5.9. Reference Substances (IPRS). Page 1018

Insert at the end

Reference standard for vaccines

Considering the inherent variability in biological assays usage of reference standards are necessary at some stage in production of vaccines and antisera for their effective quality control. Since these standards are key materials in establishing quality of products, they have to be properly established, maintained and monitored to ensure efficacy of the vaccines and antisera.

For many vaccines and antisera for human use, National Reference Standards (NRS) are established, maintained and supplied by Central Drugs Laboratory (CDL), Kasauli. NRS are calibrated against the International Reference Standard (IRS) and are supplied to various vaccine and antisera manufacturers across the country. NRS are thus traceable to the IRS supplied by NIBSC, London. To ensure judicious use of NRS and IRS, manufacturers are encouraged to develop their In House Reference Standards in comparison to the NRS and/or IRS.

2.7.1 Composition of Polysaccharide Vaccines. Page 333

Phosphorus, Method.

Para 1, line 6.

Change **from** : .....4 ml each of *water* and *ammonium molybdate reagent.*

to: .....4 ml each of *water* and *ammonium molybdate reagent* prepared by mixing 1 volume of a 25 g per litre solution of ammonium molybdate, 1 volume of a 100 g per litre solution of ascorbic acid and 1 volume of sulphuric acid (294.5 g per litre) and 2 volume of water.

Protein Content, Method.

Para 1, line 1.

Change **from** : Add 2 ml of *cupri-tartaric solution*……..

to: Add 2 ml of *cupri-tartaric solution* prepared by adding 1 ml of solution I containing 10 g per litre of copper sulphate and 20 g per litre of sodium tartrate, to 50 ml of solution II containing 40 g per litre solution of sodium carbonate in 0.2 M sodium hydroxide.

Sterile Water for Injections. Page 3518

Tests

Ammonium.

Change **to**: **Ammonium**. For containers with a nominal volume less than 50 ml: maximum 0.6 ppm; for containers with a nominal volume equal to or greater than 50 ml: maximum 0.2 g per litre.

Containers with a nominal volume less than 50 ml: To 20 ml, add 1 ml of *alkaline potassium tetraiodomercurate solution* and allow to stand for 5 minutes. When viewed vertically the solution is not more intensely coloured than a solution prepared at the same time by adding 1 ml of *alkaline potassium tetraiodomercurate solution* to a mixture of 4.0 ml of *ammonium standard solution* (*3 ppm* NH_4) and 16.0 ml of *ammonia-free water* (0.6 ppm).

Containers with a nominal volume equal to or greater than 50 ml: To 20 ml, add 1 ml of *alkaline potassium tetraiodomercurate solution* and allow to stand for 5 minutes. When viewed vertically the solution is not more intensely coloured than a solution prepared at the same time by adding 1 ml of *alkaline potassium tetraiodomercurate solution* to a mixture of 4.0 ml of *ammonium standard solution* (*1 ppm* NH_4) and 16.0 ml of *ammonia-free water* (0.2 ppm).

Chlorides.

Para 2, Insert at the end

For containers with a nominal volume greater than 100 ml, use the following test: to 10 ml add 1 ml of *dilute nitric acid* and 0.2 ml of *silver nitrate solution*. The solution shows no change in appearance for at least 15 min.

Aluminium.

Insert after **Sulphates**

Aluminium. Maximum 10 ppb, if intended for use in the manufacture of dialysis solutions.

Prescribed solution to 400 ml of the water to be examined add 10 mlof acetate buffer solution pH 6.0 and 100 ml of *distilled water* .

Reference solution. Mix 2 ml of *aluminium standard solution* (*2 ppm Al*), 10 ml of *acetate buffer solution pH 6.0* and 98 ml of *distilled water*.

Blank solution. Mix 10 ml of *acetate buffer solution pH 6.0* and 100 ml of *distilled water*.

Adsorbed Pertussis Vaccine (Acellular Component). Page 3587

Production, General provisions

Para 1, Insert at the end

Where a genetically modified form of B. Pertussis is used, production consistency and genetic stability shall be in conformity with the requirements prescribed by the National Regulatory Authority.

CHARACTERISATION OF COMPONENTS

Pertussis toxin, para1

Change **to:** It may be demonstrated by Chinese hamster ovary (CHO) cell-clustering effect and haemagglutination as *in vitro* methods; lymphocytosis-promoting activity, histamine-sensitising activity and insulin secretory activity as *in vivo* methods. The toxin shows ADP- ribosyl transferase activity using transducin as the acceptor.

Filamentous Haemagglutinin, line 2

Change **to**: Pertactin, fimbrial-2 and fimbrial-3 antigens may be demonstrated by reactivity with specific antibody.

FINAL LOT

Identification, line 3

Change **From**: *sodium citrate* to give a 10 per cent w/v solution;

to: *sodium citrate* to give a 1 per cent w/v solution;

Assay. Para 1Insert at end

or any other validated serological assay in guinea pigs or mice as approved by National Regulatory Authority may also be used.

Where a single dilution assay is used production and test consistency over time shall be monitored via suitable indicators and carrying out a full multidilution assay periodically for example every two years.

ELISA

Para 1, line 7

Change **From**: are made on the plates.

to: are made on the plates. Reference antiserum shall be included in each plate.

Hepatitis B Vaccine (rDNA). Page 3625

PROPAGATION AND HARVEST

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Inactivated Hepatitis A Vaccine (Adsorbed). Page 3628

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

FINAL LOT. Tests

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Inactivated Hepatitis B Vaccine. Page 3630

PROPAGATION AND HARVEST

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Inactivated Influenza Vaccine (Split Virion). Page 3632

PROPAGATION AND HARVEST

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Inactivated Influenza Vaccine (Surface Antigen). Page 3634

PROPAGATION AND HARVEST

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Inactivated Influenza Vaccine (Whole Virion). Page 3636

PROPAGATION AND HARVEST

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Influenza Vaccine (Human, Live Attenuated). Page 3638

PROPAGATION AND HARVEST. Identification

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Japanese Encephalitis Vaccine (Human). Page 3640

SEED LOT. **Identification**

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Japanese Encephalitis Live Vaccine (Human). Page 3642

PROPAGATION AND HARVEST

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Japanese Encephalitis Vaccine Inactivated (Adsorbed, Human). Page 3645

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. **Identification**

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Measles and Rubella Vaccine (Live). Page 3648

FINAL LOT. **Tests**.

Insert before **Assay**

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Measles Vaccine (Live). Page 3649

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Measles, Mumps and Rubella Vaccine (Live). Page 3650

FINAL LOT. Tests

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Mumps Vaccine (Live). Page 3661

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Poliomyelitis Vaccine, Live (Oral). Page 3676

PROPAGATION AND HARVEST. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Rabies Vaccine, Human. Page 3682

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Rotavirus Vaccine (Live attenuated, Oral). Page 3686

VIRUS SEED LOTS. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

VIRUS PROPAGATION AND HARVEST

Insert before **Virus concentration**

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Rubella Vaccine (Live). Page 3689

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Tick-borne Encephalitis Vaccine (Inactivated). Page 3699

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Varicella Vaccine, Live. Page 3712

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

FINAL LOT. Tests

Insert before Assay

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Yellow Fever Vaccine. Page 3714

SEED LOT. Identification

Insert at end

Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification

Insert at end

Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.