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## BRIEFING

**(660) Containers—Glass**, *USP 40* page 534. The Packaging and Distribution Expert Committee is proposing the following revision to clarify the intent of the chapter and provide additional information to aid in the execution of the [Surface Glass Test](#), [Glass Grains Test](#), and [Surface Etching Test](#). None of the proposed revisions will change the chapter's requirement. However, there will be a revision proposal in 2018 that is meant to modernize tests, test methods, and specifications within the chapter, and will be a high-impact revision. Listed below are the key changes being proposed:

1. The chapter title has been changed to "Glass Containers Used in Pharmaceutical Packaging/Delivery Systems".
2. A [Scope](#) section has been added.
3. [Table 1](#) and [Table 2](#) have been consolidated into one table which denotes the specifications for the [Surface Glass Test](#), [Glass Grains Test](#), and [Surface Etching Test](#) for a glass container to be classified as Type I, II, or III.
4. Additional requirements for the autoclave used for the various tests have been added to the chapter.
5. The list of ancillary equipment required to execute the chapter has been expanded.
6. The [Purified Water](#) requirement has been aligned with the *Pharm Europa* General Chapter 3.2.1 "Glass Containers for Pharmaceutical Use".
7. Additional information on the [Autoclaving procedure](#) has been added to the chapter, including *Reference temperature curve*, *Autoclave calibration*, and *Routine autoclave runs*.
8. Additional information on how to titrate the test and blank samples has been added to the chapter.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

A workshop, *Modernization of USP Packaging Standards for Glass and Elastomeric Components*, will be held June 19–20, 2017 at USP in Rockville, Maryland, to discuss this revision proposal, potential future revisions to this chapter, and the revision proposal for [Evaluation of the Inner Surface Durability of Glass Containers \(1660\)](#), also appearing in this issue of *PF* (for details of the workshop, go to the USP website [www.usp.org/meetings-courses/workshops/modernization-usp-packaging-standards-glass-and-elastomeric-components](http://www.usp.org/meetings-courses/workshops/modernization-usp-packaging-standards-glass-and-elastomeric-components)).

**Change to read:**

**<660>CONTAINERS—GLASS GLASS  
CONTAINERS USED IN  
PHARMACEUTICAL  
PACKAGING/DELIVERY SYSTEMS.<sup>1S</sup>**

(USP41)

**Add the following:**

SCOPE

DESCRIPTION

SPECIFIC TESTS

Hydrolytic Resistance

Surface Glass Test (Hydrolytic Resistance of the Inner Surfaces of Glass Containers)

Glass Grains Test (Hydrolytic Resistance of Glass Grains)

Surface Etching Test

Impurities

Arsenic (211)

Functionality

Spectral Transmission for Colored Glass Containers

<sup>1S</sup> (USP41)

**Add the following:**

**SCOPE**

Glass packaging components are used in packaging and delivery systems for various parenteral preparations as defined in [Injections and Implanted Drug Products \(1\)](#) and in non-parenteral preparations. Glass components

include, but are not limited to, ampules, bottles, cartridges, syringe barrels, and vials in both flint (clear) and colored (amber) glass. A packaging system, also referred to as a container–closure system, is defined in [Packaging and Storage Requirements \(659\)](#) and is the sum of packaging components that together contain, protect, and in certain cases deliver the drug product. <sup>1S (USP41)</sup>

**Change to read:**

## DESCRIPTION

Glass containers for pharmaceutical use are intended to come into direct contact with pharmaceutical products. Glass used for pharmaceutical containers is either borosilicate (neutral) <sup>1S (USP41)</sup> glass or soda-lime-silica glass. Borosilicate glass exhibits a high hydrolytic and thermic resistance due to the chemical composition of the glass itself and is classified as Type I glass. <sup>1S (USP41)</sup> Borosilicate glass contains significant amounts of boric oxide, aluminum oxide, and alkali and/or alkaline earth oxides in the glass network.

Soda-lime-silica glass is a silica glass containing alkaline metal oxides, mainly sodium oxide, and alkaline earth oxides, mainly calcium oxide, in the glass network. Soda-lime-silica glass has a moderate hydrolytic resistance due to the chemical composition of the glass itself; it <sup>1S (USP41)</sup> is classified as Type III glass. Suitable treatment of the inner surface of Type III soda-lime-silica glass containers, for example with ammonium sulfate, <sup>1S (USP41)</sup> will raise the hydrolytic resistance from a moderate to a high level, changing the classification of the glass container from Type III. <sup>1S (USP41)</sup> to Type II.

~~The following recommendations can be made as to the suitability of the glass type for containers for pharmaceutical products, based on the tests for hydrolytic resistance. Type I glass containers are suitable for most products for parenteral and nonparenteral uses. Type II glass containers are suitable for most acidic and neutral aqueous products for parenteral and nonparenteral uses. Type II containers may be used for alkaline parenteral products where stability data demonstrate their suitability. Type III glass containers usually are not used for parenteral glass products or for powders for parenteral use, except where suitable stability test data indicate that Type III glass satisfactory.~~

~~The inner surface of glass containers may be treated to improve hydrolytic resistance. The outer surface of glass containers may be treated to reduce friction or for protection against abrasion or breakage. The outer surface treatment is such that it does not contaminate the inner surface of the container.~~

Glass may be colored to provide protection from light by the addition of small amounts of metal oxides and is tested as described in *Spectral Transmission for Colored Glass Containers*. A clear and colorless container that is made light resistant by means of an opaque enclosure (see [Packaging and Storage Requirements \(659\)](#), [General Definitions, Packaging Definitions, Light-Resistant Container](#)) is exempt from the requirements for spectral transmission.

It is recommended that all glass containers for liquid preparations and for powders for parenteral administration permit the visual inspection of the contents. In order to support the visual inspection of the content, light protective glass should only be used if necessary for the protection of the drug.

The inner surface of the container may be treated, e.g., with a hydrophilic or hydrophobic coating, to prevent release of glass elements into the drug solution (see [Evaluation of the Inner Surface Durability of Glass Containers \(1660\)](#), [Formation and Processing of Molded and Tubular Glass Containers, Surface Treatments](#)). The outer surface of glass containers may be treated to reduce friction or for protection against abrasion or breakage. The outer surface treatment is such that it does not contaminate the inner surface of the container (see [\(1660\), Surface Treatments](#)).

The following recommendations can be made as to the suitability of the glass type for containers for pharmaceutical products, based on the hydrolytic resistance. Type I glass containers are suitable for all products; Type II glass containers are suitable for most acidic and neutral aqueous products and Type III glass containers are suitable for non-parenteral products. Type II and III containers may be used for parenteral applications, including alkaline products, where suitable stability test data is available.

The container chosen for a given preparation shall be such that the glass material does not release substances in quantities sufficient to affect the stability of the preparation or to present a risk of toxicity. In justified cases, further detailed information may be necessary to assess the impact on chronic use and for vulnerable patient groups.<sup>1S (USP41)</sup>

Information on chemical composition of glass types, the formation of glass containers, and factors that influence inner surface durability of glass containers is provided in [\(1660\)](#). This chapter also contains recommended approaches to evaluate the potential of a drug product to cause the formation of glass particles and delamination.

~~Glass may be colored to provide protection from light by the addition of small amounts of metal oxides and is tested as described in *Spectral Transmission for Colored Glass Containers*. A clear and colorless container that is made light resistant by means of an opaque enclosure (see [Packaging and Storage Requirements \(659\)](#), [Light-Resistant](#)) is exempt from the requirements for spectral transmission.~~

1S (USP41)

**Change to read:**

**SPECIFIC TESTS**

The combination of *Glass Grains Test*, combined with the *Surface Glass Test*, for hydrolytic resistance and *Surface Etching Test*, determines the glass container type. In all tests the hydrolytic resistance is determined by the quantity of alkali and alkaline-earth metals released from the glass under the conditions specified. The *Glass Grains Test* indicates the alkali content of the glass container, while the *Surface Glass Test* provides information on the inner surface durability of the glass container. The *Surface Etching Test* provides information on the inner surface durability of the base glass. This quantity of alkali and alkaline-earth metals released is extremely small in the case of the more resistant glasses, thus calling for particular attention to all details of the tests and the use of apparatus of high quality and precision. Conducting these tests in conjunction with a glass standard reference material (SRM) on a routine basis will help to ensure the accuracy of the method. Reference materials are available for both borosilicate glass SRM 623 and soda-lime-silica glass ((SRM 622) from the National Institute of Standards and Technology Certified Reference Standard such as National Institute of Standards and Technology soda-lime-silica glass reference material SRM 622 or certified reference material IRMM-435<sup>1</sup> on a routine basis will help to ensure the accuracy of the method. The tests should be conducted in an area relatively free from fumes and excessive dust. Test selection is shown in *Table 1* and *Table 2*.

**Table 1. Determination of Glass Types**

Container Type	Test	Reason
I, II, III	<i>Glass Grains Test</i>	Distinguishes Type I borosilicate glass from Type II and III soda-lime-silica glass

1S (USP41) The inner surface of glass containers is the contact surface for pharmaceutical preparations, and the quality of this surface is determined by the *Surface Glass Test*. for hydrolytic resistance. 1S (USP41) The *Surface Etching Test* may be used to determine whether the high hydrolytic resistance is due to chemical composition or due to ammonium sulfate surface treatment. Alternatively, the comparison of data from the *Glass Grains Test* and the *Surface Glass Test* may be used in *Table 2*. Glass containers must

comply with their respective specifications for the *Glass Grains Test*, *Surface Glass Test*, and *Surface Etching Test* to be classified as Type I, II, or III glass (see [Table 1](#)).<sup>1S (USP41)</sup>

**Table 2. Determination of Inner Surface Hydrolytic Resistance**

Container Type	Test	Reason
I, II, III	<i>Surface Glass Test</i>	Determines hydrolytic resistance of inner surface; distinguishes between <i>Type I</i> and <i>Type II</i> containers with high hydrolytic resistance and <i>Type III</i> containers with moderate hydrolytic resistance
I, II	<i>Surface Etching Test</i> or comparison of <i>Glass Grains Test</i> and <i>Surface Glass Test</i> data	Where it is necessary, determines whether high hydrolytic resistance is due to inner surface treatment or to the chemical composition of the glass containers

**Table 1. Determination of Identity and Quality of the Inner Surface Durability of the Glass Container**

Glass Container Type	Glass Grains Results	Inner Surface Results	Inner Surface Etching Results
I	I	I	I
II	III	I	III
III	III	III	III

<sup>1S (USP41)</sup>

Glass containers must comply with their respective specifications for identity and surface hydrolytic resistance to be classified as Type I, II, or III glass. The combination of the *Glass Grains Test* and *Surface Glass Test* or *Surface Glass Test* and *Surface Etching Test* differentiates Type I containers from Types II and III. Type III glass containers are defined by the *Surface Glass Test* or the *Glass Grains Test*.<sup>1S (USP41)</sup> Type I or Type II containers for aqueous parenteral products are tested for extractable arsenic.

### Hydrolytic Resistance

**SURFACE GLASS TEST (HYDROLYTIC RESISTANCE OF THE INNER SURFACES OF GLASS CONTAINERS).**<sup>1S (USP41)</sup>

## Apparatus

**Autoclave:** ~~For these tests, use~~ Use <sup>1S (USP41)</sup> an autoclave <sup>1S (USP41)</sup> or steam sterilizer <sup>1S (USP41)</sup> capable of maintaining <sup>1S (USP41)</sup> withstanding <sup>1S (USP41)</sup> a temperature, <sup>1S (USP41)</sup> pressure <sup>1S (USP41)</sup> of  $121 \pm 1^\circ$  at least  $2.5 \times 10^5$  N/m<sup>2</sup> (equivalent to 0.25 MPa = 2.5 bar) and capable of carrying out the heating and cooling cycle described in *Autoclaving procedure*. The autoclave shall be preferably <sup>1S (USP41)</sup> equipped with a continuous-pressure regulator or other suitable means in order to maintain the temperature at  $121 \pm 1^\circ$ . The autoclave vessel shall be equipped with a heating device, a <sup>1S (USP41)</sup> thermometer, ~~or a calibrated thermocouple device, allowing a temperature measurement independent of the autoclave system; a suitable recorder;~~ integrated in the autoclave, <sup>1S (USP41)</sup> a pressure gauge and vent cock <sup>1S (USP41)</sup> (for manually-operated autoclaves only) <sup>1S (USP41)</sup> and a tray of sufficient capacity to accommodate <sup>1S (USP41)</sup> above the water level <sup>1S (USP41)</sup> the number of containers needed to carry out the test. ~~above the water level. Clean the autoclave and other apparatus thoroughly with Purified Water before use.~~ The autoclave shall have the possibility to connect a calibrated resistance thermometer or a calibrated thermocouple from the inner chamber to an external measuring device to allow a temperature measurement independent from the autoclave system. <sup>1S (USP41)</sup>

**Mortar and pestle:** ~~Use a hardened steel mortar and pestle, made according to the specifications in *Figure 1*.~~



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~~Figure 1. Mortar and pestle for pulverizing glass.~~

~~**Other apparatus:** Also required are a set of three square-mesh stainless steel sieves mounted on frames consisting of US Sieve Nos. 25, 40, and 50 (see *Particle Size Distribution Estimation by Analytical Sieving* (786), Table 1. *Sizes of Standard Sieve Series in Range of Interest*); a mechanical sieve-shaker or a sieving machine that may be used to sieve the grains; a tempered, magnetic steel hammer; a permanent magnet; weighing bottles;~~

stoppers; metal foil (e.g., aluminum, stainless steel); a hot air oven, capable of maintaining  $140 \pm 5^\circ$ ; a balance, capable of weighing up to 500 g with an accuracy of 0.005 g; a desiccator; and an ultrasonic bath.

**Ancillary equipment:** Calibrated resistance thermometer or calibrated thermocouple connected to a suitable temperature measuring device. Burets with a suitable capacity; one-mark volumetric flasks, with a capacity of 1000 mL; pipettes and beakers; conical flasks with capacities of 100 mL and 250 mL; a water-bath; metal foil (e.g., aluminum, stainless steel). Clean the autoclave and all ancillary equipment thoroughly with [Purified Water](#) before use.<sup>1S (USP41)</sup>

## Reagents

**Carbon dioxide-free water:** ~~This is Purified Water that has been boiled vigorously for 5 min or more and allowed to cool while protected from absorption of carbon dioxide from the atmosphere, or Purified Water that has a resistivity of not less than 18 Mohm-cm.~~

**Methyl red solution:** ~~Dissolve 50 mg of methyl red in 1.86 mL of 0.1 M sodium hydroxide and 50 mL of ethanol (96%), and dilute with Purified Water to 100 mL. To test for sensitivity, add 100 mL of carbon dioxide-free water and 0.05 mL of 0.02 M hydrochloric acid to 0.1 mL of the methyl red solution. The resulting solution should be red. NMT 0.1 mL of 0.02 M sodium hydroxide is required to change the color to yellow. A color change from red to yellow corresponds to a change in pH from pH 4.4 (red) to pH 6.0 (yellow).~~

**Purified water:** [Purified Water](#) is designated for use for all steps in the determination of *Surface Glass Test*, *Glass Grains Test*, and *Surface Etching Test*. Reagent grade water<sup>2</sup> with a conductivity of NMT 5.0  $\mu\text{S}/\text{cm}$  at  $25^\circ$  may be used to clean autoclave equipment and in the *Determination of the filling volume* and the cleaning steps in the *Surface Glass Test*.

**Methyl red solution:** Dissolve 50 mg of methyl red in 1.86 mL of 0.1 M sodium hydroxide and 50 mL of ethanol (96%), and dilute with [Purified Water](#) to 100 mL or dissolve 25 mg of the sodium salt of methyl red in 100 mL of [Purified Water](#). [NOTE—The solution should be periodically tested for sensitivity to ensure its fitness for use.]

To test for sensitivity, add 100 mL of [Purified Water](#) and 0.05 mL of 0.02 M hydrochloric acid to 0.1 mL of the *Methyl red solution*. The resulting solution should be red. NMT 0.1 mL of 0.02 M sodium hydroxide is required to change the color to yellow. A color change from red to yellow corresponds to a change from pH 4.4 (red) to pH 6.0 (yellow).

## Determination of the filling volume

The filling volume is the volume of water to be introduced into the container for the purpose of the test. For vials and bottles the filling volume is 90% of the brimful capacity. For ampules it is the volume up to the height of the shoulder.

*Vials and bottles:* Select 6 containers at random from the sample lot, or 3 if their capacity exceeds 100 mL, and remove any debris or dust. Weigh the empty containers with an accuracy of 0.1 g. Place the containers on a horizontal surface and fill them with [Purified Water](#) until about the rim edge, avoiding overflow and introduction of air bubbles. Adjust the liquid levels to the brimful line. Weigh the filled containers to obtain the mass of the water expressed to two decimal places for containers having a nominal volume less than or equal to 30 mL, and expressed to one decimal place for containers having a nominal volume greater than 30 mL. Calculate the mean value of the brimful capacity in milliliters and multiply it by 0.9. This volume, expressed to one decimal place, is the filling volume for the particular container lot.

*Ampules:* Place at least 6 dry ampules on a flat, horizontal surface and fill them with [Purified Water](#) from a buret until the water reaches point A, where the body of the ampule declines to the shoulder (see [Figure 1](#)). Read the capacities (expressed to two decimal places) and calculate the mean value. This volume, expressed to one decimal place, is the filling volume for the particular ampule lot. The filling volume may also be determined by weighing.

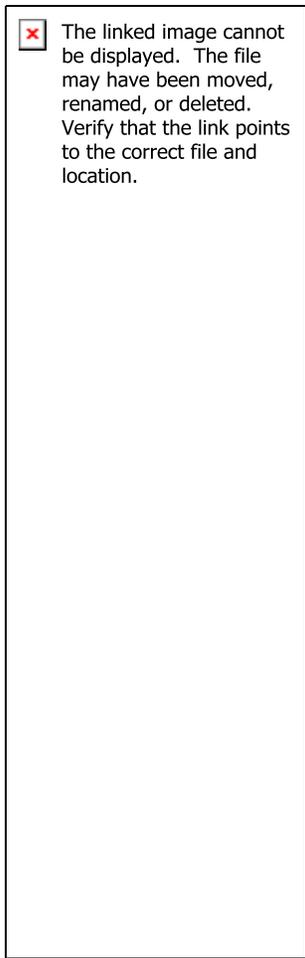


Figure 1. Filling volumes of ampules up to point A.

*Syringes and cartridges:* Select 6 syringes or cartridges. Close the small opening (mouth of cartridges and needle and/or luer cone of syringes) using an inert material (e.g., a tip cap) or any other suitable means to prevent water leakage. Determine the mean brimful volume in accordance with the procedure described under *Vials and bottles* and multiply it by 0.9. This volume, expressed to one decimal place, is the filling volume for the particular container lot.

*Test:* The determination is carried out on unused containers. The volumes of the test solution necessary for the final determination are shown in [Table 2](#).

**Table 2. Volume of Test Solution and Number of Titrations**

<b>Filling Volume (mL)</b>	<b>Volume of Test Liquid for One Titration (mL)</b>	<b>Number of Titrations</b>
NMT 3	25.0	1

Filling Volume (mL)	Volume of Test Liquid for One Titration (mL)	Number of Titrations
3–30	50.0	2
30–100	100.0	2
NLT 100	100.0	3

## Method

**Cleaning:** Remove any debris or dust. Shortly before the test carefully rinse the containers three times with [Purified Water](#) and allow to drain.

Closed ampules shall not be rinsed before testing. Closed ampules can be warmed on a water bath or in an air oven at about 40° for approximately 2 min to avoid pressure when opening.

**Filling:** Fill the containers with [Purified Water](#) up to the filling volume. Loosely cap each container with an inert material, for example with inverted beakers of such a size that the bottoms of the beakers fit snugly down on the rims of the sample. Ampules and vials capped with clean aluminum foil are further examples. Place syringes and cartridges in an open rack to allow steam circulation and cover each container individually with clean aluminum foil. Ensure that they are held above the level of the water in the autoclave.

Containers of a volume of 2 mL or less, in which the water is not sufficiently retained during the autoclaving process, may be closed in a suitable way, e.g., with a stopper or plug of inert material, such as silicone, and fixed using a plunger or a stable fixing or clamping device.

### Autoclaving procedure

[NOTE—Additional guidance on the operation of the autoclave is provided in [\(1660\)](#).]

**REFERENCE TEMPERATURE CURVE:** The autoclave shall be run in a way that the temperature in the containers to be tested follows a temperature curve with the following parameters: temperature raised from room temperature to 100° within 20–30 min; temperature maintained at 100 ± 1° for 10 ± 1 min; temperature in the containers raised from 100° to 121° at a rate of 1°/min within 20–22 min; temperature maintained at 121 ± 1° for 60 ± 1 min; temperature cooled to 100° at a rate of 0.5°/min within 40–44 min.

[NOTE—The rate of heating to 121° and the rate of cooling to 100° are critical. Variations from the specified conditions may cause variable results due to significant temperature variations inside the containers.]

**AUTOCLAVE CALIBRATION:** Before being used for the first time, the autoclave and the temperature measuring system must be calibrated to ensure that the autoclave settings are suitable to guarantee that the temperature inside

the containers is  $121 \pm 1^\circ$ . From time to time verify the validation of the calibration. Establish a recalibration plan based on sound quality control criteria, recalibrate as appropriate and keep records. [NOTE—Significant differences can be observed between the temperature measured in the autoclave chamber and inside the containers.]

Take a set of containers of mean capacity (10 mL for instance) and fill them with *Purified Water*. Select a sufficient number of containers to completely fill the tray within the autoclave chamber. Insert the end of the calibrated resistance thermometer or calibrated thermocouple into a filled container through a hole in the closure having approximately the same diameter as the probe and connect it to the external measuring device. If the container is too small to insert a thermocouple, place the thermocouple in a similar container of suitable size. Close the autoclave door or lid securely and run the autoclave to achieve the target temperature curve in the containers. Where a manual autoclave is run, leave the vent cock open. Heat the autoclave at a regular rate such that steam issues vigorously from the vent cock after 20–30 min, and maintain a vigorous evolution of steam for an additional 10 min.

Close the vent cock, follow the temperature increase on the calibrated thermocouple measuring device by comparison with readings taken from the autoclave thermometer, and adjust the autoclave settings accordingly in order to match the target temperature curve. Keep the temperature ramp as smooth as possible and avoid spikes.

Using the calibrated thermocouple measuring device ensure that deviations from the holding temperature of  $121 \pm 1^\circ$  are within the tolerance. When cooling down, vent to prevent the formation of a vacuum. For safety reasons (boiling retardation) do not open the autoclave before the water in the containers has reached a temperature of  $95^\circ$ . Remove the hot samples from the autoclave and cool cautiously to room temperature within 30 min. Record the autoclave settings used to carry out the thermal cycle and use these settings for routine autoclave runs.

[NOTE—Where a steam autoclave equipped with a vacuum system is run, excess air is expelled through internal gauges and free steaming is not always possible. For this type of autoclave, a purposely designed temperature program is run according to the manufacturer's instructions. The holding temperature at  $100^\circ$  for 10 min is not necessary provided complete air purging is achieved. All other stages foreseen by the reference temperature curve must be strictly followed as described above.]

**ROUTINE AUTOCLAVE RUNS:** Use the autoclave settings established during the calibration stage and follow the same thermal cycle described above. Container sets of different capacity can be tested during the same run. If necessary, keep the glass load very close to the load used during the calibration stage. The use of the calibrated thermocouple is no longer

necessary provided the calibration is proved to be valid over a defined time span. At the end of the cycle, remove the hot samples from the autoclave and cool them cautiously to room temperature within 30 min.

**Titration:** Carry out the titration within 1 h of the removal of the containers from the autoclave. Combine the liquids obtained from the containers, and mix. Introduce the prescribed volume (see [Table 3](#)) into a conical flask. Transfer the same volume of [Purified Water](#), to be used as a blank, into a second similar flask. Add to each flask 0.05 mL of *Methyl red solution* for each 25 mL of liquid. Titrate the blank with 0.01 M hydrochloric acid. Titrate the test solution with the same acid until the color of the resulting solution is the same as that obtained for the blank. Subtract the value found for the blank titration from that found for the test solution, and express the results in milliliters of 0.01 M hydrochloric acid per 100 mL of test solution. Alternatively, an autotitrator may be used. Express titration values of less than 1.0 mL to two decimal places; express titration values of greater than or equal to 1.0 mL to one decimal place.

### Limits

The results, or the average of the results if more than one titration is performed, are not greater than the values stated in [Table 3](#).

**Table 3. Limit Values for the Surface Glass Test**

**Maximum Volume of 0.01 M Hydrochloric Acid per 100 mL of Test Solution (mL)**

<b>Filling Volume (mL)</b>	<b>Types I and II Glass Containers</b>	<b>Type III Glass Containers</b>
NMT 1	2.0	20.0
1-2	1.8	17.6
2-3	1.6	16.1
3-5	1.3	13.2
5-10	1.0	10.2
10-20	0.80	8.1
20-50	0.60	6.1
50-100	0.50	4.8
100-200	0.40	3.8
200-500	0.30	2.9
NLT 500	0.20	2.2

•1S (USP41)

The *Glass Grains Test* may be performed either on the canes used for the manufacture of tubing glass containers or on ~~the containers~~ components that would be representative of their use in a packaging or delivery system, which includes any manufacturing or processing (e.g., inner surface treatments).

### **Apparatus**

*Mortar and pestle:* Use a hardened-steel mortar and pestle, made according to the specifications in [Figure 2](#).

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Figure 2. Mortar and pestle for pulverizing glass.

*Ancillary equipment:* A set of three square-mesh stainless steel sieves mounted on frames consisting of US Sieve Nos. 25, 40, and 50 (see [Particle Size Distribution Estimation by Analytical Sieving \(786\), Table 1. Sizes of Standard Sieve Series in Range of Interest](#)); a mechanical sieve-shaker or a sieving machine that may be used to sieve the grains; a tempered, magnetic steel hammer; a permanent magnet; weighing bottles; stoppers; metal foil (e.g., aluminum, stainless steel); a hot air oven capable of maintaining  $140 \pm 5^\circ$ ; a balance capable of weighing up to 500 g with an accuracy of 0.005 g; a desiccator; and an ultrasonic bath..<sup>1S (USP41)</sup>

### Sample preparation

Rinse the containers to be tested with [Purified Water](#), and dry in the oven. Wrap at least three of the glass articles in clean paper, and crush to produce two samples of about 100 g each in pieces NMT 30 mm across. Place in the mortar 30–40 g of the pieces between 10 and 30 mm across taken from one of the samples, insert the pestle, and strike it heavily with the hammer once only. Alternatively, transfer samples into a ball mill-breaker, add the balls, and crush the glass or use a mortar grinder..<sup>1S (USP41)</sup> Transfer the contents of the mortar or ball mill to the coarsest sieve (No. 25) of the set. Repeat the operation until all fragments have been transferred to the sieve. Shake the set of sieves for a short time by hand, and remove the glass that remains on sieves No. 25 and No. 40. Submit these portions to further fracture, repeating the operation until about 10 g of glass remains on sieve No. 25. Reject this portion and the portion that passes through sieve No. 50. Reassemble the set of sieves, and shake for 5 min. Transfer to a weighing bottle the glass grains that passed through sieve No. 40 and are retained on sieve No. 50. Repeat the crushing and sieving procedure with the second glass sample until two samples of grains are obtained, each of which weighs more than 10 g.

Spread each sample on a piece of clean glazed paper, and remove any iron particles by passing the magnet over them. Transfer each sample into a beaker for cleaning. Add 30 mL of acetone to the grains in each beaker, and scour the grains, using suitable means such as a rubber-tipped or plastic-coated glass rod. After scouring the grains, allow to settle, and decant as much acetone as possible. Add another 30 mL of acetone, swirl, decant, and add a new portion of acetone. Fill the bath of the ultrasonic vessel with water at room temperature, then place the beaker in the rack, and immerse it until the level of the acetone is at the level of the water; apply the ultrasound for 1 min. Swirl the beaker, allow to settle, and decant the acetone as completely as possible; then repeat the ultrasonic cleaning operation. If a fine turbidity persists, repeat the ultrasonic cleaning and

acetone washing until the solution remains clear. Swirl, and decant the acetone. Dry the grains, first by putting the beaker on a warm plate in a fume hood, <sup>.1S (USP41)</sup> then by heating at 140° for 20 min in a drying oven. Transfer the dried grains from each beaker into separate weighing bottles, insert the stoppers, and cool in a desiccator.

## Method

~~Filling: and heating~~ <sup>.1S (USP41)</sup> Weigh 10.00 g of the cleaned and dried grains into two separate conical flasks. Pipet 50 mL of ~~carbon dioxide-free~~ <sup>.1S (USP41)</sup> Purified Water into each of the conical flasks (test solutions). Pipet 50 mL of ~~carbon dioxide-free~~ <sup>.1S (USP41)</sup> Purified Water into a third conical flask that will serve as a blank. Distribute the grains evenly over the flat bases of the flasks by shaking gently. Close the flasks with neutral glass dishes or aluminum foil rinsed with Purified Water or with inverted beakers so that the inner surfaces of the beakers fit snugly down onto the top rims of the flasks. Place all three flasks in the autoclave containing the water at ambient temperature, and ensure that they are held above the level of the water in the vessel. Carry out the following operations:

- ~~1. Insert the end of a calibrated thermometric 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. Alternatively, use the internal thermometer of the autoclave.~~
- ~~2. Close the autoclave door or lid securely but leave the vent cock open.~~
- ~~3. 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 20–30 min, and maintain a vigorous evolution of steam for a further 10 min. For autoclaves using a steam generator, it is not necessary to maintain the temperature for 10 min at 100°.~~
- ~~4. Close the vent cock, and raise the temperature from 100° to 121° at a rate of 1°/min within 20–22 min.~~
- ~~5. Maintain the temperature at 121 ± 1° for 30 ± 1 min from the time when the holding temperature is reached.~~
- ~~6. Cool down to 100° at a rate of 0.5°/min, venting to prevent formation of a vacuum, within 40–44 min.~~
- ~~7. Do not open the autoclave until it has cooled to 95°.~~
- ~~8. Remove the hot samples from the autoclave using appropriate safety precautions, and cool the samples cautiously down to room temperature within 30 min, avoiding thermal shock.~~

**Autoclaving procedure:** Carry out the autoclaving procedure in a similar manner to that described under *Surface Glass Test*, but maintain the temperature of  $121 \pm 1^\circ$  for only  $30 \pm 1$  min. Do not open the autoclave until it has cooled to  $95^\circ$ . Remove the hot samples from the autoclave and cool the flasks in running tap water as soon as possible, avoiding thermal shock.<sup>1S (USP41)</sup>

**Titration:** To each of the three flasks add 0.05 mL of *Methyl red solution*. Titrate the blank solution immediately with 0.02 M hydrochloric acid, then titrate the test solutions until the color matches that obtained with the blank solution. Subtract the titration volume for the blank solution from that for the test solutions. Calculate the mean value of the results in mL of 0.02 M hydrochloric acid per gram of the sample. Alternatively, an autotitrator may be used.<sup>1S (USP41)</sup> Repeat the test if the highest and lowest observed values differ by more than the permissible range given in [Table 4](#).

**Table 4. Permissible Range for Values Obtained**

Mean of the Values Obtained for the Consumption of Hydrochloric Acid Solution per Gram of Glass Grains (mL/g)	Permissible Range of the Values Obtained
NMT 0.10	25% of the mean
0.10–0.20	20% of the mean
NLT 0.20	10% of the mean

[NOTE—Where necessary to obtain a sharp endpoint, decant the clear solution into a separate 250-mL flask. Rinse the grains by swirling with three 15-mL portions of carbon dioxide-free water *Purified Water*.<sup>1S (USP41)</sup> and add the washings to the main solution. Add 0.05 mL of the *Methyl red solution*. Titrate, and calculate as before. In this case also add 45 mL of carbon dioxide-free *Purified Water*.<sup>1S (USP41)</sup> and 0.05 mL of *Methyl red solution* to the blank solution.]

**Limits**

The volume does not exceed the values indicated in [Table 5](#).

**Table 5. Test Limits for Glass Grains Test**

Filling Volume (mL)	Maximum Volume of 0.02 M Hydrochloride per Gram of Test Glass (mL)	
	Type I	Types II and III
All	0.1	0.85

## Surface Glass Test

### DETERMINATION OF THE FILLING VOLUME

The filling volume is the volume of Purified Water to be added to the container for the purpose of the test. For vials, bottles, cartridges, and syringes, the filling volume is 90% of the brimful capacity. For ampuls, it is the volume up to the height of the shoulder.

**Vials and bottles:**— Select six dry vials or bottles from the sample lot, or three if their capacity exceeds 100 mL, and remove any dirt or debris. Weigh the empty containers with an accuracy of 0.1 g. Place the containers on a horizontal surface, and fill them with Purified Water to about the rim edge, avoiding overflow and the introduction of air bubbles. Adjust the liquid levels to the brimful line. Weigh the filled containers to obtain the mass of the water expressed to two decimal places, for containers having a nominal volume less than or equal to 30 mL, and expressed to one decimal place, for containers having a nominal volume greater than 30 mL. Calculate the mean value of the brimful capacity in mL, and multiply it by 0.9. This volume, expressed to one decimal place, is the filling volume for the particular container lot.

**Cartridges and syringes:**— Select six dry syringes or cartridges, and seal the small opening (mouth of cartridges; Luer cone or staked needle of syringes), using an inert material. Determine the mean brimful capacity and filling volume according to *Vials and Bottles*.

**Ampuls:**— Place at least six dry ampuls on a flat, horizontal surface, and fill them with Purified Water from a buret until the water reaches point A, where the body of the ampul starts to decrease to the shoulder of the ampul (see *Figure 2*). Read the capacities, expressed to two decimal places, and calculate the mean value. This volume, expressed to one decimal place, is the filling volume for the particular ampul lot. The filling volume may also be determined by weighing.

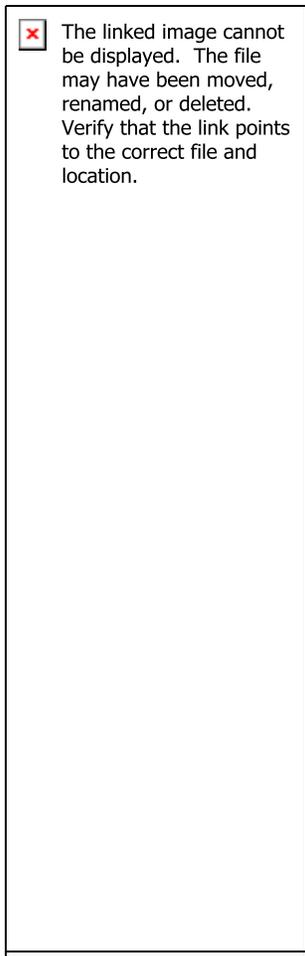


Figure 2. Filling volumes of ampuls up to point A.

### TEST

The determination is carried out on unused containers. The volumes of the test solution necessary for the final determination are shown in *Table 5*.

**Table 5. Volume of Test Solution and Number of Titrations**

<b>Filling Volume (mL)</b>	<b>Volume of Test Liquid for One Titration (mL)</b>	<b>Number of Titrations</b>
NMT-3	25.0	1
3-30	50.0	2
30-100	100.0	2
NLT-100	100.0	3

### METHOD

**Cleaning:**— Remove any debris or dust. Shortly before the test, rinse each container carefully at least twice with Purified Water, refilled, and allow to stand. Immediately before testing, empty the containers; rinse once with Purified Water, then with carbon dioxide-free water; and allow to drain. Complete the cleaning procedure from the first rinsing within 20–30 min. Closed ampules may be warmed in a water bath or in an air oven at about 40° for approximately 2 min before opening to avoid container pressure when opening. Do not rinse before testing.

**Filling and heating:**— The containers are filled with carbon dioxide-free water up to the filling volume. Containers in the form of cartridges or prefillable syringes are closed in a suitable manner with material that does not interfere with the test. Each container, including ampuls, shall be loosely capped with an inert material such as a dish of neutral glass or aluminum foil previously rinsed with Purified Water. Place the containers on the tray of the autoclave. Place the tray in an autoclave containing a quantity of water such that the tray remains clear of the water. Close the autoclave, and carry out autoclaving procedure steps 1–8 as described in the *Glass Grains Test*, except that the temperature is maintained at  $121 \pm 1^\circ$  for  $60 \pm 1$  min. If a water bath is used for cooling samples, take care that the water does not make contact with the loose foil caps to avoid contamination of the extraction solution. The extraction solutions are analyzed by titration according to the method described below.

**Titration:**— Carry out the titration within 1 h of the removal of the containers from the autoclave. Combine the liquids obtained from the containers, and mix. Introduce the prescribed volume (see *Table 5*) into a conical flask. Transfer the same volume of carbon dioxide-free water, to be used as a blank, into a second similar flask. Add to each flask 0.05 mL of *Methyl red solution* for each 25 mL of liquid. Titrate the blank with 0.01-M hydrochloric acid. Titrate the test solution with the same acid until the color of the resulting solution is the same as that obtained for the blank. Subtract the value found for the blank titration from that found for the test solution, and express the results in mL of 0.01-M hydrochloric acid per 100 mL of test solution. Express titration values of less than 1.0 mL to two decimal places; express titration values of greater than or equal to 1.0 mL to one decimal place.

## LIMITS

The results, or the average of the results if more than one titration is performed, are not greater than the values stated in *Table 6*.

### **Table 6. Limit Values for the Surface Glass Test**

Filling Volume (mL)	Maximum Volume of 0.01 M HCl per 100 mL of Test Solution (mL)	
	Types I and II	Type III
NMT 1	2.0	20.0
1-2	1.8	17.6
2-3	1.6	16.1
3-5	1.3	13.2
5-10	1.0	10.2
10-20	0.80	8.1
20-50	0.60	6.1
50-100	0.50	4.8
100-200	0.40	3.8
200-500	0.30	2.9
NLT-500	0.20	2.2

• 1S (USP41)

### SURFACE ETCHING TEST

The *Surface Etching Test* is used in addition to the *Surface Glass Test* when it is necessary to determine whether a container has been surface treated and/or to distinguish between Type I and Type II glass containers.

Alternatively, the *Glass Grains Test* and *Surface Glass Test* may be used.

The *Surface Etching Test* may be carried out either on unused samples or on samples used in the *Surface Glass Test*.

### Method

*Vials and bottles:* The volumes of test solution required are shown in [Table 5](#). Rinse the containers twice with [Purified Water](#), fill to the brimful point with a mixture of 1 volume of hydrofluoric acid and 9 volumes of hydrochloric acid, and allow to stand for 10 min. Empty the containers, and rinse carefully five times with [Purified Water](#). Immediately before the test, rinse once again with [Purified Water](#). Submit these containers to the same autoclaving and determination procedure as described in the *Surface Glass Test*. If the results are considerably higher than those obtained from the original surfaces (by a factor of about 5-10), the samples have been surface treated.

[**CAUTION**—Hydrofluoric acid is extremely aggressive. Even small quantities can cause life threatening injuries.]

*Ampules, cartridges, and syringes:* Apply the test method as described in *Vials and bottles*. If the ampules, cartridges, and syringes are not surface treated, the values obtained are slightly lower than those obtained in the previous tests. [NOTE—Ampules, cartridges, and syringes made from Type I glass tubing are not normally subjected to internal surface treatment.]

### **Distinction between Type I and Type II glass containers**

The results obtained from the *Surface Etching Test* are compared to those obtained from the *Surface Glass Test*. For Type I glass containers, the values obtained are close to those found in the *Surface Glass Test*. For Type II glass containers, the values obtained greatly exceed those found in the *Surface Glass Test*; and they are similar to, but not greater than, those obtained for Type III glass containers of the same filling volume.

### **Impurities**

#### **ARSENIC (211)**

Use as the *Test preparation* 35 mL of the water from one Type I or Type II glass container, or, in the case of smaller containers, 35 mL of the combined contents of several Type I or Type II glass containers, prepared as directed in the *Surface Glass Test*. The limit does not exceed 0.1 µg/g mL<sub>0.1S</sub> (USP41)

### **Functionality**

#### **SPECTRAL TRANSMISSION FOR COLORED GLASS CONTAINERS**

### **Apparatus**

A UV-Vis spectrophotometer, equipped with either a photodiode detector or a photomultiplier tube coupled with an integrating sphere

### **Sample preparation**

Break the glass container or cut it with a circular saw fitted with a wet abrasive wheel, such as a carborundum or a bonded diamond wheel. Select sections representative of the wall thickness, and trim them as suitable for mounting in a spectrophotometer. After cutting, wash and dry each specimen, taking care to avoid scratching the surfaces. If the specimen is too small to cover the opening in the specimen holder, mask the uncovered portion of the opening with opaque paper or tape, provided that the length of the specimen is greater than that of the slit. Before placing in the holder, wash, dry, and wipe the specimen with lens tissue. Mount the specimen with the aid of wax, or by other convenient means, taking care to avoid leaving fingerprints or other marks.

### **Method**

Place the specimen in the spectrophotometer with its cylindrical axis parallel to the slit and in such a way that the light beam is perpendicular to the surface of the section and the losses due to reflection are at a minimum.

Measure the transmission of the specimen with reference to air in the spectral region of 290–450 nm, continuously or at intervals of 20 nm.

### Limits

The observed spectral transmission for colored glass containers for products for non-parenteral use does not exceed 10% at any wavelength in the range of 290–450 nm, irrespective of the type and capacity of the glass container. The observed spectral transmission in colored glass containers for parenteral products does not exceed the limits given in [Table 6](#).

**Table 6. Limits of Spectral Transmission for Colored Glass Containers for Parenteral Products**

Nominal Volume (mL)	Maximum Percentage of Spectral Transmission at Any Wavelength between 290 nm and 450 nm	
	Flame-Sealed Containers	Containers with Closures
NMT 1	50	25
1–2	45	20
2–5	40	15
5–10	35	13
10–20	30	12
NLT 20	25	10

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<sup>1</sup> IRMM-435 is available from [www.ec.europa.eu/jrc/en](http://www.ec.europa.eu/jrc/en)..<sup>1S</sup> (USP41)

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<sup>2</sup> Type IV water. Latest edition of ASTM D1193 Standard Specification for Reagent Water. ASTM 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959..<sup>1S</sup> (USP41)