Silicone oil. Calculate the internal surface area of a syringe in square centimetres using the following 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 cm^2 to 200 cm^2. 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 100-105 °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 (*2.2.24*). 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 *sulfuric 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 thiosulfate* 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 opalescent suspension (*2.2.1*). 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.* Using 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. Inject per kilogram of the rabbit's mass 10 mL of the solution.

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.

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3.2.9. RUBBER CLOSURES FOR CONTAINERS FOR AQUEOUS PARENTERAL PREPARATIONS, FOR POWDERS AND FOR FREEZE-DRIED POWDERS

Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders are made of materials obtained by vulcanisation (cross-linking) of macromolecular organic substances (elastomers), with appropriate additives. The specification also applies to closures for containers for powders and freeze-dried products to be dissolved in water immediately before use. The specification does not apply to closures made from silicone elastomer (which are dealt with in *3.1.9. Silicone elastomer for closures and tubing*), to laminated closures or to lacquered closures. The elastomers are produced from natural or synthetic substances by polymerisation, polyaddition or polycondensation. The nature of the principal components and of the various additives (for example vulcanisers, accelerators, stabilisers, pigments) depends on the properties required for the finished article.

Rubber closures may be classified in 2 types: type I closures are those which meet the strictest requirements and which are to be preferred; type II closures are those which, having mechanical properties suitable for special uses (for example, multiple piercing), cannot meet requirements as severe as those for the first category because of their chemical composition.

The closures chosen for use with a particular preparation are such that:

- the components of the preparation in contact with the closure are not adsorbed onto the surface of the closure and do not migrate into or through the closure to an extent sufficient to affect the preparation adversely,
- the closure does not yield to the preparation substances in quantities sufficient to affect its stability or to present a risk of toxicity.

The closures are compatible with the preparation for which they are used throughout its period of validity.

The manufacturer of the preparation must obtain from the supplier an assurance that the composition of the closure does not vary and that it is identical to that of the closure used during compatibility testing. When the supplier informs the manufacturer of the preparation of changes in the composition, compatibility testing must be repeated, totally or partly, depending on the nature of the changes.

The closures are washed and may be sterilised before use.

CHARACTERS

Rubber closures are elastic; they are translucent or opaque and have no characteristic colour, the latter depending on the additives used. They are practically insoluble in tetrahydrofuran, in which, however, a considerable reversible swelling may occur. They are homogeneous and practically free from flash and adventitious materials (for example fibres, foreign particles, waste rubber).

Identification of the type of rubber used for the closures is not within the scope of this specification. The identification test given below distinguishes elastomer and non-elastomer closures but does not differentiate the various types of rubber. Other identity tests may be carried out with the aim of detecting differences in a batch compared to the closures used for compatibility testing. One or more of the following analytical methods may be applied for this purpose:

determination of relative density, determination of sulfated ash, determination of sulfur content, thin-layer chromatography carried out on an extract, ultraviolet absorption spectrophotometry of an extract, infrared absorption spectrophotometry of a pyrolysate.

IDENTIFICATION

A. The elasticity is such that a strip of material with a cross-section of 1 mm^2 to 5 mm^2 can be stretched by hand to at least twice its original length. Having been stretched to twice its length for 1 min, it contracts to less than 1.2 times its original length within 30 s.

B. Heat 1 g to 2 g in a heat-resistant test-tube over an open flame to dry the sample and continue heating until pyrolysate vapours are condensed near the top edge of the test-tube. Deposit a few drops of the pyrolysate on a potassium bromide disc and examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with the type sample.

C. The total ash (*2.4.16*) is within ± 10 per cent of the result obtained with the type sample.

TESTS

The samples to be analysed may be washed and sterilised before use.

Solution S. Introduce a number of uncut closures corresponding to a surface area of about 100 cm^2 in a suitable glass container, cover with *water for injections R*, boil for 5 min and rinse 5 times with cold *water for injections R*. Place the washed closures in a wide-necked flask (glass type I, *3.2.1*), add 200 mL of *water for injections R* and weigh. Cover the mouth of the flask with a borosilicate-glass beaker. Heat in an autoclave so that a temperature of 121 ± 2 °C is reached within 20 min to 30 min and maintain at this temperature for 30 min. Cool to room temperature over about 30 min. Make up to the original mass with *water for injections R*. Shake and immediately separate the solution from the rubber by decantation. Shake solution S before each test

Blank. Prepare a blank in the same manner using 200 mL of *water for injections R*.

Appearance of solution. Solution S is not more opalescent than reference suspension II for type I closures and is not more opalescent than reference suspension III for type II closures (*2.2.1*). Solution S is not more intensely coloured than reference solution GY_5 (*2.2.2, Method II*).

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 0.8 mL of *0.01 M hydrochloric acid* is required to obtain either a blue or a yellow colour, respectively.

Absorbance. *Carry out the test within 5 h of preparation of solution S.* Filter solution S on a membrane filter having approximately 0.45 µm pores rejecting the first few millilitres of filtrate. Measure the absorbance (*2.2.25*) of the filtrate at wavelengths from 220 nm to 360 nm using the blank (see solution S) as compensation liquid. At these wavelengths, the absorbance does not exceed 0.2 for type I closures or 4.0 for type II closures. If necessary, dilute the filtrate before measurement of the absorbance and correct the result for the dilution.

Reducing substances. *Carry out the test within 4 h of preparation of solution S.* To 20.0 mL of solution S add 1 mL of *dilute sulfuric acid R* and 20.0 mL of *0.002 M potassium permanganate*. Boil for 3 min. Cool. Add 1 g of *potassium iodide R* and titrate immediately with *0.01 M sodium thiosulfate*, using 0.25 mL of *starch solution R* as indicator. Carry out a titration using 20.0 mL of the blank. The difference between the titration volumes is not greater than 3.0 mL for type I closures and 7.0 mL for type II closures.

Ammonium (*2.4.1*): maximum 2 ppm.

Dilute 5 mL of solution S to 14 mL with *water R*. The solution complies with limit test A.

Extractable zinc: maximum of 5 µg of extractable Zn per millilitre of solution S.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution. Dilute 10.0 mL of solution S to 100 mL with *0.1 M hydrochloric acid*.

Reference solutions. Prepare the reference solutions using *zinc standard solution (10 ppm Zn) R* diluted with *0.1 M hydrochloric acid*.

Source: zinc hollow-cathode lamp.

Wavelength: 213.9 nm.

Flame: air-acetylene.

Extractable heavy metals (*2.4.8*): maximum 2 ppm.

Solution S complies with limit test A. Prepare the standard using *lead standard solution (2 ppm Pb) R*.

Residue on evaporation. Evaporate 50.0 mL of solution S to dryness on a water-bath and dry at 100 °C to 105 °C. The residue weighs not more than 2.0 mg for type I rubber and not more than 4.0 mg for type II rubber.

Volatile sulfides. Place closures, cut if necessary, with a total surface area of 20 ± 2 cm^2 in a 100 mL conical flask and add 50 mL of a 20 g/L solution of *citric acid R*. Place a piece of *lead acetate paper R* over the mouth of the flask and maintain the paper in position by placing over it an inverted weighing bottle. Heat in an autoclave at 121 ± 2 °C for 30 min. Any black stain on the paper is not more intense than that of a standard prepared at the same time in the same manner using 0.154 mg of *sodium sulfide R* and 50 mL of a 20 g/L solution of *citric acid R*.

For the tests for penetrability, fragmentation and self-sealing, use the closures treated as described for the preparation of solution S and allowed to dry.

Penetrability. For closures intended to be pierced by a hypodermic needle, carry out the following test. Fill 10 suitable vials to the nominal volume with *water R*, fit the closures to be examined and secure with a cap. Using for each closure a new, lubricated long-bevel(1) (bevel angle 12 ± 2°) hypodermic needle with an external diameter of 0.8 mm, pierce the closures with the needle perpendicular to the surface. The force required for piercing, determined with an accuracy of ± 0.25 N (25 gf), is not greater than 10 N (1 kgf) for each closure.

Fragmentation. For closures intended to be pierced by a hypodermic needle, carry out the following test. If the closures are to be used for aqueous preparations, place in 12 clean vials a volume of *water R* corresponding to the nominal volume minus 4 mL, close the vials with the closures to be examined, secure with a cap and allow to stand for 16 h. If the closures are to be used with dry preparations, close 12 clean vials with the closures to be examined. Using a lubricated long-bevel(1) (bevel angle 12 ± 2°) hypodermic needle with an external diameter of 0.8 mm fitted to a clean syringe, inject into the vial 1 mL of *water R* and remove 1 mL of air; carry out this operation 4 times for each closure, piercing each time at a different site. Use a new needle for each closure and check that the needle is not blunted during the test. Pass the liquid in the vials through a filter having approximately 0.5 µm pores. Count the fragments of rubber visible to the naked eye. The total number of fragments does not exceed 5. This limit is based on the assumption that fragments with a diameter equal to or greater than 50 µm are visible to the naked eye; in cases of doubt or dispute, the fragments are examined with a microscope to verify their nature and size.

Self-sealing test. For closures intended to be used with multidose containers, carry out the following test. Fill 10 suitable vials to the nominal volume with *water R*, fit the closures to be examined and secure with a cap. Using for each

(1) See ISO 7864 "Sterile hypodermic needles for single use".

closure a new hypodermic needle with an external diameter of 0.8 mm, pierce each closure 10 times, piercing each time at a different site. Immerse the vials upright in a 1 g/L solution of *methylene blue R* and reduce the external pressure by 27 kPa for 10 min. Restore atmospheric pressure and leave the vials immersed for 30 min. Rinse the outside of the vials. None of the vials contains any trace of coloured solution.