

**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*.

**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<sub>4</sub>) 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 tritrate R* and 0.5 ml of 0.01 M *sodium edetate*. A pure blue colour is produced.

**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*.

**Residue on evaporation:** maximum 4 mg (0.004 per cent) for containers with a nominal volume of 10 ml or less; maximum 3 mg (0.003 per cent) for containers with a nominal volume greater than 10 ml.

Evaporate 100 ml to dryness on a water-bath and dry in an oven at 100-105 °C.

**Particulate contamination: sub-visible particles (2.9.19).** It complies with test A or test B, as appropriate.

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

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

Current production methods include for example double-pass reverse osmosis coupled with other suitable techniques such as ultrafiltration and deionisation. Correct operation and maintenance of the system is essential.

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 10 micro-organisms per 100 ml when determined by membrane filtration, using agar medium S, at least 200 ml of highly purified water and incubating at 30-35 °C for 5 days.

**Total organic carbon (2.2.44):** maximum 0.5 mg/l.

**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 µS·cm<sup>-1</sup>.

*Conductometer:* resolution 0.1 µS·cm<sup>-1</sup> 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 µS·cm<sup>-1</sup>.

*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

##### Stage 1

1. Measure the conductivity without temperature compensation, recording simultaneously the temperature. Temperature-compensated measurement may be performed after suitable validation.
2. Using Table 1927-1, find the closest temperature value that is not greater than the measured temperature. The corresponding conductivity value is the limit at that temperature.
3. If the measured conductivity is not greater than the value in Table 1927-1, the water to be examined meets the requirements of the test for conductivity. If the conductivity is higher than the value in Table 1927-1, proceed with stage 2.

01/2005:1927  
corrected

## WATER, HIGHLY PURIFIED

### Aqua valde purificata

H<sub>2</sub>O

M<sub>r</sub> 18.02

#### DEFINITION

Water intended for use in the preparation of medicinal products where water of high biological quality is needed, except where *Water for injections (0169)* is required.

#### PRODUCTION

Highly purified water is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority.

Table 1927-1. – Stage 1 - Temperature and conductivity requirements (for non-temperature-compensated conductivity measurements)

Temperature (°C)	Conductivity ( $\mu\text{S}\cdot\text{cm}^{-1}$ )
0	0.6
5	0.8
10	0.9
15	1.0
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

## Stage 2

- Transfer a sufficient amount of the water to be examined (100 ml or more) to a suitable container, and stir the test sample. Adjust the temperature, if necessary, and while maintaining it at  $25 \pm 1$  °C, begin vigorously agitating the test sample while periodically observing the conductivity. When the change in conductivity (due to uptake of atmospheric carbon dioxide) is less than  $0.1 \mu\text{S}\cdot\text{cm}^{-1}$  per 5 min, note the conductivity.
- If the conductivity is not greater than  $2.1 \mu\text{S}\cdot\text{cm}^{-1}$ , the water to be examined meets the requirements of the test for conductivity. If the conductivity is greater than  $2.1 \mu\text{S}\cdot\text{cm}^{-1}$ , proceed with stage 3.

## Stage 3

- Perform this test within approximately 5 min of the conductivity determination in step 5 under stage 2, while maintaining the sample temperature at  $25 \pm 1$  °C. Add a recently prepared saturated solution of *potassium chloride R* to the test sample (0.3 ml per 100 ml of the test sample), and determine the pH (2.2.3) to the nearest 0.1 pH unit.
- Using Table 1927-2, determine the conductivity limit at the measured pH value in step 6. If the measured conductivity in step 4 under stage 2 is not greater than the conductivity requirements for the pH determined, the water to be examined meets the requirements of the test for conductivity. If either the measured conductivity is greater than this value or the pH is outside the range of 5.0-7.0, the water to be examined does not meet the requirements of the test for conductivity.

In order to ensure the appropriate quality of the water, validated procedures and in-process monitoring of the electrical conductivity and regular microbial monitoring are applied.

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

Table 1927-2. – Stage 3 - pH and conductivity requirements (for atmosphere and temperature equilibrated samples)

pH	Conductivity ( $\mu\text{S}\cdot\text{cm}^{-1}$ )
5.0	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8	2.4
5.9	2.4
6.0	2.4
6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6

## 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<sub>3</sub>) 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.

#### 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<sub>2</sub>O *M<sub>r</sub>* 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 µS·cm<sup>-1</sup>.

**Conductometer:** resolution 0.1 µS·cm<sup>-1</sup> 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 µS·cm<sup>-1</sup>.

**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 (µS·cm <sup>-1</sup> )
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<sub>3</sub>) 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.