DIPHTHERIA AND TETANUS VACCINE (ADSORBED)

Vaccinum diphtheriae et tetani adsorbatum

DEFINITION
Diphtheria and tetanus vaccine (adsorbed) is a preparation of diphtheria formol toxoid and tetanus formol toxoid with a mineral adsorbent. The formol toxoids are prepared from the toxins produced by the growth of Corynebacterium diphtheriae and Clostridium tetani, respectively.

PRODUCTION

GENERAL PROVISIONS

Specific toxicity of the diphtheria and tetanus components. The production method is validated to demonstrate that the product, if tested, would comply with the following test: inject subcutaneously 5 times the single human dose stated on the label into each of 5 healthy guinea-pigs, each weighing 250-350 g, that have not previously been treated with any material that will interfere with the test. If within 42 days of the injection any of the animals shows signs of or dies from diphtheria toxaemia or tetanus, the vaccine does not comply with the test. If more than 1 animal dies from non-specific causes, repeat the test once; if more than 1 animal dies in the second test, the vaccine does not comply with the test.

BULK PURIFIED DIPHTHERIA AND TETANUS TOXOIDS

The bulk purified diphtheria and tetanus toxoids are prepared as described in the monographs on Diphtheria vaccine (adsorbed) (0443) and Tetanus vaccine (adsorbed) (0452) and comply with the requirements prescribed therein.

FINAL BULK VACCINE

The final bulk vaccine is prepared by adsorption of suitable quantities of bulk purified diphtheria toxoid and tetanus toxoid onto a mineral carrier such as hydrated aluminium phosphate or aluminium hydroxide; the resulting mixture is approximately isotonic with blood. Suitable antimicrobial preservatives may be added. Certain antimicrobial preservatives, particularly those of the phenolic type, adversely affect the antigenic activity and must not be used. Only a final bulk vaccine that complies with the following requirements may be used in the preparation of the final lot.

Antimicrobial preservative. Where applicable, determine the amount of antimicrobial preservative by a suitable chemical method. The content is not less than the minimum amount shown to be effective and is not greater than 115 per cent of the quantity stated on the label.

Sterility (2.6.1). The vaccine complies with the test for sterility.

ASSAY

Diphtheria component. Carry out one of the prescribed methods for the assay of diphtheria vaccine (adsorbed) (2.7.6). The lower confidence limit (P = 0.95) of the estimated potency is not less than 30 IU per single human dose.

Tetanus component. Carry out one of the prescribed methods for the assay of tetanus vaccine (adsorbed) (2.7.8). The lower confidence limit (P = 0.95) of the estimated potency is not less than 40 IU per single human dose.

LABELLING

The label states:

– the minimum number of International Units of each component per single human dose,
– where applicable, that the vaccine is intended for primary vaccination of children and is not necessarily suitable for reinforcing doses or for administration to adults,
– the name and the amount of the adsorbent,
– that the vaccine must be shaken before use,
– that the vaccine is not to be frozen.

DIPHTHERIA AND TETANUS VACCINE (ADSORBED) FOR ADULTS AND ADOLESCENTS

Vaccinum diphtheriae et tetani adulti et adolescentis adsorbatum

DEFINITION
Diphtheria and tetanus vaccine (adsorbed) for adults and adolescents is a preparation of diphtheria formol toxoid and tetanus formol toxoid with a mineral adsorbent. The
formol toxoids are prepared from the toxins produced by the growth of Corynebacterium diphtheriae and Clostridium tetani, respectively. It shall have been demonstrated to the competent authority that the quantity of diphtheria toxoid used does not produce adverse reactions in subjects from the age groups for which the vaccine is intended.

**PRODUCTION**

**GENERAL PROVISIONS**

**Specific toxicity of the diphtheria and tetanus components.** The production method is validated to demonstrate that the product, if tested, would comply with the following test: inject subcutaneously 5 times the single human dose stated on the label into each of 5 healthy guinea-pigs, each weighing 250-350 g, that have not previously been treated with any material that will interfere with the test. If within 42 days of the injection any of the animals shows signs of or dies from diphtheria toxaemia or tetanus, the vaccine does not comply with the test. If more than 1 animal dies from non-specific causes, repeat the test once; if more than 1 animal dies in the second test, the vaccine does not comply with the test.

**BULK PURIFIED DIPHTHERIA TOXOID AND TETANUS TOXOIDS**

The bulk purified diphtheria and tetanus toxoids are prepared as described in the monographs on Diphtheria vaccine (adsorbed) (0443) and Tetanus vaccine (adsorbed) (0452) and comply with the requirements prescribed therein.

**FINAL BULK VACCINE**

The vaccine is prepared by adsorption of suitable quantities of bulk purified diphtheria toxoid and tetanus toxoid onto a mineral carrier such as hydrated aluminium phosphate or aluminium hydroxide: the resulting mixture is approximately isotonic with blood. Suitable antimicrobial preservatives may be added. Certain antimicrobial preservatives, particularly those of the phenolic type, adversely affect the antigenic activity and must not be used.

Only a final bulk vaccine that complies with the following requirements may be used in the preparation of the final lot.

**Antimicrobial preservative.** Where applicable, determine the amount of antimicrobial preservative by a suitable chemical method. The amount is not less than 85 per cent of the quantity stated on the label.

**Sterility** (2.6.1). Carry out the test for sterility using 10 ml for each medium.

**FINAL LOT**

The final bulk vaccine is distributed aseptically into sterile, tamper-proof containers. The containers are closed so as to prevent contamination.

Only a final lot that is satisfactory with respect to each of the requirements given below under Identification, Tests and Assay may be released for use. Provided the test for antimicrobial preservative and the assay have been carried out with satisfactory results on the final bulk vaccine, they may be omitted on the final lot.

**IDENTIFICATION**

A. Diphtheria toxoid is identified by a suitable immunochemical method (2.7.1). The following method, applicable to certain vaccines, is given as an example. Dissolve in the vaccine to be examined sufficient sodium citrate R to give a 100 g/l solution. Maintain at 37 °C for about 16 h and centrifuge until a clear supernatant liquid is obtained. The clear supernatant liquid reacts with a suitable diphtheria antitoxin, giving a precipitate. If a satisfactory result is not obtained with a vaccine adsorbed on aluminium hydroxide, carry out the test as follows. Centrifuge 15 ml of the vaccine to be examined and suspend the residue in 5 ml of a freshly prepared mixture of 1 volume of a 56 g/l solution of sodium edetate R and 49 volumes of a 90 g/l solution of disodium hydrogen phosphate R. Maintain at 37 °C for not less than 6 h and centrifuge. The clear supernatant liquid reacts with a suitable diphtheria antitoxin, giving a precipitate.

B. Tetanus toxoid is identified by a suitable immunochemical method (2.7.1). The following method, applicable to certain vaccines, is given as an example. The clear supernatant liquid obtained during identification test A reacts with a suitable tetanus antitoxin, giving a precipitate.

**TESTS**

**Aluminium (2.5.13):** maximum 1.25 mg per single human dose, if aluminium hydroxide or hydrated aluminium phosphate is used as the adsorbent.

**Free formaldehyde (2.4.18):** maximum 0.2 g/l.

**Antimicrobial preservative.** Where applicable, determine the amount of antimicrobial preservative by a suitable chemical method. The content is not less than the minimum amount shown to be effective and is not greater than 115 per cent of the quantity stated on the label.

**Sterility** (2.6.1). The vaccine complies with the test for sterility.

**ASSAY**

**Diphtheria component.** Carry out one of the prescribed methods for the assay of diphtheria vaccine (adsorbed) (2.7.6). The lower confidence limit ($P = 0.95$) of the estimated potency is not less than 2 IU per single human dose.

**Tetanus component.** Carry out one of the prescribed methods for the assay of tetanus vaccine (adsorbed) (2.7.8). The lower confidence limit ($P = 0.95$) of the estimated potency is not less than 20 IU per single human dose.

**LABELLING**

The label states:

- the minimum number of International Units of each component per single human dose,
- the name and the amount of the adsorbent,
- that the vaccine must be shaken before use,
- that the vaccine is not to be frozen.