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

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

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

*Partie 1: Détermination par analyse titrimétrique et classification*

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see [www.iso.org/directives](http://www.iso.org/directives)).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see [www.iso.org/patents](http://www.iso.org/patents)).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: [www.iso.org/iso/foreword.html](http://www.iso.org/iso/foreword.html).

The committee responsible for this document is ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

This third edition cancels and replaces the second edition (ISO 4802-1:2010), which has been technically revised in particular by amending

- the subclauses on water (test water and purified water),
- the test procedure, and
- the subclause on autoclave and steam sterilizer respectively.

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.

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# 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  $121\text{ °C} \pm 1\text{ °C}$  for  $60\text{ min} \pm 1\text{ min}$ . 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 documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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 degrees C — Method of test and classification*

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

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

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 1 to entry: Ampoules are usually 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 1 to entry: Bottles are normally thick-walled and have a capacity usually of more than 5 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 1 to entry: 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 1 to entry: 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

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Note 1 to entry: Borosilicate glass contains a mass fraction of boric oxide usually between 5 % and 13 %. This glass type can also contain aluminium oxide and/or alkaline earth oxides.

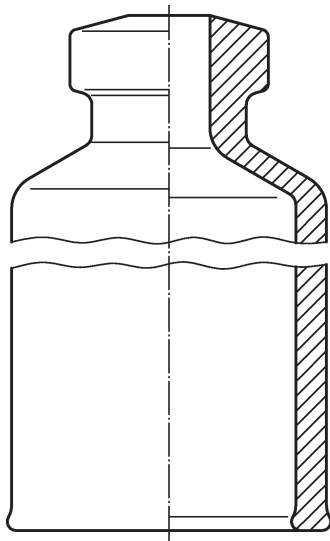
Note 2 to entry: Neutral glass is a borosilicate glass having a very high hydrolytic resistance and a high thermal shock resistance. When tested in accordance with ISO 720, it meets the requirements of class HGA 1. Containers properly made from this glass comply with hydrolytic resistance container class HC<sub>T</sub> 1 of this part of ISO 4802.

**3.7  
soda-lime-silica glass**

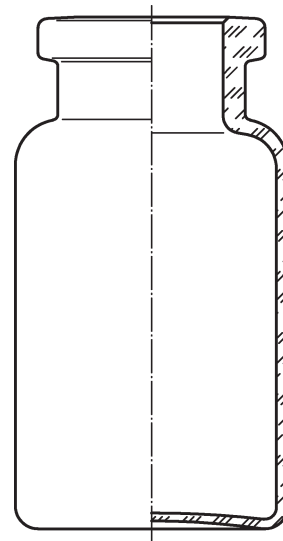
silicate glass containing a mass fraction up to approximately 15 % of alkali metal oxides – mainly sodium oxide – and a mass fraction up to about 15 % of alkaline earth oxides, mainly calcium oxide

Note 1 to entry: 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<sub>T</sub> 3.

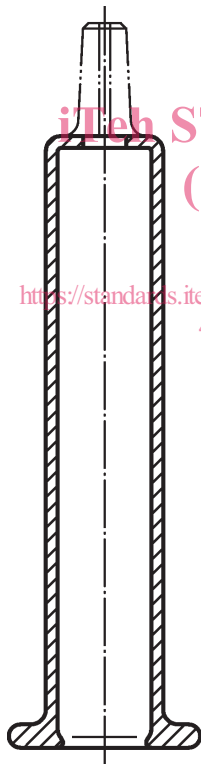




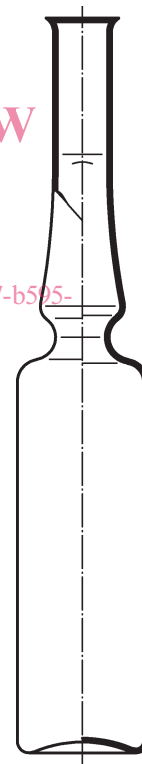
a) Example of a glass cylinder for pen-injectors  
(see ISO 13926-1)



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)

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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 1 to entry: Surface treatment is used, for example, in order to change a soda-lime-silica glass container of hydrolytic resistance class HC<sub>T</sub> 3 to a container of hydrolytic resistance class HC<sub>T</sub> 2 container. Treated containers are rinsed before use.

### 3.9 vial

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

Note 1 to entry: 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

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

### 5.1 Test water, to be prepared as follows: [SIST ISO 4802-1:2018](https://standards.iteh.ai/catalog/standards/sist/eb8d30b7-5a6a-4c57-b595-40c5edc12817/sist-4802-1-2016)

Prepare the test water from distilled water (5.6) by multiple distillations. Remove the carbon dioxide by boiling for at least 15 min before use in a boiling flask (6.3) of fused silica or borosilicate glass and cool.

NOTE 1 Any other suitable method can be used.

When tested immediately before use, water prepared as described above shall produce an orange-red (not violet-red or yellow) colour corresponding to the neutral point of methyl red indicator of pH  $5,5 \pm 0,1$  when 0,05 ml of methyl red indicator solution (5.5) is added to 50 ml of the water to be examined.

This water may also be used as the reference solution (see 8.4).

The conductivity of the water shall not exceed 1  $\mu\text{S}/\text{cm}$ , determined at 25 °C by an in-line conductivity meter.

NOTE 2 This description is based on the European Pharmacopoeia 3.2.1<sup>[12]</sup>. In the European Pharmacopoeia, water prepared as described above is designated water R1.

NOTE 3 Water of Grade 2 according to ISO 3696<sup>[2]</sup> is suitable for this test.

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

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

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

**CAUTION — Hydrofluoric acid is very toxic and highly corrosive. Consider material safety data sheet!**

### 5.5 Methyl red, indicator solution.

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

**5.6 Purified water**, prepared by distillation, by ion exchange, by reverse osmosis or by any other suitable method from water having drinking water quality.

NOTE 1 See national or regional regulation on water intended for human consumption.

NOTE 2 Water that corresponds to Grade 3 according to ISO 3696[2] is suitable.

NOTE 3 In the European Pharmacopoeia 3.2.1[12], water as described above is designated water R.

## 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  $(121 \pm 1)$  °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.

Most recent autoclave models are not provided with a vent cock that can be operated manually. The operator is referred to the user instructions and/or technical description provided by the manufacturer of the autoclave with regard to the functioning of the venting operations. A time/temperature printout can be used as evidence of a proper venting stage.

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

**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 719 or ISO 720<sup>1)</sup>.

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 flask shall be pretreated by filling with purified water (5.6) and autoclaving at 121 °C for at least 1 h (see 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.

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