Heavy metals (*2.4.8*): maximum 0.1 ppm.

Heat 200 ml in a glass evaporating dish on a water-bath until the volume is reduced to 20 ml. 12 ml of the concentrated solution complies with limit test A. Prepare the standard using 10 ml of *lead standard solution (1 ppm Pb) R*.

Bacterial endotoxins (*2.6.14*): less than 0.25 IU/ml.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

01/2005:0008
corrected

WATER, PURIFIED

Aqua purificata

H_2O M_r 18.02

DEFINITION

Water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised.

Purified water in bulk

PRODUCTION

Purified water in bulk is prepared by distillation, by ion exchange, by reverse osmosis or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by the competent authority.

During production and subsequent storage, appropriate measures are taken to ensure that the total viable aerobic count is adequately controlled and monitored. Appropriate alert and action limits are set so as to detect adverse trends. Under normal conditions, an appropriate action limit is a total viable aerobic count (*2.6.12*) of 100 micro-organisms per millilitre, determined by membrane filtration, using agar medium S and incubating at 30-35 °C for 5 days. The size of the sample is to be chosen in relation to the expected result.

In addition, the test for total organic carbon (*2.2.44*) with a limit of 0.5 mg/l or alternatively the following test for oxidisable substances is carried out: to 100 ml add 10 ml of *dilute sulphuric acid R* and 0.1 ml of *0.02 M potassium permanganate* and boil for 5 min; the solution remains faintly pink.

Conductivity. Determine the conductivity off-line or in-line under the following conditions.

EQUIPMENT

Conductivity cell:

- electrodes of a suitable material such as stainless steel;
- cell constant: within 2 per cent of the given value determined using a certified reference solution with a conductivity less than 1500 $\mu S \cdot cm^{-1}$.

Conductometer: resolution 0.1 $\mu S \cdot cm^{-1}$ on the lowest range.

System calibration (conductivity cell and conductometer):

- against one or more suitable certified standard solutions;
- accuracy: within 3 per cent of the measured conductivity plus 0.1 $\mu S \cdot cm^{-1}$.

Conductometer calibration: by means of precision resistors or equivalent devices, after disconnecting the conductivity cell, for all ranges used for conductivity measurement and cell calibration (with an accuracy within 0.1 per cent of the stated value, traceable to the official standard).

If in-line conductivity cells cannot be dismantled, system calibration may be performed against a calibrated conductivity cell placed close to the cell to be calibrated in the water flow.

PROCEDURE

Measure the conductivity without temperature compensation, recording simultaneously the temperature. Temperature-compensated measurement may be performed after suitable validation.

The water to be examined meets the requirements if the measured conductivity at the recorded temperature is not greater than the value in Table 0008.-1.

Table 0008.-1. – *Temperature and conductivity requirements*

Temperature (°C)	Conductivity ($\mu S \cdot cm^{-1}$)
0	2.4
10	3.6
20	4.3
25	5.1
30	5.4
40	6.5
50	7.1
60	8.1
70	9.1
75	9.7
80	9.7
90	9.7
100	10.2

For temperatures not listed in Table 0008.-1, calculate the maximal permitted conductivity by interpolation between the next lower and next higher data points in the table.

Purified water in bulk is stored and distributed in conditions designed to prevent growth of micro-organisms and to avoid any other contamination.

CHARACTERS

Appearance: clear and colourless liquid.

TESTS

Nitrates: maximum 0.2 ppm.

Place 5 ml in a test-tube immersed in iced water, add 0.4 ml of a 100 g/l solution of *potassium chloride R*, 0.1 ml of *diphenylamine solution R* and, dropwise with shaking, 5 ml of *nitrogen-free sulphuric acid R*. Transfer the tube to a water-bath at 50 °C. After 15 min, any blue colour in the solution is not more intense than that in a reference solution prepared at the same time in the same manner using a mixture of 4.5 ml of *nitrate-free water R* and 0.5 ml of *nitrate standard solution (2 ppm NO_3) R*.

Aluminium (*2.4.17*): 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 ml of *acetate buffer solution pH 6.0 R* and 100 ml of *distilled water R*.

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

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

Heavy metals (*2.4.8*): maximum 0.1 ppm.

Heat 200 ml in a glass evaporating dish on a water-bath until the volume is reduced to 20 ml. 12 ml of the concentrated solution complies with limit test A. Prepare the standard using 10 ml of *lead standard solution (1 ppm Pb) R*.

Bacterial endotoxins (*2.6.14*): less than 0.25 IU/ml, if intended for use in the manufacture of dialysis solutions without a further appropriate procedure for removal of bacterial endotoxins.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

Purified water in containers

DEFINITION

Purified water in bulk that has been filled and stored in conditions designed to assure the required microbiological quality. It is free from any added substances.

CHARACTERS

Appearance: clear and colourless liquid.

TESTS

It complies with the tests prescribed in the section on Purified water in bulk and with the following additional tests.

Acidity or alkalinity. To 10 ml, freshly boiled and cooled in a borosilicate glass flask, add 0.05 ml of *methyl red solution R*. The solution is not coloured red.

To 10 ml add 0.1 ml of *bromothymol blue solution R1*. The solution is not coloured blue.

Oxidisable substances. To 100 ml add 10 ml of *dilute sulphuric acid R* and 0.1 ml of *0.02 M potassium permanganate* and boil for 5 min. The solution remains faintly pink.

Chlorides. To 10 ml add 1 ml of *dilute nitric acid R* and 0.2 ml of *silver nitrate solution R2*. The solution shows no change in appearance for at least 15 min.

Sulphates. To 10 ml add 0.1 ml of *dilute hydrochloric acid R* and 0.1 ml of *barium chloride solution R1*. The solution shows no change in appearance for at least 1 h.

Ammonium: maximum 0.2 ppm.

To 20 ml add 1 ml of *alkaline potassium tetraiodomercurate solution R*. After 5 min, examine the solution down the vertical axis of the tube. The solution is not more intensely coloured than a standard prepared at the same time by adding 1 ml of *alkaline potassium tetraiodomercurate solution R* to a mixture of 4 ml of *ammonium standard solution (1 ppm NH_4) R* and 16 ml of *ammonium-free water R*.

Calcium and magnesium. To 100 ml add 2 ml of *ammonium chloride buffer solution pH 10.0 R*, 50 mg of *mordant black 11 triturate R* and 0.5 ml of *0.01 M sodium edetate*. A pure blue colour is produced.

Residue on evaporation: maximum 0.001 per cent.

Evaporate 100 ml on a water-bath and dry in an oven at 100-105 °C. The residue weighs a maximum of 1 mg.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^2 micro-organisms per millilitre, determined by membrane filtration, using agar medium B.

LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of dialysis solutions.

01/2005:0359

WHEAT STARCH

Tritici amylum

DEFINITION

Wheat starch is obtained from the caryopsis of *Triticum aestivum* L. (*T. vulgare* Vill.).

CHARACTERS

Appearance: very fine, white powder which creaks when pressed between the fingers.

Solubility: practically insoluble in cold water and in alcohol.

Wheat starch does not contain starch grains of any other origin. It may contain a minute quantity, if any, of tissue fragments of the original plant.

IDENTIFICATION

A. Examined under a microscope using equal volumes of *glycerol R* and *water R*, it presents large and small granules, and, very rarely, intermediate sizes. The large granules, 10 µm to 60 µm in diameter, are discoid or, more rarely, reniform when seen face-on. The central hilum and striations are invisible or barely visible and the granules sometimes show cracks on the edges. Seen in profile, the granules are elliptical and fusiform and the hilum appears as a slit along the main axis. The small granules, rounded or polyhedral, are 2 µm to 10 µm in diameter. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum.

B. Suspend 1 g in 50 ml of *water R*, boil for 1 min and cool. A thin, cloudy mucilage is formed.

C. To 1 ml of the mucilage obtained in identification test B, add 0.05 ml of *iodine solution R1*. A dark blue colour is produced which disappears on heating.

TESTS

pH (*2.2.3*): 4.5 to 7.0.

Shake 5.0 g with 25.0 ml of *carbon dioxide-free water R* for 60 s. Allow to stand for 15 min.

Foreign matter. Examined under a microscope using a mixture of equal volumes of *glycerol R* and *water R*, not more than traces of matter other than starch granules are present. No starch grains of any other origin are present.

Total protein: maximum 0.3 per cent of total protein (corresponding to 0.048 per cent N_2, conversion factor: 6.25), determined on 6.0 g by sulphuric acid digestion (*2.5.9*) modified as follows: wash any adhering particles from the neck into the flask with 25 ml of *sulphuric acid R*; continue the heating until a clear solution is obtained; add 45 ml of *strong sodium hydroxide solution R*.

Oxidising substances (*2.5.30*): maximum 20 ppm, calculated as H_2O_2.

Sulphur dioxide (*2.5.29*): maximum 50 ppm.

Iron (*2.4.9*): maximum 10 ppm.

Shake 1.5 g with 15 ml of *dilute hydrochloric acid R*. Filter. The filtrate complies with the limit test for iron.

Loss on drying (*2.2.32*): maximum 15.0 per cent, determined on 1.000 g by drying in an oven at 130 °C for 90 min.

Sulphated ash (*2.4.14*): maximum 0.6 per cent, determined on 1.0 g.