INTERNATIONAL STANDARD

ISO 4802-1

Second edition
2010-04-01

Glassware — Hydrolytic resistance of the interior surfaces of glass containers —

Part 1: Determination by titration method and classification

Verrerie — Résistance hydrolytique des surfaces internes des récipients en verre —

Partie 1: Détermination par analyse titrimétrique et classification

Reference number
ISO 4802-1:2010(E)

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 4802-1 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection equipment for medical and pharmaceutical use*.

This second edition cancels and replaces the first edition (ISO 4802-1:1988), which has been technically revised.

ISO 4802 consists of the following parts, under the general title *Glassware — Hydrolytic resistance of the interior surfaces of glass containers*:

— *Part 1: Determination by titration method and classification*

— *Part 2: Determination by flame spectrometry and classification*

Introduction

This part of ISO 4802 is largely based on a method of test approved by the International Commission on Glass (ICG), Technical Committee 2, *Chemical Durability and Analysis,* for measuring the hydrolytic resistance of the interior surfaces of glass containers.

The European Pharmacopoeia Commission has adopted the principle of the determination by titration and has set up a classification for glass containers for injectable preparations which is now included in this part of ISO 4802. In addition, this part of ISO 4802 contains a classification of containers other than for injectable preparations.

According to many results of international interlaboratory tests this part of ISO 4802 specifies the test conditions in more detail than the European Pharmacopoeia in order to increase the reproducibility of the test results. In particular, the autoclaving cycle is described in detail. The principle of the test method described in this part of ISO 4802 is, however, in full compliance with the corresponding test method of the European Pharmacopeia[11].

Glassware — Hydrolytic resistance of the interior surfaces of glass containers —

Part 1:
Determination by titration method and classification

1 Scope

This part of ISO 4802 specifies:

a) a method for determining the hydrolytic resistance of the interior surfaces of glass containers when subjected to attack by water at 121 °C ± 1 °C for 60 min ± 1 min. The resistance is measured by titration of a known aliquot portion of the extraction solution produced with hydrochloric acid solution, in which case the resistance is inversely proportional to the volume of acid required;

b) a classification of glass containers according to the hydrolytic resistance of the interior surfaces determined by the methods specified in this part of ISO 4802.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 385, *Laboratory glassware — Burettes*

ISO 648, *Laboratory glassware — Single-volume pipettes*

ISO 719, *Glass — Hydrolytic resistance of glass grains at 98 °C — Method of test and classification*

ISO 720, *Glass — Hydrolytic resistance of glass grains at 121 °C — Method of test and classification*

ISO 1773, *Laboratory glassware — Narrow-necked boiling flasks*

ISO 3696, *Water for analytical laboratory use — Specification and test methods*

ISO 3819, *Laboratory glassware — Beakers*

ISO 9187-1, *Injection equipment for medical use — Part 1: Ampoules for injectables*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
ampoule
small, normally flat-bottomed container having stems in many different forms

NOTE Ampoules are thin-walled and have a capacity normally up to 30 ml. They are intended to be closed, after filling, by flame sealing.

3.2
bottle
flat-bottomed container, made from moulded glass

NOTE Bottles are normally thick-walled and have a capacity usually of more than 50 ml. They may be of circular or other geometric cross-section. Bottles are sealed with a closure made from a material other than glass, and not by flame-sealing.

3.3
brimful capacity
volume of water required to fill a container, placed on a flat, horizontal surface

3.4
container
article made from glass to be used as primary packaging material intended to come into direct contact with the pharmaceutical preparations

EXAMPLE Bottles, vials, syringes, ampoules and cartridges. See also Figure 1.

NOTE These containers are made from borosilicate or soda-lime-silica glass.

3.5
filling volume
defined volume of water to fill the test specimen

NOTE For the determination of the filling volume, see 7.2. The filling volume is a test-specific quantity that is used to compare container sets from different sources or lots. It has no relation to the nominal product volume.

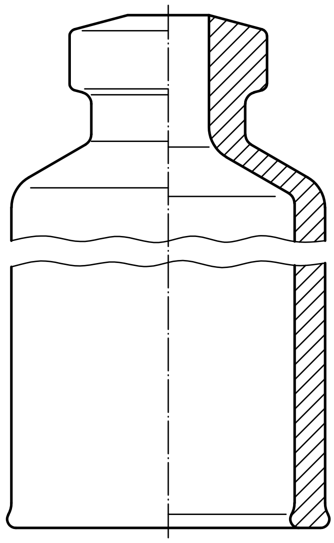
3.6
borosilicate glass
silicate glass having a very high hydrolytic resistance due to its composition, containing significant amounts of boric oxide

NOTE 1 Borosilicate glass contains a mass fraction of boric oxide usually between 5 % and 13 %. This glass type may also contain aluminium oxide and/or alkaline earth oxides.

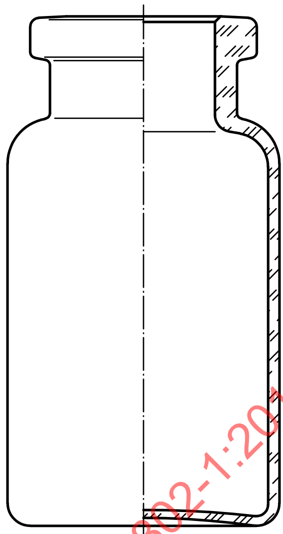
NOTE 2 Neutral glass is a borosilicate glass having a very high hydrolytic resistance and a high thermal shock resistance. When tested in accordance with ISO 720 it meets the requirements of class HGA 1. Containers properly made from this glass comply with hydrolytic resistance container class HC_T 1 of this part of ISO 4802.

3.7
soda-lime-silica glass
silicate glass containing a mass fraction up to approximately 15 % of alkali metal oxides – mainly sodium oxide – and a mass fraction up to about 15 % of alkaline earth oxides, mainly calcium oxide

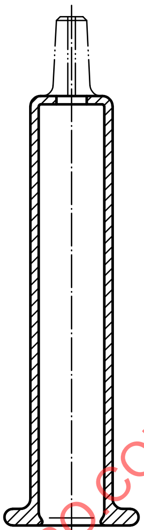
NOTE Containers made from this glass have a moderate hydrolytic resistance due to the chemical composition of the glass, and comply with hydrolytic resistance container class HC_T 3.



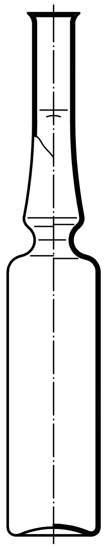
a) **Example of a glass cylinder for pen–injectors** (see ISO 13926-1)



b) **Example of an injection vial made of glass tubing** (see ISO 8362-1)



c) **Example of a glass barrel** (see ISO 11040-4)



d) **Example of a stem cut ampoule with constriction** (see ISO 9187-1)

Figure 1 — Examples of containers

3.8
surface treatment
treatment of the internal surface of glass containers with reagents in order to achieve a de-alkalized surface and to produce a significantly lower release of alkali metal ions (and alkali earth metal ions)

NOTE Surface treatment is used, for example, in order to change a soda-lime-silica glass container of hydrolytic resistance class HC_T 3 to a container of hydrolytic resistance class HC_T 2 container. Treated containers are rinsed before use.

3.9
vial
small, flat-bottomed container, made from tubing or from moulded glass

NOTE Vials are normally thick-walled and have a capacity up to 100 ml. They are normally sealed with a closure made from a material other than glass, and not by flame-sealing.

4 Principle

This method of test is a surface test applied to glass containers as produced and/or as delivered.

The containers to be tested are filled with specified water to a specified capacity. They are loosely capped and then heated under specified conditions. The degree of the hydrolytic attack is measured by titration of the extraction solutions.

5 Reagents

During the test, unless otherwise stated, use only reagents of recognised analytical grade.

5.1 Test water, complying with the requirements specified in ISO 3696 for Grade 2 water or better.

The test water can be produced, e.g. by double distillation or reverse osmosis.

Such test water can normally be stored for 24 h in a stoppered flask without change of the pH value. In case of longer storage, the water shall be freed from dissolved gases, such as carbon dioxide, by boiling for at least 15 min in a boiling flask of fused silica or borosilicate glass. The boiling flask shall be pretreated once as specified in 8.3 before it is used for the first time.

Performed correctly and tested immediately before use, this test water will produce an orange-red (not a violent-red or yellow) colour when four drops of the methyl red indicator solution (5.5) are added to 50 ml of the test water. This is the neutral point of methyl red corresponding to pH 5,5 ± 0,1.

The water, so coloured, may also be used as the reference solution (see 8.4).

5.2 Hydrochloric acid, standard volumetric solution, $c(\mathrm{HCl}) = 0{,}01$ mol/l.

5.3 Hydrochloric acid, solution, $c(\mathrm{HCl}) \approx 2$ mol/l.

5.4 Hydrofluoric acid, $c(\mathrm{HF}) \approx 22$ mol/l (i.e. ≈ 400 g HF/l solution).

5.5 Methyl red, indicator solution.

Dissolve 25 mg of the sodium solution salt of methyl red ($C_{15}H_{14}N_3NaO_2$) in 100 ml of the test water (5.1).

5.6 Distilled water or **water of equivalent purity** (grade 3 water complying with the requirements specified in ISO 3696).

6 Apparatus

Ordinary laboratory apparatus and those specified in 6.1 to 6.6.

6.1 Autoclave or **steam sterilizer**, capable of withstanding a pressure of at least 250 kPa (2,5 bar) and of carrying out the heating cycle specified in 8.3. It shall be capable of maintaining a temperature of (121 ± 1) °C, equipped with a calibrated thermometer or a calibrated thermocouple recorder, a pressure gauge and a vent-cock.

When necessary and appropriate, the autoclave vessel and ancillary equipment shall be thoroughly cleaned before use using the test water (5.1) in order to avoid contamination that can influence the test results.

6.2 Burettes, having a suitable capacity of 50 ml, 25 ml, 10 ml or 2 ml, complying with the requirements specified for class A burettes in ISO 385 and made of glass of hydrolytic resistance grain class HGA 1 as specified in ISO 720[1)] or ISO 719.

The capacity of the burettes shall be chosen according to the expected consumption of hydrochloric acid (5.2).

6.3 Conical flasks, having a capacity of 100 ml and 250 ml and complying with the requirements of ISO 1773.

Before its first use, each new flask shall be pretreated by subjecting it to the autoclaving conditions described in 8.3.

IMPORTANT — If it is intended to use these flasks for other purposes, before being re-used in accordance with this part of ISO 4802, the flasks shall be properly cleaned (e.g. by treatment with hydrochloric acid and/or by autoclave cleaning).

6.4 Pipettes, having a suitable capacity and complying with the requirements specified for class A pipettes described in ISO 648.

6.5 Water bath, capable of being heated to approximately 80 °C.

6.6 Beakers, having a suitable capacity and complying with the requirements specified in ISO 3819.

Before use, each new beaker shall be pretreated by subjecting it to the autoclaving conditions described in 8.3.

7 Sample preparation

7.1 Sample size

The number of containers to be tested depends on the capacity of the container, the volume of extraction solution necessary for one titration and the number of titration results required. It shall be calculated according to the requirements given in Table 1.

Table 1 — Number of containers for the determination of the hydrolytic resistance by titration

Capacity of container [volume corresponding to filling volume (see 7.2)] ml	**Minimum number of containers for one titration**	**Volume of extraction solution for one titration** ml	**Number of titrations**
$\leqslant 3$	10	25,0	1
$> 3 \leqslant 30$	5	50,0	2
$> 30 \leqslant 100$	3	100,0	2
> 100	1	100,0	3

1) Glass of hydrolytic resistance grain class ISO 719-HGB 1 adequately meets the requirements of class HGA 1 specified in ISO 720.

7.2 Determination of the filling volume

7.2.1 Flat-bottomed containers ⩽ 20 mm bore diameter (except ampoules, syringes and cartridges)

Select six containers (having a capacity ⩽ 100 ml) or three containers (having a capacity > 100 ml) at random from the sample lot and remove any dirt or packaging debris by shaking the containers. Allow the dry containers to reach room temperature. Weigh each of the empty containers to the nearest 0,01 g for containers having a nominal volume ⩽ 30 ml, and to the nearest 0,1 g for containers having a nominal volume > 30 ml. Place the containers on a horizontal surface and fill them nearly to the top with distilled water (5.6), avoiding overflow and introduction of air bubbles. Adjust the liquid levels to the brimful line using distilled water (5.6).The meniscus shall be equal to the upper edge of the bore.

Weigh the filled container to the nearest 0,01 g for containers having a nominal volume ⩽ 30 ml, and to the nearest 0,1 g for containers having a nominal volume > 30 ml. Calculate the mass of water, in grams, contained within the container.

Calculate the mean value of the results from six containers and express the result in millilitres of water; this value is the mean brimful capacity of the containers.

Calculate 90 % of this mean brimful capacity to one decimal place. This volume is the filling volume for the particular sample lot.

7.2.2 Flat-bottomed containers > 20 mm bore diameter

Proceed as described in 7.2.1 but cover each container with a strike-plate (for measuring the brimful capacity of small and other bottles). The strike-plate shall be made of rigid, inert, transparent material of any convenient shape, but with a central hole approximately 5 mm in diameter. The strike-plate shall be large enough to fit snugly on and completely cover the sealing surface of the container for which the brimful capacity is to be measured.

Calculate 90 % of this mean brimful capacity to one decimal place. This volume is the filling volume for the particular sample lot.

7.2.3 Round-bottomed containers

Select six containers (having a capacity ⩽ 100 ml) or three containers (having a capacity > 100 ml) at random from the sample lot and remove any dirt or packaging debris by shaking the containers. Allow the dry containers to reach room temperature. Fix each container vertically in an appropriate device and determine the brimful capacity in accordance with 7.2.1.

Then calculate 90 % of the mean brimful capacity to one decimal place. This volume is the filling volume for the particular sample lot.

7.2.4 Lipped containers

Wrap adhesive plastic tape around the rim of the containers such that the tape around the lip is level with the rim. Weigh the container, then fill and reweigh as described in 7.2.1.

7.2.5 Ampoules

Place at least six dry ampoules on a flat, horizontal surface and fill them with distilled water (5.6), at room temperature, from a burette (6.2), until the meniscus of the water reaches h_6 of ISO 9187-1, where the body of the ampoules declines to the shoulder (see Figure 2). Read the capacities to two decimal places and calculate the mean value.

This volume, expressed to one decimal place, is the filling volume and shall be filled in all ampoules of the same lot.

7.2.6 Syringes and cartridges

Select six syringes or cartridges. Close the small opening (mouth of cartridges and needle and/or Luer cone of syringes) using an inert material (e.g. Tip Cap). Determine the mean brimful volume in accordance with 7.2.1.

Then calculate 90 % of the mean brimful capacity to one decimal place. This volume is the filling volume.

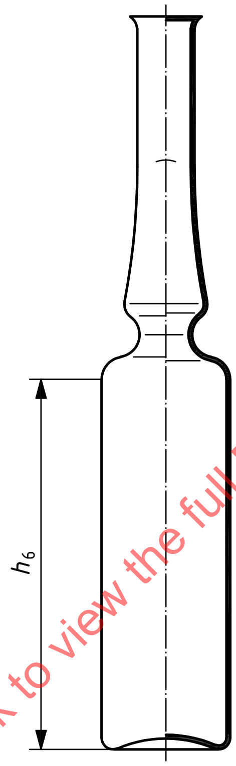


Figure 2 — Filling volume of ampoules (up to h_6)

8 Procedure

8.1 General

This procedure shall be completed within one working day.

8.2 Cleaning of samples

The following cleaning process for each container shall be completed within 30 min.

Remove from all open samples any packaging debris or dirt which has collected during storage and transport. Rinse each sample thoroughly at least twice with the distilled water (5.6) at ambient temperature, then allow to stand, filled with the distilled water. Immediately before testing, empty the samples, rinse once with distilled water and then once with the test water (5.1).

Closed ampoules shall not be rinsed before testing.

NOTE For opening by flame, closed ampoules can be warmed, e.g., in a water bath or air-oven at about 40 °C for approximately 2 min before opening, or cut and broken at the height of the sealing point.

8.3 Filling and heating

Fill each container, selected for the sample size in accordance with 7.1 and cleaned in accordance with 8.2, to the filling volume with the test water (5.1) by means of suitable volumetric measuring devices.

Each container, including ampoules, shall be loosely capped with an inert material, for example with inverted beakers (6.6) of such a size that the bottoms of the beakers fit snugly down on the rims of the sample. Ampoules capped with clean aluminium foil is another example. Syringes and cartridges shall be placed in a beaker and the beaker shall be covered with clean aluminium foil.

Ensure that the foil does not release measurable ions into the test water.

Place the samples, gathered in groups in Petri dishes or in the beaker, on the rack in the autoclave (6.1), containing distilled water (5.6) at ambient temperature, and ensure that they are held above the level of the water in the vessel.

Insert the end of a calibrated thermal device in a filled container through a hole of approximately the diameter of the thermocouple and connect it to an external measuring device. If the container is too small to insert a thermocouple, apply a thermocouple in a suitable, similar container. Close the autoclave door or lid securely but leave the vent-cock open. Start automatic recording of the temperature versus time and heat the autoclave at a regular rate such that steam issues vigorously from the vent-cock after 20 min to 30 min, and maintain a vigorous evolution of steam for a further 10 min. Close the vent-cock and raise the temperature from 100 °C to 121 °C at a rate of 1 °C/min within 20 min to 22 min. Maintain the temperature at (121 ± 1) °C for (60 ± 1) min from the time when the holding temperature is reached. Cool down to 100 °C at a rate of 0,5 °C/min, venting to prevent formation of a vacuum, within 40 min to 44 min.

NOTE 1 For autoclaves using a steam generator it is not necessary to maintain the temperature for 10 min at 100 °C.

CAUTION — For security reasons (boiling retardation) do not open the autoclave before the water in the containers has reached a temperature of 95 °C.

NOTE 2 Experience has shown that the rate of heating to 121 °C, the holding temperature of (121 ± 1) °C and the rate of cooling to 100 °C are critical. Deviations from the specified conditions can produce variable results to the extent of invalidating them.

Remove the hot samples from the autoclave and cool to room temperature within 30 min. Start the titration after cooling. Special care shall be taken in cooling down large capacity containers as thermal drops larger than 40 °C may cause the fracture of the glass by thermal shock.

8.4 Analysis of the extraction solutions

Combine the extraction solutions of the containers in accordance with column 2 of Table 1. When emptying small stemmed ampoules the extraction solution might be partly neutralized by absorbing carbon dioxide (CO_2) from the atmosphere. To obviate this, invert the ampoules and heat the bases gently with a cool flame. In the case of combined extraction solutions from containers having a capacity $\leqslant$ 3 ml, pipette a volume of 25,0 ml (see column 3 of Table 1) into a conical flask (6.3) having a capacity of 100 ml. In the case of combined extraction solutions from containers having larger capacities, pipette the required volumes (see column 3 of Table 1) into separate conical flasks (6.3) of suitable capacity.

Prepare reference solutions (blank) by pipetting volumes of the test water (5.1), equivalent to those taken from the extraction solutions, into conical flasks (6.3) having a capacity commensurate with the size of the containers being tested. Add two drops of methyl red indicator solution (5.5) for each 25 ml of test water (5.1) and titrate the blank solution with hydrochloric acid (5.2) until a clearly visible colour change occurs.

Add two drops of methyl red indicator solution (5.5) to each flask for each 25 ml of extraction solution and titrate with hydrochloric acid (5.2) until the colour matches exactly that of the coloured reference solution.

Titration values of less than 1,0 ml shall be expressed to two decimal places, titration values greater than or equal to 1,0 ml to one decimal place.

NOTE Automatic titration equipment giving results with the same or better accuracy may also be used, provided they are properly calibrated.

8.5 Testing to determine whether the containers have been surface treated

NOTE The hydrolytic resistance of the interior surface of vials and bottles made from soda-lime-silica glass can be considerably increased by treating these surfaces during the course of production. Ampoules made from borosilicate glass tubing are not normally subjected to an internal surface treatment because their high chemical resistance is dependent upon the chemical composition of the glass as a material (see Clause 3).

If it is necessary to determine whether or not a container has been surface-treated, the sample previously tested shall be used.

Fill the samples with a mixture of one volume of hydrofluoric acid (5.4) and nine volumes of hydrochloric acid (5.3) to the brimful point. Allow the filled samples to stand at ambient temperature for 10 min, then empty the solution very carefully. Rinse the samples three times with distilled water (5.6), then at least twice with test water (5.1). Then test the samples as specified in 8.3 and 8.4.

CAUTION — Hydrofluoric acid is extremely aggressive. Even tiny quantities can cause life-threatening injuries.

If the results are considerably higher than those obtained from the original surfaces (about five to ten times), the samples shall be considered to have been surface-treated.

9 Expression of results

9.1 Calculation

Calculate the mean value of the titration results and express it in millilitres of hydrochloric acid solution (5.2) per 100 ml of the extraction solution. The blank value (see 8.4) shall be considered.

9.2 Classification

The containers shall be classified as shown in Table 2, according to the consumption of hydrochloric acid solution (5.2), when tested as specified in 8.4 and calculated according to 9.1.

9.3 Distinction between containers of hydrolytic resistance container class HC_T 1 and hydrolytic resistance container class HC_T 2

After etching and re-testing in accordance with 8.5, containers of hydrolytic resistance container class HC_T 1 shall satisfy the requirements for hydrolytic resistance container classes HC_T 1 and HC_T 2 in Table 2.

After etching and re-testing in accordance with 8.5, containers of hydrolytic resistance container class HC_T 2 shall produce values that are significantly greater than those given in column 2 of Table 2 and which are much closer to those values for hydrolytic resistance container class HC_T 3 in Table 2.

Table 2 — Maximum values in the hydrolytic resistance container surface test (titration method)

Capacity of container [volume corresponding to the filling volume (see 7.2)] ml	**Maximum values for the consumption of hydrochloric acid solution** [c(HCL) = 0,01 mol/l] **(5.2) per** 100 ml **of the extraction solution,** mol/100 ml			
	Classes HC_T 1 and HC_T 2	Class HC_T 3	Class HC_T B	Class HC_T D
⩽ 1	2,0	20,0	4,0	32,0
> 1 ⩽ 2	1,8	17,6	3,6	28,0
> 2 ⩽ 3	1,6	16,1	3,2	25,7
> 3 ⩽ 5	1,3	13,2	2,6	21,0
> 5 ⩽ 10	1,0	10,2	2,0	17,0
> 10 ⩽ 20	0,80	8,1	1,6	13,5
> 20 ⩽ 50	0,60	6,1	1,2	9,8
> 50 ⩽ 100	0,50	4,8	1,0	7,8
> 100 ⩽ 200	0,40	3,8	0,80	6,2
> 200 ⩽ 500	0,30	2,9	0,60	4,6
> 500	0,20	2,2	0,40	3,6

9.4 Designation

The hydrolytic resistance of the interior surface of glass containers measured in accordance with this part of ISO 4802 shall be designated as follows:

EXAMPLE The designation for a 9 ml capacity container with a consumption of 1,6 ml of hydrochloric solution [c(HCL) = 0,01 mol/l] per 100 ml extraction solution shall be:

Glass, hydrolytic resistance container class ISO 4802-HC_T B

10 Test report

The test report shall include the following information:

a) a reference to this part of ISO 4802, i.e. ISO 4802-1:2010;

b) an identification of the samples;

c) mean brimful capacity of samples (except ampoules);

d) the filling volume of the samples;

e) the number of samples used for one titration;

f) the mean value of the titrations;

g) hydrolytic resistance container class HC_T (designation of the container tested);

h) for hydrolytic resistance container class HC_T 2, a statement whether the test has been repeated after etching of the surface (see 8.5) and the results obtained;

i) a statement whether closed ampoules were tested;

j) any unusual features noted during the determination.

