Claims

1. A method for producing a stable liquid formulation of a six combined vaccine against diphtheria, pertussis, tetanus, polio, Haemophilus influenzae type b (Hib), and hepatitis B (HepB), the method comprising the following steps of:

(1) mixing diphtheria toxoid (D) and tetanus toxoid (T) with an aluminum adjuvant to produce a DT adjuvant;

(2) mixing a hepatitis B surface (HBs) antigen with the DT adjuvant obtained in step (1) to produce a DT-HBs adjuvant;

(3) mixing a pertussis antigen (P) with the DT-HBs adjuvant obtained in step (2) to produce a DPT-HBs adjuvant;

(4) mixing inactivated poliovirus (IPV) with the DPT-HBs adjuvant obtained in step (3) to produce a DPT-IPV-HBs adjuvant;

(5) adding a succinate phosphate buffer to the DPT-IPV-HBs adjuvant obtained in step (4), and then adding PRP (PRP-T conjugate) as a Hib antigen to produce a mixture of DPT-IPV-Hib-HBs adjuvant and PRP-T conjugate; and

(6) adjusting pH of the mixture of DPT-IPV-Hib-HBs adjuvant and PRP-T conjugate obtained in step (5) to 5.4 to 5.9, wherein the aluminum adjuvant is an aluminum phosphate gel.

2. The method according to claim 1, wherein an amount of the aluminum adjuvant added is 200 to 400 μg/dose.

3. The method according to claim 1, wherein in step (5), the succinate phosphate buffer (pH 5.5) is added so that an addition concentration of phosphoric acid is 2 to 8 mmol/L in terms of final concentration.

4. The method according to claim 2, wherein the amount of the aluminum adjuvant added is 200 μg/dose, and the addition concentration of phosphoric acid is 2 to 6 mmol/L in terms of final concentration.

5. The method according to claim 2, wherein the amount of the aluminum adjuvant added is 300 μg/dose, and the addition concentration of phosphoric acid is 3 to 6 mmol/L in terms of final concentration.

6. The method according to claim 2, wherein the amount of the aluminum

adjuvant added is 400 μg/dose, and the addition concentration of phosphoric acid is 6 to 8 mmol/L in terms of final concentration.

7. The method according to claim 1, wherein an adsorption ratio of HBs antigen to the aluminum adjuvant is 99% or more, and a free PRP content of Hib is less than 20%.

8. A stable liquid formulation of a six combined vaccine produced by the method according to any one of claims 1 to 7.