衛生福利部食品藥物管理署管制藥品製藥工廠

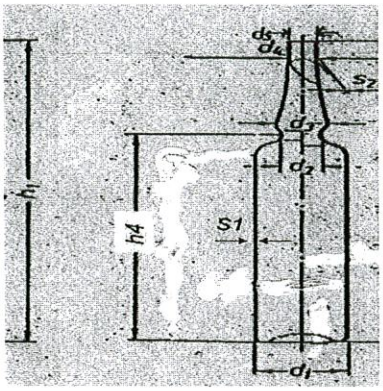
材料規格

文件名稱	1毫升茶色玻璃安瓿			頁　　碼	第 3 頁 共 6 頁
文件編號	P101	版次	12	生效日期	104. 1. 13

1. 材質：注射劑玻璃容器依最新 USP 規定為 Type I ，硼矽質硬質玻璃容器（High resistant, borosilicate glass），其玻璃管厚度為 0.50 ± 0.03 mm，由廠商提供材質證明。
2. 包裝:每 400~800 支盒裝，盒具雙面開口，寬度 26 公分，瓶口向上，外箱應標明品名、數量、批號或製造日期及廠名，箱內外應清潔，不得有異物污染。
3. 外　　觀：

	項　　目	樣本數	AQL	Ac	Re
1	本品為茶褐色玻璃安瓿，以安瓿用玻璃管加工製成之直筒型，外型平滑完整，瓶口鍛燒平整呈圓形，色澤均勻，不得有深淺不一。	125	1.5	5	6
2	本品不得有底歪頸斜，中心線不正，影響藥液充填作業情形。一次取 10 支安瓿使站立排列成直線，旋轉不同角度檢視，挑出瓶身異常傾斜者，測量瓶身中心線（瓶口圓心至瓶底圓心）之傾斜角度，不得大於 5°。	125	0.65	2	3
3	本品不得有肉眼可查覺之雜物、絲紋、氣泡及裂痕。	125	1.5	5	6
4	本品不得有直徑大於 1mm 之污點。	125	0.25	1	2
5	本品為 One-point 預割產品，不得有無預割之情形。	125	0.65	2	3
6	本品為 One-point 預割產品，有預割且有標示，並無位置標示不當。	125	1.5	5	6
7	本品不得混雜任何他廠已印字之安瓿。	1250	0.010	0	1

4. 重量及尺寸單位：重量為 gm，尺寸為 mm（廠商需附每生產批之品質管制紀錄）。口徑 d4 及頸壁厚 S2 之量測點為安瓿開口下方 15 mm 處（約熔封點）。



項　目	代號	範　圍	樣本數
重量	W	1.4～1.8	32
胴徑	d1	9.80～10.20	32
絞徑	d2	5.3～6.3	32
玉徑	d3	6.2～7.2	32
口徑	d4	5.0～6.0	32
內徑	d5	4.0～5.3	32
全長	h1	63～65	32
胴高	h4	27～29	32
管壁厚	S1	0.47～0.53	10
頸壁厚	S2	0.25～0.40	10

標準書發放章 104.01.13 翁台安

註：尺寸及重量如不合格數 ≥ 2 支即判不合格。如不合格數為 1 支，則加倍取樣，兩次量測如不合格數 ≥ 3 支即判不合格。

5. 折斷面平整度測試：折斷時安瓿瓶身不得破碎。(樣本數 125, Ac=0, Re=1)

6. **CHEMICAL RESISTANCE**：詳見 2014 USP 37〈**660**〉**CONTAINERS—GLASS**

6.1 Powdered Glass Test：安瓿清潔乾燥後，將之折斷，棄去有預割標示點之上半截，保留下半截進行本試驗。

Table 2. Test Limits for Powdered Glass Test

			Limits	
Type	**General Description**[a]	**Type of Test**	**Size,**[b] **mL**	**mL of 0.020 N Acid**
I	Highly resistant, borosilicate glass	*Powdered Glass*	All	1.0
III	Soda-lime glass	*Powdered Glass*	All	8.5

[a] The description applies to containers of this type of glass usually available.
[b] Size indicates the overflow capacity of the container.

6.2 Surface Glass Test

Table 3. Volume of Test Liquid and Number of Titrations

Filling Volume (mL)	Volume of Test Liquid for One Titration (mL)	Number of Titrations
Up to 3	25.0	1
Above 3 and up to 30	50.0	2
Above 30 and up to 100	100.0	2
Above 100	100.0	3

標準書發放章
104.01.13
翁台安

Table 4. Test Limits for Surface Glass Test

	Maximum Volume of 0.01 M HCl per 100 mL of Test Liquid (mL)	
Filling Volume (mL)	**Types I and II**	**Type III**
Up to 1	2.0	20.0
Above 1 and Up to 2	1.8	17.6
Above 2 and Up to 5	1.3	13.2
Above 5 and Up to 10	1.0	10.2
Above 10 and Up to 20	0.80	8.1
Above 20 and Up to 50	0.60	6.1
Above 50 and Up to 100	0.50	4.8
Above 100 and Up to 200	0.40	3.8
Above 200 and Up to 500	0.30	2.9
Above 500	0.20	2.2

7. 砷(Arsenic)：限量 0.1 ppm 。

檢品試液取自 Surface Glass Test。

測定法：以原子吸收光譜儀測定之。

8. LIGHT TRANSMISSION TEST：詳見 2014 USP 37〈671〉

CONTAINERS—PERFORMANCE TESTING

Table 2. Limits for Plastic Classes I–VI and

Glass Types I, II, and III

	Maximum Percentage of Light Transmission at Any Wavelength between 290 and 450 nm	
Nominal Size (in mL)	**Flame-sealed Containers**	**Closure-sealed Containers**
1	50	25
2	45	20
5	40	15
10	35	13
20	30	12
50	15	10

9. 附件：

(1)2014 USP 37 版 (660) Containers-Glass。

(2)2014 USP 37 版 (671) Containers-Performance Testing。

標準書
發放章
104.01.13
翁台安

〈 660 〉 CONTAINERS—GLASS

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) glass or soda-lime-silica glass. Borosilicate glass contains significant amounts of boric oxide, aluminum oxide, and alkali and/or alkaline earth oxides. Borosilicate glass has a high hydrolytic resistance and a high thermal shock resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Soda-lime-silica glass is a silica glass containing alkaline metal oxides, mainly sodium oxide; and alkaline earth oxides, mainly calcium oxide. Soda-lime-silica glass has a moderate hydrolytic resistance due to the chemical composition of the glass itself; it is classified as Type III glass. Suitable treatment of the inner surface of Type III soda-lime-silica glass containers will raise the hydrolytic resistance from a moderate to a high level, changing the classification of the glass 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 use. Type II glass containers are suitable for most acidic and neutral aqueous products for parenteral and non-parenteral uses. Type II glass containers may be used for alkaline parenteral products where stability data demonstrate their suitability. Type III glass containers usually are not used for parenteral products or for powders for parenteral use, except where suitable stability test data indicate that Type III glass is 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 *Light-Resistant Container* in 〈 659 〉 *Packaging and Storage Requirements*) is exempt from the requirements for spectral transmission. Containers for aqueous parenteral products are tested for arsenic release.

SPECIFIC TESTS

The *Glass Grains Test* combined with the *Surface Glass Test* for hydrolytic resistance determines the glass type. The hydrolytic resistance is determined by the quantity of alkali released from the glass under the conditions specified. This quantity of alkali 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. 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	*Glass Grains Test*	Distinguishes Type I borosilicate glass from Type II and III soda-lime-silica glass

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. The *Surface Etching Test* may be used to determine whether high hydrolytic resistance is due to chemical

composition or to surface treatement. Alternatively, the comparison of data from the *Glass Grains Test* and the *Surface Glass Test* may be used in *Table 2*.

Table 2. Determination of Inner Surface Hydrolytic Resistance

Container Type	Test	Reason
I, II, III	*Surface Glass Test*	Determines hydrolytic resistance of inner surface. Distinguishes between *Type I* and *Type II* containers with high hydrolytic resistance and *Type III* containers with moderate hydrolytic resistance
I, II	*Surface Etching Test* or comparison of *Glass Grains Test* and *Surface Glass Test* data	Where it is necessary to determine whether high hydrolytic resistance is due to inner surface treatment or to the chemical composition of the glass containers

Glass containers must comply with their respective specifications for identity and surface hydrolytic resistance to be classified as Type I, II, or III glass. Type I or Type II containers for aqueous parenteral products are tested for extractable arsenic.

Hydrolytic Resistance

Apparatus

Autoclave— For these tests, use an autoclave capable of maintaining a temperature of 121 ± 1°, equipped with a thermometer, a pressure gauge, a vent cock, and a tray of sufficient capacity to accommodate 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.

Mortar and Pestle— Use a hardened-steel mortar and pestle, made according to the specifications in *Figure 1*.

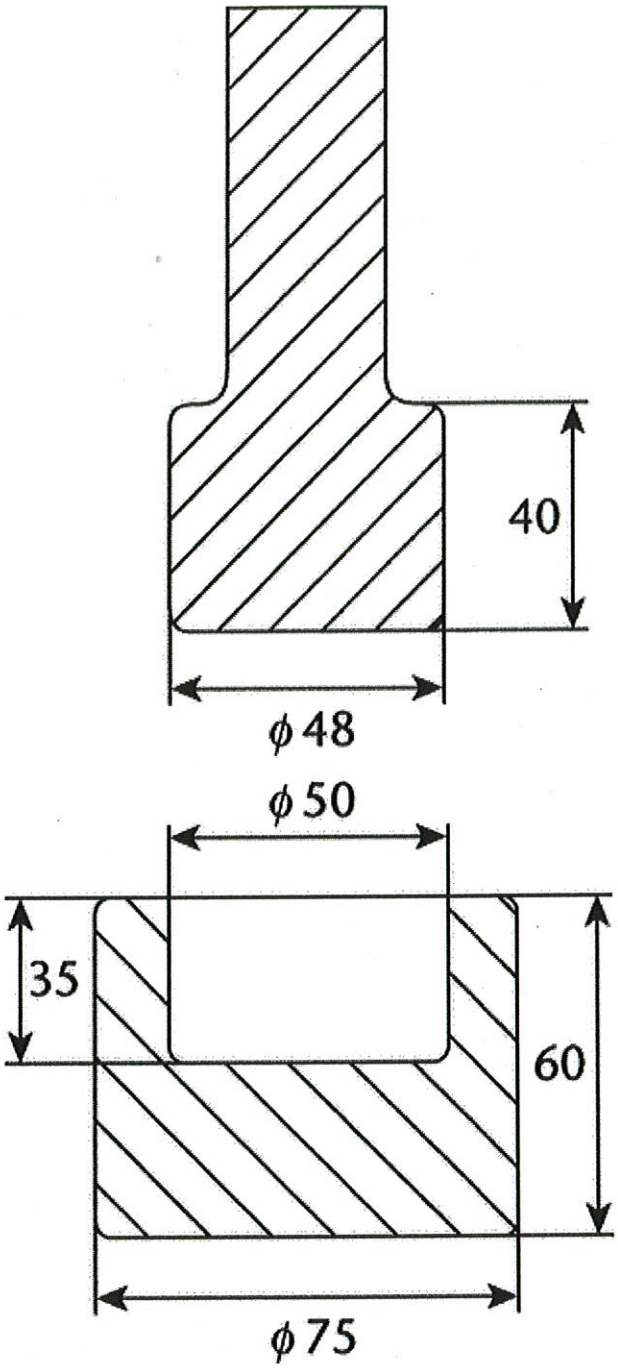


Figure 1. Mortar and pestle for pulverizing glass.

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 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 ± 5°; a balance, capable of weighing up to 500 g with an accuracy of 0.005 g; a desiccator; and an ultrasonic bath.

Reagents

Carbon Dioxide-Free Water— This is Purified Water that has been boiled vigorously for 5 minutes 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. Not more than 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).

GLASS GRAINS TEST

The *Glass Grains Test* may be performed either on the canes used for the manufacture of tubing glass containers or on the containers.

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 not more than 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. 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 minutes. 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 weigh 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 minute. 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 and then by heating at 140° for 20 minutes 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— Weigh 10.00 g of the cleaned and dried grains into two separate conical flasks. Pipet 50 mL of carbon dioxide-free Purified Water into each of the conical flasks (test solutions). Pipet 50 mL of carbon dioxide-free 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. Heat the autoclave to 100°, and allow the steam to issue from the vent cock for 10 minutes.
2. Close the vent cock, and raise the temperature from 100° to 121° at a rate of 1° per minute.

3. Maintain the temperature at 121 ± 1° for 30 ± 1 minutes.
4. Lower the temperature from 121° to 100° at a rate of 0.5° per minute, venting to prevent a vacuum.
5. Do not open the autoclave before it has cooled to 95°. Remove the containers from the autoclave, using normal precautions, and cool the flasks in running tap water.

Titration— To each of the 3 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. Repeat the test if the highest and lowest observed values differ by more than 20%.

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, 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 Purified Water and 0.05 mL of *Methyl Red Solution* to the blank solution.

Limits: The volume does not exceed the values indicated in *Table 3*.

Table 3. Test Limits for Glass Grains Test

	Maximum Volume of 0.02 M HCl per g of Test Glass (mL)	
Filling Volume (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 2 decimal places, for containers having a nominal volume less than or equal to 30 mL; and expressed to 1 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 1 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 2 decimal places, and calculate the mean value. This volume, expressed to 1 decimal place, is the filling volume for the particular ampul lot. The filling volume may also be determined by weighing.

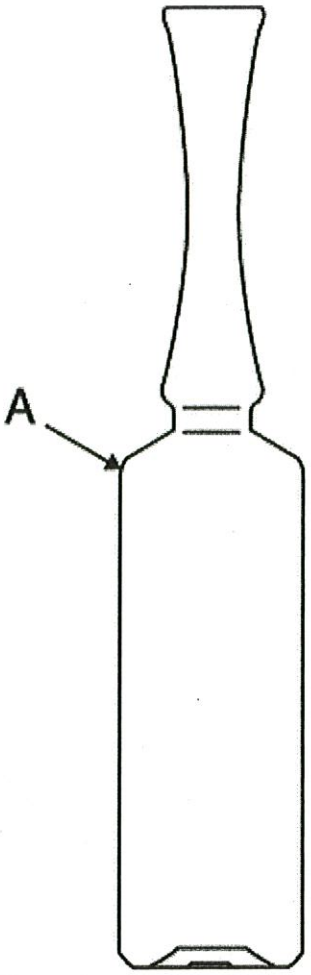


Figure 2. Filling volumes of ampuls up to point A.

Test: The determination is carried out on unused containers. The volumes of the test liquid necessary for the final determination are shown in *Table 4*.

Table 4. Volume of Test Liquid and Number of Titrations

Filling Volume (mL)	Volume of Test Liquid for One Titration (mL)	Number of Titrations
Up to 3	25.0	1
Above 3 and up to 30	50.0	2
Above 30 and up to 100	100.0	2
Above 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, 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 in not less than 20 minutes and not more than 25 minutes. Heat closed ampuls in a water bath or in an air oven at about 50° for approximately 2 minutes before 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 the autoclaving procedure as described for the *Glass Grains Test*, except that the temperature is maintained at 121 ± 1° for 60 ± 1 minutes. Remove the containers from the autoclave using normal precautions, place them in a water bath at 80°, and run cold tap water into the water bath. To avoid contamination of the extraction solution, take care that the water does not contact the loose foil caps. The cooling time does not exceed 30 minutes. The extraction solutions are analyzed by titration according to the method described below.

Titration— Carry out the titration within 1 hour of removal of the containers from the autoclave. Combine the liquids obtained from the containers, and mix. Introduce the prescribed volume (see *Table 4*) 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 liquid 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 liquid, and express the results in mL of 0.01 M hydrochloric acid per 100 mL of test liquid. Express titration values of less than 1.0 mL to two decimal places; express titration values of more 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 5*.

Table 5. Limit Values for the Surface Glass Test

	Maximum Volume of 0.01 M HCl per 100 mL of Test Liquid (mL)	
Filling Volume (mL)	**Types I and II**	**Type III**
Up to 1	2.0	20.0
Above 1 and up to 2	1.8	17.6
Above 2 and up to 5	1.3	13.2
Above 5 and up to 10	1.0	10.2
Above 10 and up to 20	0.80	8.1
Above 20 and up to 50	0.60	6.1
Above 50 and up to 100	0.50	4.8
Above 100 and up to 200	0.40	3.8
Above 200 and up to 500	0.30	2.9
Above 500	0.20	2.2

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 liquid required are shown in *Table 4*. 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 minutes. 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 for the *Surface Glass Test*. If the results are considerably higher than those obtained from the original surfaces (by a factor of about 5 to 10), the samples have been surface treated. [*Caution— Hydrofluoric acid is extremely aggressive. Even small quantities can cause life threatening injuries.*]

Ampuls, Cartridges, and Syringes— Apply the test method as described for *Vials and Bottles*. If the ampuls, cartridges, and syringes are not surface treated, the values obtained are slightly lower than those obtained in the previous tests. [NOTE — Ampuls, 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 larger 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 one 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 for the *Surface Glass Test*. The limit does not exceed 0.1 µg per g.

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.

Preparation of Sample: 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 nonparenteral 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

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

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
General Chapter	Desmond G. Hunt, Ph.D. Senior Scientific Liaison (301) 816-8341	(GCPS2010) General Chapters - Packaging Storage and Distribution

USP37–NF32 Page 318
Pharmacopeial Forum: Volume No. 37(2)

〈 671 〉 CONTAINERS—PERFORMANCE TESTING

It is the purpose of this chapter to provide standards for the functional properties of containers and their components used to package regulated articles (pharmaceuticals, biologics, dietary supplements, and devices). Definitions that apply to this chapter are provided in 〈 659 〉 *Packaging and Storage Requirements*. The tests that follow are provided to determine the moisture permeability and light transmission of containers utilized for regulated articles. The section *Multiple-Unit Containers for Capsules and Tablets* applies to multiple-unit containers. The section *Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets* applies to single-unit and unit-dose containers. The section *Multiple-Unit Containers for Capsules and Tablets (Without Closure)* applies to polyethylene and polypropylene containers that have no closures. The section *Multiple-Unit and Single-Unit Containers for Liquids* applies to multiple-unit and single-unit containers.

A container intended to provide protection from light or offered as a *light-resistant* container meets the requirements for *Light Transmission*, where such protection or resistance is by virtue of the specific properties of the material of which the container is composed, including any coating applied thereto. A clear and colorless or a translucent container that is made *light-resistant* by means of an opaque enclosure (see *General Notices and Requirements*) is exempt from the requirements for *Light Transmission*. As used herein, the term "container" refers to the entire system comprising, usually, the container itself, the liner (if used), the closure in the case of multiple-unit containers, and the lidding and blister in the case of unit-dose containers.

MOISTURE PERMEATION

Multiple-Unit Containers for Capsules and Tablets

Desiccant— Place a quantity of 4- to 8-mesh, anhydrous calcium chloride[1] in a shallow container, taking care to exclude any fine powder, then dry at 110° for 1 hour, and cool in a desiccator.

Procedure— Select 12 containers of a uniform size and type, clean the sealing surfaces with a lint-free cloth, and close and open each container 30 times. Apply the closure firmly and uniformly each time the container is closed. Close screw-capped containers with a torque that is within the range of tightness specified in the accompanying table. Add *Desiccant* to 10 of the containers, designated *test containers,* filling each to within 13 mm of the closure if the container volume is 20 mL or more, or filling each to two-thirds of capacity if the container volume is less than 20 mL. If the interior of the container is more than 63 mm in depth, an inert filler or spacer may be placed in the bottom to minimize the total weight of the container and *Desiccant;* the layer of *Desiccant* in such a container shall be not less than 5 cm in depth. Close each immediately after adding *Desiccant,* applying the torque designated in the accompanying table when closing screw-capped containers. To each of the remaining 2 containers, designated *controls*, add a sufficient number of glass beads to attain a weight approximately equal to that of each of the *test containers,* and close, applying the torque designated in the accompanying table when closing screw-capped containers. Record the weight of the individual containers so prepared to the nearest 0.1 mg if the container volume is less than 20 mL; to the nearest mg if the container volume is 20 mL or more but less than 200 mL; or to the nearest centigram (10 mg) if the container volume is 200 mL or more; and store at 75 ± 3% relative humidity and a temperature of 23 ± 2°. [NOTE—A saturated system of 35 g of sodium chloride with each 100 mL of water placed in the bottom of a desiccator maintains the specified humidity. Other methods may be employed to maintain these conditions.] After 336 ± 1 hours (14 days), record the weight of the individual containers in the same manner. Completely fill 5 empty containers of the same size and type as the containers under test with

water or a noncompressible, free-flowing solid such as well-tamped fine glass beads, to the level indicated by the closure surface when in place. Transfer the contents of each to a graduated cylinder, and determine the average container volume, in mL. Calculate the rate of moisture permeability, in mg per day per L, by the formula:

$$(1000/14V)[(T_F - T_I) - (C_F - C_I)]$$

in which V is the volume, in mL, of the container; $(T_F - T_I)$ is the difference, in mg, between the final and initial weights of each *test container;* and $(C_F - C_I)$ is the difference, in mg, between the average final and average initial weights of the 2 *controls.* For containers used for drugs being dispensed on prescription, the containers so tested are *tight containers* if not more than 1 of the 10 *test containers* exceeds 100 mg per day per L in moisture permeability, and none exceeds 200 mg per day per L. For containers used for drugs being dispensed on prescription, the containers are *well-closed containers* if not more than 1 of the 10 *test containers* exceeds 2000 mg per day per L in moisture permeability, and none exceeds 3000 mg per day per L.

Table 1. Torque Applicable to Screw-Type Container

Closure Diameter[a] (mm)	Suggested Tightness Range with Manually Applied Torque[b] (inch-pounds)
8	5
10	6
13	8
15	5–9
18	7–10
20	8–12
22	9–14
24	10–18
28	12–21
30	13–23
33	15–25
38	17–26
43	17–27
48	19–30
53	21–36
58	23–40

[a] The torque designated for the next larger closure diameter is to be applied in testing containers having a closure diameter intermediate to the diameters listed.

[b] A suitable apparatus is available from SecurePak, PO Box 1210, Maumee, Ohio 43537-8210. MRA Model with indicators on both the removal and application sides available in the following ranges: 1) 0–25 inch lbs., read in 1-inch lb. increments, 2) 0–50 inch lbs., read in 2-inch lb. increments, and 3) 0–100 inch lbs., read in 5-inch lb. increments. For further detail regarding instructions, reference may be made to "Standard Test Method for Application and Removal Torque of Threaded or Lug-Style Closures" ASTM Method D3198-02, published by the American Society for Testing and Materials, 100 Barr Harbor Drive, P.O. Box C700, West Conshohocken, PA 19428-2959.

Closure Diameter[a] (mm)	Suggested Tightness Range with Manually Applied Torque[b] (inch-pounds)
63	25–43
66	26–45
70	28–50
83	32–65
86	40–65
89	40–70
100	45–70
110	45–70
120	55–95
132	60–95

[a] The torque designated for the next larger closure diameter is to be applied in testing containers having a closure diameter intermediate to the diameters listed.

[b] A suitable apparatus is available from SecurePak, PO Box 1210, Maumee, Ohio 43537-8210. MRA Model with indicators on both the removal and application sides available in the following ranges: 1) 0–25 inch lbs., read in 1-inch lb. increments, 2) 0–50 inch lbs., read in 2-inch lb. increments, and 3) 0–100 inch lbs., read in 5-inch lb. increments. For further detail regarding instructions, reference may be made to "Standard Test Method for Application and Removal Torque of Threaded or Lug-Style Closures" ASTM Method D3198-02, published by the American Society for Testing and Materials, 100 Barr Harbor Drive, P.O. Box C700, West Conshohocken, PA 19428-2959.

Multiple-Unit Containers for Capsules and Tablets (Without Closure)

Polyethylene Container— Fit the containers with impervious seals obtained by heat-sealing the bottles with an aluminum foil–polyethylene laminate or other suitable seal.[2] Test the containers as specified under *Multiple-Unit Containers for Capsules and Tablets:* the high-density polyethylene containers so tested meet the requirements if the moisture permeability exceeds 10 mg per day per L in not more than 1 of the 10 test containers and exceeds 25 mg per day per L in none of them. The low-density polyethylene containers so tested meet the requirements if the moisture permeability exceeds 20 mg per day per L in not more than 1 of the 10 test containers and exceeds 30 mg per day per L in none of them.

Polypropylene Containers— Fit the containers with impervious seals obtained by heat-sealing the bottles with an aluminum foil–polyethylene laminate or other suitable seal. Test the containers as described under *Multiple-Unit Containers for Capsules and Tablets.* The containers meet the requirements if the moisture permeability exceeds 15 mg per day per L in not more than 1 of the 10 test containers and exceeds 25 mg per day per L in none of them.

Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets

To permit an informed judgment regarding the suitability of the packaging for a particular type of product, the following procedure and classification scheme are provided for evaluating the moisture-permeation characteristics of single-unit and unit-dose containers. Inasmuch as equipment and operator performance may affect the moisture permeation of a container formed or closed, the moisture-permeation characteristics of the packaging system being utilized shall be determined.

Desiccant— Dry suitable desiccant pellets[3] at 110° for 1 hour prior to use. Use pellets weighing approximately 400 mg each and having a diameter of approximately 8 mm. [NOTE— If necessary due to limited unit-dose container size, pellets weighing less than 400 mg each and having a diameter of less than 8 mm may be used.]

Procedure—

Method I— Seal not fewer than 10 unit-dose containers with 1 pellet in each, and seal 10 additional, empty unit-dose containers to provide the controls, using finger cots or padded forceps to handle the sealed containers. Number the containers, and record the individual weights[4] to the nearest mg. Weigh the controls as a unit, and divide the total weight by the number of controls to obtain the average. Store all of the containers at 75 ± 3% relative humidity and at a temperature of 23 ± 2°. [NOTE— A saturated system of 35 g of sodium chloride with each 100 mL of water placed in the bottom of a desiccator maintains the specified humidity. Other methods may be employed to maintain these conditions.] After a 24-hour interval, and at each multiple thereof (see *Results*), remove the containers from the chamber, and allow them to equilibrate for 15 to 60 minutes in the weighing area. Again record the weight of the individual containers and the combined controls in the same manner. [NOTE— If any indicating pellets turn pink during this procedure, or if the pellet weight increase exceeds 10%, terminate the test, and regard only earlier determinations as valid.] Return the containers to the humidity chamber. Calculate the rate of moisture permeation, in mg per day, of each container taken by the formula:

$$(1/N)[(W_F - W_I) - (C_F - C_I)]$$

in which N is the number of days expired in the test period (beginning after the initial 24-hour equilibration period); $(W_F - W_I)$ is the difference, in mg, between the final and initial weights of each test container; and $(C_F - C_I)$ is the difference, in mg, between the average final and average initial weights of the controls, the data being calculated to two significant figures. [NOTE— Where the permeations measured are less than 5 mg per day, and where the controls are observed to reach equilibrium within 7 days, the individual permeations may be determined more accurately by using the 7-day test container and control container weights as W_I and C_I, respectively, in the calculation. In this case, a suitable test interval for *Class A* (see *Results*) would be not less than 28 days following the initial 7-day equilibration period (a total of 35 days).]

Method II— Use this procedure for packs (e.g., punch-out cards) that incorporate a number of separately sealed unit-dose containers or blisters. Seal a sufficient number of packs, such that not fewer than 4 packs and a total of not fewer than 10 unit-dose containers or blisters filled with 1 pellet in each unit are tested. Seal a corresponding number of empty packs, each pack containing the same number of unit-dose containers or blisters as used in the test packs, to provide the controls. Store all of the containers at 75 ± 3% relative humidity and at a temperature of 23 ± 2°. [NOTE— A saturated system of 35 g of sodium chloride with each 100 mL of water placed in the bottom of a desiccator maintains the specified humidity. Other methods may be employed to maintain these conditions.] After 24 hours, and at each multiple thereof (see *Results*), remove the packs from the chamber, and allow them to equilibrate for about 45 minutes. Record the weights of the individual packs, and return them to the chamber. Weigh the control packs as a unit, and divide the total weight by the number of control packs to obtain the average empty pack weight. [NOTE— If any indicating pellets turn pink during the procedure, or if the average pellet weight increase in any pack exceeds 10%, terminate

the test, and regard only earlier determinations as valid.] Calculate the average rate of moisture permeation, in mg per day, for each unit-dose container or blister in each pack taken by the formula:

$$(1/NX)[(W_F - W_I) - (C_F - C_I)]$$

in which N is the number of days expired in the test period (beginning after the initial 24-hour equilibration period); X is the number of separately sealed units per pack; $(W_F - W_I)$ is the difference, in mg, between the final and initial weights of each test pack; and $(C_F - C_I)$ is the difference, in mg, between the average final and average initial weights of the control packs, the rates being calculated to two significant figures.

Results— The individual unit-dose containers as tested in *Method I* are designated *Class A* if not more than 1 of 10 containers tested exceeds 0.5 mg per day in moisture permeation rate and none exceeds 1 mg per day; they are designated *Class B* if not more than 1 of 10 containers tested exceeds 5 mg per day and none exceeds 10 mg per day; they are designated *Class C* if not more than 1 of 10 containers tested exceeds 20 mg per day and none exceeds 40 mg per day; and they are designated *Class D* if the containers tested meet none of the moisture permeation rate requirements.

The packs as tested in *Method II* are designated *Class A* if no pack tested exceeds 0.5 mg per day in average blister moisture permeation rate; they are designated *Class B* if no pack tested exceeds 5 mg per day in average blister moisture permeation rate; they are designated *Class C* if no pack tested exceeds 20 mg per day in average blister moisture permeation rate; and they are designated *Class D* if the packs tested meet none of the above average blister moisture permeation rate requirements.

With the use of the *Desiccant* described herein, as stated for *Method I* and *Method II*, after every 24 hours, the test and control containers or packs are weighed; and suitable test intervals for the final weighings, W_F and C_F, are as follows: 24 hours for *Class D;* 48 hours for *Class C;* 7 days for *Class B;* and not less than 28 days for *Class A.*

Multiple-Unit Containers and Unit-Dose Containers for Liquids

The standards and tests provided in this section measure the functional and performance characteristics of bottles used to package aqueous products by measuring the liquid water weight loss as a percent of the contents. This test can also be used to demonstrate performance or functional comparability. [NOTE— Throughout the following procedure, determine the weights of individual container–closure systems (bottle, innerseal if used, and closure) both as tare weights and fill weights, to the nearest 0.1 mg if the bottle capacity is less than 200 mL; to the nearest mg if the bottle capacity is 200 mL or more but less than 1000 mL; or to the nearest centigram (10 mg) if the bottle capacity is 1000 mL or more.]

Procedure— Select 12 bottles of a uniform size and type, and clean the sealing surfaces with a lint-free cloth. Fit each bottle with a seal, closure liner (if applicable), and closure. Number each container–closure system, and record the tare weight.

Remove the closures and, using a pipet, fill 10 bottles with water to the fill capacity. Fill 2 containers with glass beads to the same approximate weight of the filled test containers. If using screw closures, apply a torque that is within the range specified in *Table 1,* and store the sealed containers at a temperature of 25 ± 2° and a relative humidity of 40 ± 2%. After 336 ± 1 hours (14 days), record the weight of the individual containers, and calculate the water weight loss rate, in percent per year, for each bottle taken by the formula:

$$(W_{1i} - W_T) - (W_{14i} - W_T) - (WC_1 - WC_{14}) \; 365 \times 100/(W_{1\,i} - W_T)14 = \text{Percent per year}$$

in which W_{1i} is the initial weight of each individual bottle (i); W_T is the tare weight; W_{14i} is the weight of each individual bottle (i) at 14 days; and ($WC_1 - WC_{14}$) is the average weight change of the controls from initial to 14 days.

The containers so tested meet the requirements and are tight containers if the percentage of water weight loss does not exceed 2.5% per year in not more than 1 of the 10 test containers and does not exceeds 5.0% per year in none of them.

LIGHT TRANSMISSION TEST

Apparatus [5]—Use a spectrophotometer of suitable sensitivity and accuracy, adapted for measuring the amount of light transmitted by either transparent or translucent glass or plastic materials used for pharmaceutical containers. In addition, the spectrophotometer is capable of measuring and recording light transmitted in diffused as well as parallel rays.

Procedure— Select sections to represent the average wall thickness. Cut circular sections from two or more areas of the container and trim them as necessary to give segments of a size convenient for mounting in the 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 masking tape, provided that the length of the specimen is greater than that of the slit in the spectrophotometer. Immediately before mounting in the specimen holder, wipe the specimen with lens tissue. Mount the specimen with the aid of a tacky wax, or by other convenient means, taking care to avoid leaving fingerprints or other marks on the surfaces through which light must pass. Place the section in the spectrophotometer with its cylindrical axis parallel to the plane of the slit and approximately centered with respect to the slit. When properly placed, the light beam is normal to the surface of the section and reflection losses are at a minimum.

Continuously measure the transmittance of the section with reference to air in the spectral region of interest with a recording instrument or at intervals of about 20 nm with a manual instrument, in the region of 290 to 450 nm.

Limits— The observed light transmission does not exceed the limits given in *Table 2* for containers intended for parenteral use.

Table 2. Limits for Plastic Classes I–VI and Glass Types I, II, and III

	Maximum Percentage of Light Transmission at Any Wavelength between 290 and 450 nm	
Nominal Size (in mL)	**Flame-sealed Containers**	**Closure-sealed Containers**
1	50	25
2	45	20
5	40	15
10	35	13
20	30	12
50	15	10

[NOTE—Any container of a size intermediate to those listed above exhibits a transmission not greater than that of the next larger size container listed in the table. For containers larger than 50 mL, the limits for 50 mL apply.]

The observed light transmission for plastic containers for products intended for oral or topical administration does not exceed 10% at any wavelength in the range from 290 to 450 nm.

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[1] Suitable 4- to 8-mesh, anhydrous calcium chloride is available commercially as Item JT1313-1 from VWR International. Consult the VWR International catalog for ordering information or call 1-800-234-9300.

[2] A suitable laminate for sealing has, as the container layer, polyethylene of not less than 0.025 mm (0.001 inch) and a second layer of aluminum foil of not less than 0.018 mm (0.0007 inch), with additional layers of suitable backing materials. A suitable seal can be obtained also by using glass plates and a sealing wax consisting of 60% of refined amorphous wax and 40% of refined crystalline paraffin wax.

[3] Suitable moisture-indicating desiccant pellets are available commercially from sources such as Medical Packaging, Inc., 470 Route 31, Ringoes, NJ 08551-1409 [Telephone 800-257-5282; in NJ, 609-466-8991; FAX 609-466-3775], as Indicating Desiccant Pellets, Item No. TK-1002.

[4] Accurate comparisons of *Class A* containers may require test periods in excess of 28 days if weighings are performed on a *Class A* prescription balance (see *Prescription Balances and Volumetric Apparatus* ⟨ 1176 ⟩). The use of an analytical balance on which weights can be recorded to 4 or 5 decimal places may permit more precise characterization between containers and/or shorter test periods.

[5] For further detail regarding apparatus and procedures, reference may be made to the following publications of the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19428-2959: "Standard Method of Test for Haze and Luminous Transmittance of Transparent Plastics," ASTM Method D1003-07; "Tentative Method of Test for Luminous Reflectance, Transmittance and Color of System"ASTM Method E308-06.

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
General Chapter	Desmond G. Hunt, Ph.D. Senior Scientific Liaison (301) 816-8341	(GCPS2010) General Chapters - Packaging Storage and Distribution

USP37–NF32 Page 329
Pharmacopeial Forum: Volume No. 39(2)