3.2.8. Sterile single-use plastic syringes

EUROPEAN PHARMACOPOEIA 6.0

Carry out a blank test using 20 ml of water for injections R. The difference between the titration volumes is not greater than 2.0 ml.

Extraneous particles. Fill the set via the normal inlet with a 0.1 g/1 solution of sodium lauryl sulfate R, previously filtered through a sintered-glass filter (16) (2.1.2) and heated to 37 °C. Collect the liquid via the normal outlet. When examined under suitable conditions of visibility, the liquid is clear and practically free from visible particles and filaments (it is assumed that particles and filaments with a diameter equal to or greater than 50 μm are visible to the naked eye).

Flow rate. Pass through a complete set with the flow regulator fully open 50 ml of a solution having a viscosity of 3 mPa·s (3 cP) (for example a 33 g/l solution of macrogol 4000 R at 20 °C) under a static head of 1 m. The time required for passage of 50 ml of the solution is not greater than 90 s.

Resistance to pressure. Make tight the extremities of the set and any air-inlet device. Connect the set to a compressed air outlet fitted with a pressure regulator. Immerse the set in a tank of water at 20 °C to 23 °C. Apply progressively an excess pressure of 100 kPa and maintain for 1 min. No air bubble escapes from the set.

Transparency. Use as reference suspension the primary opalescent suspension (2.2.1) diluted 1 in 8 for sets having tubing with an external diameter less than 5 mm and diluted 1 in 16 for sets having tubing with an external diameter of 5 mm or greater. Circulate the reference suspension through the set and compare with a set from the same batch filled 5 mm or greater. Circulate the reference suspension through tubing with an external diameter less than 5 mm and diluted air outlet fitted with a pressure regulator. Immerse the set 4000 R at 20 °C) under a static head of 1 m. The time required for passage of 50 ml of the solution is not greater than 90 s.

Residue on evaporation. Evaporate 50.0 ml of solution S to dryness on a water-bath and dry to constant mass in an oven at 100 °C to 105 °C. Carry out a blank test using 50.0 ml of water for injections R. The difference between the masses of the residues is not greater than 1.5 mg.

Sterility (2.6.1). The sets comply with the test for sterility. If the sets are stated to be sterile only internally, pass 50 ml of buffered sodium chloride-peptone solution pH 7.0 (2.6.12) through the set and use to carry out the test by the membrane-filtration method.

If the sets are stated to be sterile both internally and externally, open the package with the necessary aseptic precautions and:

- for the direct inoculation method, place the set or its components in a suitable container containing a sufficient quantity of the culture medium to ensure complete immersion;

- for the membrane filtration method, place the set or its components in a suitable container containing a sufficient quantity of buffered sodium chloride-peptone solution pH 7.0 (2.6.12) to allow total rinsing for 10 min.

Pyrogens (2.6.8). Connect together five sets and pass through the assembly at a flow rate not exceeding 10 ml/min 250 ml of a sterile, pyrogen-free 9 g/l solution of sodium chloride R. Collect the solution aseptically in a pyrogen-free container. The solution complies with the test for pyrogens. Inject 10 ml per kilogram of the rabbit’s mass.

LABELLING

The label states, where applicable, that the set has been sterilised using ethylene oxide.

3.2.8. STERILE SINGLE-USE PLASTIC SYRINGES

Sterile single-use plastic syringes are medical devices intended for immediate use for the administration of injectable preparations. They are supplied sterile and pyrogen-free and are not to be re-sterilised or re-used. They consist of a syringe barrel and a piston which may have an elastomer sealing ring; they may be fitted with a needle which may be non-detachable. Each syringe is presented with individual protection for maintaining sterility.

The barrel of the syringe is sufficiently transparent to permit dosages to be read without difficulty and allow air bubbles and foreign particles to be discerned.

The plastics and elastomer materials of which the barrel and piston are made comply with the appropriate specification or with the requirements of the competent authority. The most commonly used materials are polypropylene and polyethylene. The syringes comply with current standards regarding dimensions and performance.

Silicone oil (3.1.8) may be applied to the internal wall of the barrel to assist in the smooth operation of the syringe, but there remains no excess capable of contaminating the contents at the time of use.

The inks, glues and adhesives for the marking on the syringe or on the package and, where necessary, the assembly of the syringe and its package, do not migrate across the walls.

TESTS

Solution S. Prepare the solution in a manner that avoids contamination by foreign particles. Using a sufficient number of syringes to produce 50 ml of solution, fill the syringes to their nominal volume with water for injections R and maintain at 37 °C for 24 h. Combine the contents of the syringes in a suitable borosilicate-glass container.

Appearance of solution. Solution S is clear (2.2.1) and colourless (2.2.2, Method II) and is practically free from foreign solid particles.

Acidity or alkalinity. To 20 ml of solution S add 0.1 ml of bromothymol blue solution R1. Not more than 0.3 ml of 0.01 M sodium hydroxide or 0.01 M hydrochloric acid is required to change the colour of the indicator.

Absorbance (2.2.25). Measure the absorbance of solution S from 220 nm to 360 nm. The absorbance does not exceed 0.40.

Ethylene oxide. If the label states that ethylene oxide has been used for sterilisation, the content of ethylene oxide, determined by the method described below, is not greater than 10 ppm. Examine by gas chromatography (2.2.28).

The chromatographic procedure may be carried out using:

- a stainless steel column 1.5 m long and 6.4 mm in internal diameter packed with silanised diatomaceous earth for gas chromatography R impregnated with macrogol 1500 R (3 g per 10 g),

- helium for chromatography R as the carrier gas at a flow rate of 20 ml/min,

- a flame-ionisation detector,
maintaining the temperature of the column at 40 °C, that of the injector at 100 °C and that of the detector at 150 °C. Verify the absence of peaks interfering with the ethylene oxide peak, either by carrying out the test using an unsterilised syringe or using a different chromatographic system such as:

- a stainless-steel column 3 m long and 3.2 mm in internal diameter packed with silanised diatomaceous earth for gas chromatography R impregnated with trislyanoethoxypropane R (2 g per 10 g),

- helium for chromatography R as carrier gas at a flow rate of 20 ml/min,

- a flame-ionisation detector,

maintaining the temperature of the column at 60 °C, that of the injector at 100 °C and that of the detector at 150 °C.

**Ethylene oxide solution.** Prepare under a ventilated hood. Place 50.0 ml of dimethylacetamide R in a 50 ml vial, stopper, secure the stopper and weigh to the nearest 0.1 mg. Fill a 50 ml polyethylene or polypropylene syringe with gaseous ethylene oxide R, allow the gas to remain in contact with the syringe for about 3 min, empty the syringe and fill again with 50 ml of gaseous ethylene oxide R. Fit a hypodermic needle to the syringe and reduce the volume of gas in the syringe from 50 ml to 25 ml. Inject these 25 ml of ethylene oxide slowly into the vial, shaking gently and avoiding contact between the needle and the liquid. Weigh the vial again: the increase in mass is 45 mg to 60 mg and is used to calculate the exact concentration of the solution (about 1 g/l).

**Calibration curve.** In a series of seven vials of the same type as that used for the test and each containing 150 ml of dimethylacetamide R, place respectively 0 ml, 0.05 ml, 0.10 ml, 0.20 ml, 0.50 ml, 2.00 ml and 2.50 ml of the ethylene oxide solution, i.e. about 0 µg, 50 µg, 100 µg, 200 µg, 500 µg, 1000 µg and 2000 µg of ethylene oxide. Stopper the vials, secure the stoppers and place the vials in an oven at 70 ± 1 °C for 16 h. Inject 1 ml of the hot gas from each vial onto the column and draw a calibration curve from the heights of the peaks and the mass of ethylene oxide in each flask.

**Test.** Weigh the syringe after removing the package. Cut the syringe into pieces of maximum dimension 1 cm and place the pieces in a 250 ml to 500 ml vial containing 150 ml of dimethylacetamide R. Close the vial with a suitable stopper and secure the stopper. Place the vial in an oven at 70 ± 1 °C for 16 h. Remove 1 ml of the hot gas from the vial and inject it onto the column. From the calibration curve and the height of the peak obtained, calculate the mass of ethylene oxide in the vial.

**Silicone oil.** Calculate the internal surface area of a syringe in square centimetres using the expression:

\[
2\sqrt{V \cdot \pi \cdot h}
\]

*V* = nominal volume of the syringe, in cubic centimetres,

*h* = height of the graduation, in centimetres.

Take a sufficient number of syringes to give an internal surface area of 100 cm² to 200 cm². Aspirate into each syringe a volume of methylene chloride R equal to half the nominal volume and make up to the nominal volume with air. Rinse the internal surface corresponding to the nominal volume with the solvent by inverting the syringe ten times in succession with the needle fitting closed by a finger covered by a plastic film inert to methylene chloride. Expel the extracts into a tared dish and repeat the operation. Evaporate the combined extracts to dryness on a water-bath. Dry at 100 °C to 105 °C for 1 h. The residue weighs not more than 0.25 mg per square centimetre of internal surface area.

Examine the residue by infrared absorption spectrophotometry (2.2.4). It shows absorption bands typical of silicone oil at 805 cm⁻¹, 1020 cm⁻¹, 1095 cm⁻¹, 1260 cm⁻¹ and 2960 cm⁻¹.

**Reducing substances.** To 20.0 ml of solution S add 2 ml of sulphuric acid R and 20.0 ml of 0.002 M potassium permanganate. Boil for 3 min. Cool immediately. Add 1 g of potassium iodide R and titrate immediately with 0.01 M sodium thiosulphate using 0.25 ml of starch solution R as indicator. Carry out a blank titration using 20.0 ml of water for injections R. The difference between the titration volumes is not greater than 3.0 ml.

**Transparency.** Fill a syringe with water R (blank) and fill another with a 1 in 10 dilution of primary opalescence suspension (2.2.7). Use primary opalescent suspension that has been allowed to stand at 20 ± 2 °C for 24 h before use. Compare with the naked eye in diffused light against a dark background. The opalescence of the suspension is detectable when compared with the blank.

**Sterility (2.6.1).** Syringes stated to be sterile comply with the test for sterility carried out as follows. Use aseptic technique, open the package, withdraw the syringe, separate the components and place each in a suitable container containing sufficient culture media to cover the part completely. Use both the recommended media (2.6.1).

**Syringes stated to be sterile only internally comply with the test for sterility carried out as follows.** Use 50 ml of inoculation medium for each test syringe. Using aseptic technique, remove the needle protector and submerge the needle in the culture medium. Flush the syringe five times by withdrawing the plunger to its fullest extent.

**Pyrogens (2.6.8).** Syringes with a nominal volume equal to or greater than 15 ml comply with the test for pyrogens. Fill a minimum of three syringes to their nominal volume with a pyrogen-free 9 g/l solution of sodium chloride R and maintain at a temperature of 37 °C for 2 h. Combine the solutions aseptically in a pyrogen-free container and carry out the test immediately using for each rabbit 10 ml of the solution per kilogram of body mass.

**LABELLING**

The label on the package states:

- the batch number,
- a description of the syringe,
- that the syringe is for single-use only.

The label on the outer package states:

- the method of sterilisation,
- that the syringe is sterile or that it is sterile only internally,
- the identity of the manufacturer,
- that the syringe is not to be used if the packaging is damaged or the sterility protector is loose.