is 40 to 740 μ g/mL;

(b) the concentration of the buffer is 10mM to 26 mM, preferably 10 mM, 18mM or 26 mM;

(c) the concentration of the osmotic pressure regulator is 150mM to 320 mM, preferably 150 mM or 320 mM;

(d) the concentration of the surfactant is 0 to 0.02 wt%;

(e) the concentration of the adjuvant is about 1.0mg/mL;

(f) the pH of the formulation is from 5.9 to 6.5, preferably 5.9, 6.2 or 6.5.

4. The formulation according to claim 3, wherein the concentration of any single type of papillomavirus virus-like particles included in the multivalent papillomavirus virus-like particles is 40 μ g/mL to 120 μ g/mL.

5. The formulation according to any of claims 1-4, comprising 0.74mg/mL of the total papillomavirus virus-like particles of all types, 1.0mg/mL of aluminum phosphate adjuvant, 18mM histidine buffer, 320mM sodium chloride, a pH of 6.2; and

optionally, polysorbate 80 at a concentration of not more than 0.3mg/mL.

6. The formulation according to claim 5, wherein the one or more other pathogenic HPV types are selected from HPV type 35, 39, 51, 56 and 59.

7. The formulation according to claim 6, wherein at least one of the HPV virus-like particles is a chimeric HPV virus-like particle comprising a chimeric HPV L1 protein; the chimeric HPV L1 protein comprises from that N-terminal to the C-terminal thereof:

a. an N-terminal fragment derived from L1 protein of the first papilloma virus type, said N-terminal fragment maintains the immunogenicity of the L1 protein of the first papilloma virus type, wherein said L1 protein of the first papilloma virus type is selected from HPV Types 6, 11, 16, 18, 31, 35, 39, 45, 51, 52, 56, 58, and one or more other pathogenic HPV types; and

b. a C-terminal fragment derived from L1 protein of the second papilloma virus type, said L1 protein of the second papilloma virus type has a better expression level and solubility compared to L1 proteins of other types;

wherein the chimeric HPV L1 protein has the immunogenicity of the L1 protein of the first papilloma virus type.

8. The formulation according to claim 7, wherein

said N-terminal fragment is a fragment obtained by truncating the C-terminus of the natural sequence of said L1 protein of the first papilloma virus type at any amino acid position within its $\alpha 5$ region, and a fragment having at least 98% identity therewith; and

said C-terminal fragment is a fragment obtained by truncating the N-terminus of the natural sequence of said L1 protein of the second papilloma virus type at any amino acid position within its $\alpha 5$ region and functional variants resulting from further mutations, deletions and/or additions to the fragment.

9. The formulation according to claim 8, wherein the C-terminal fragment comprises one or more nuclear localization sequences.

10. The formulation according to claim 7,

wherein the papilloma L1 protein of the first type is selected from HPV type 6, 11, 16, 18, 31, 35, 39, 45, 51, 52, 56 or 58; preferably, the natural sequence thereof is an amino acid sequence encoded by a coding gene shown in SEQ ID No: 30, SEQ ID No: 31, SEQ ID No: 32, SEQ ID No: 33, SEQ ID No: 34, SEQ ID No: 35, SEQ ID No: 36, SEQ ID No: 37, SEQ ID No: 38, SEQ ID No: 39, SEQ ID No: 40, or SEQ ID No: 41, respectively;

wherein that papillomavirus L1 protein of the second type is selected from HPV type 16, 28, 33, 59 or 68 L1 protein;

more preferably, the papilloma L1 protein of the second type is selected from the group consisting of an HPV type 33 or 59 L1 protein.

11. The formulation according to claim 10, wherein the C-terminal fragment is SEQ ID No: 1; or a fragment thereof having a length of m_1 amino acids, preferably a fragment covering amino acids 1- m_1 of SEQ ID No: 1; wherein m_1 is an integer from 8 to 26; or that C-terminal fragment is SEQ ID No: 2; or fragments thereof having a length of m_2 amino acids,

preferably a fragment comprising amino acids 1-m₂ of SEQ ID No: 2; wherein m₂ is an integer from 13 to 31.

12. The formulation according to claim 10, wherein the C-terminal fragment is SEQ ID No: 3; or a fragment thereof having a length of n amino acids, preferably a fragment covering amino acids 1-n of SEQ ID No: 3; wherein n is an integer from 16 to 38.

13. The formulation according to claim 7, wherein

the N-terminal fragment of the HPV type 6 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:4 at any amino acid site within the α 5 region thereof;

the N-terminal fragment of the HPV type 11 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:5 at any amino acid site within the α 5 region thereof;

the N-terminal fragment of the HPV type 16 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:6 at any amino acid site within the α 5 region thereof;

the N-terminal fragment of the HPV type 18 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No: 7 at any amino acid site within the α 5 region thereof;

the N-terminal fragment of the HPV type 31 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:8 at any amino acid site within the α 5 region thereof;

the N-terminal fragment of the HPV type 35 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No: 9 at any amino acid site within the α 5 region thereof;

the N-terminal fragment of the HPV type 39 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of

the sequence shown in SEQ ID No: 10 at any amino acid site within the $\alpha 5$ region thereof;

the N-terminal fragment of the HPV type 45 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No: 11 at any amino acid site within the $\alpha 5$ region thereof;

the N-terminal fragment of the HPV type 51 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No: 12 at any amino acid site within the $\alpha 5$ region thereof;

the N-terminal fragment of the HPV type 52 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:13 to any amino acid site in the $\alpha 5$ region;

the N-terminal fragment of the HPV type 56 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No:14 to any amino acid site in the $\alpha 5$ region; and

the N-terminal fragment of the HPV type 58 L1 protein has 98%, 98.5%, 99%, 99.5%, 99% or 100% identity with a fragment obtained by truncating the C-terminal of the sequence shown in SEQ ID No: 15 at any amino acid site within the $\alpha 5$ region thereof.

14. The formulation according to claim 7, wherein the C-terminal of the N-terminal fragment is connected directly to the N-terminal of the C-terminal fragment or by a linker.

15. The formulation according to claim 7, wherein when the C-terminus of said N-terminal fragment is connected to the N-terminus of said C-terminal fragment, the continuous amino acid sequence RKFL is present within a range of plus or minus 4 amino acid positions of the splicing site,

preferably, the continuous amino acid sequence LGRKFL is present within a range of plus or minus 6 amino acid positions of the splicing site.

16. The formulation according to claim 7, wherein

the chimeric HPV L1 protein of type 6, 11, 16, 18, 31, 35, 39, 45, 51, 52, 56, and 58 have 98%, 98.5%, 99%, 99.5% or 100% identity to SEQ ID No:16, SEQ ID No:17, SEQ ID No:18, SEQ ID No:19, SEQ ID No:20, SEQ ID No:21, SEQ ID No:22, SEQ ID No:23, SEQ ID No:24, SEQ ID No:25, SEQ ID No:26 and SEQ ID No: 27, respectively; and

the HPV type 33 L1 protein and the HPV type 59 L1 protein have 98%, 98.5%, 99%, 99.5%, or 100% identity to SEQ ID No:28 and SEQ ID No: 29, respectively.

17. The formulation according to claim 16, comprising

HPV type 6, 11, 16, 18, 31, 35, 39, 45, 51, 52, 56 and 58 chimeric HPV L1 protein having the amino acid sequences shown in SEQ ID No:16, SEQ ID No:17, SEQ ID No:18, SEQ ID No:19, SEQ ID No:20, SEQ ID No:21, SEQ ID No:22, SEQ ID No:23, SEQ ID No:24, SEQ ID No:25, SEQ ID No:26 and SEQ ID No: 27, respectively; and

HPV type 33 L1 protein and HPV type 59 L1 protein having the amino acid sequences shown in SEQ ID No:28 and SEQ ID No: 29, respectively.

18. The formulation of a papilloma virus vaccine according to claims 1-17, characterized in that it can be stably stored at 2 to 8 °C for at least 24 months and at 25 °C for at least 16 weeks.

19. A method of preventing an HPV-related disease or infection comprising:

administering the formulation according to any of claims 1-18 to a subject.

20. Use of the formulation according to any of claims 1-18 in the formulation of a vaccine for the prevention of HPV-related diseases or infections.