

■ {671} CONTAINERS— PERFORMANCE TESTING

It is the purpose of this chapter to provide standards for the functional properties of plastic containers and their components used to package regulated articles (pharmaceuticals, biologics, dietary supplements, and devices). Definitions that apply to this chapter are provided in the *Preservation, Packaging, Storage, and Labeling* section of the *General Notices and Requirements*. The tests that follow are provided to determine the moisture permeability and light transmission of plastic 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.

MULTIPLE-UNIT CONTAINERS FOR CAPSULES AND TABLETS

Desiccant—Place a quantity of 4- to 8-mesh, anhydrous calcium chloride¹ 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 pre-

pared 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
63	25–43
66	26–45
70	28–50
83	32–65
86	40–65
89	40–70
100	45–70
110	45–70

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

Table 1. Torque Applicable to Screw-Type Container (*Continued*)

Closure Diameter ^a (mm)	Suggested Tightness Range with Manually Applied Torque; ^b (inch-pounds)
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., which reads in 1 inch lb increments, 2) 0-50 inch lbs., which reads in 2 inch lb increments, and 3) 0-100 inch lbs., which reads 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

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.

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 pellets³ 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 weights⁴ 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

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.

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:

$$(1/NX)[(W_F - W_T) - (C_F - C_T)]$$

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; $(W_F - W_T)$ is the difference, in mg, between the final and initial weights of each test pack; and $(C_F - C_T)$ 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 plastic containers 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 overflow capacity is less than 200 mL; to the nearest mg if the bottle overflow capacity is 200 mL or more but less than 1000 mL; or to the nearest centigram (10 mg) if the bottle overflow capacity is 1000 mL or more.]

Procedure for Testing Unopened Market Containers (cap liner [if applicable], innerseal, and cap)—Select 10 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 pipette, fill bottles with water to the overflow capacity. Fit the bottles with seals and apply the closures. 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 $25 \pm 2^\circ$ and a relative humidity of $50 \pm 2\%$. Af-

ter 168 ± 1 hours (7 days), record the weight of the individual containers. Return the containers to storage for another 168 ± 1 hours. After the second 168 ± 1 hours, remove the containers, record the weights of each of the individual container systems, and calculate the water vapor permeation rate, in percent water weight loss, for each bottle taken by the formula:

$$(W_7 - W_{14})365 \times 100 / (W_7 - W_T)7 = \text{Percent per year}$$

in which W_7 is the weight, in mg, of the container at 7 days; W_{14} is the weight, in mg, of the container at 14 days; W_T is the tare weight in g; and 7 is the test time, in days, after the 7-day equilibration period. 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 exceeds 5.0% per year in none of them.

Unit-dose containers for liquids meet the requirement of a tight container if the average water weight loss is less than or equal to 2.5% (w/w) loss per year (5% at the end of 2 years).

Procedure for Testing Multiple-Unit Containers Under Conditions of Use—Select 10 bottles of a uniform size and type. If an innerseal is used, carefully open the individual containers and remove the innerseal from each container. Fit each bottle with a closure liner (if applicable) and closure. Number each container–closure system, and record the tare weight. Open and close the containers 30 times being careful not to lose liquid in the process. Close screw-capped bottles with a torque that is within the range of tightness provided in *Table 1*, and store the sealed containers at a temperature of $25 \pm 2^\circ$ and a relative humidity of $50 \pm 2\%$. After 168 ± 1 hours (7 days), record the weight of the individual containers. Return the containers to storage for another 168 ± 1 hours. After the second 168 ± 1 hours, remove the containers, record the weights of each of the individual container systems, in percent water weight loss, for each bottle taken by the formula:

$$(W_7 - W_{14})365 \times 100 / (W_7 - W_T)7 = \text{Percent per year}$$

in which W_7 is the weight, in mg, of the container at 7 days; W_{14} is the weight, in mg, of the container at 14 days; W_T is the tare weight, in g; and 7 is the test time, in days, after the 7-day equilibration period. 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 exceeds 5.0% per year in none of them.

LIGHT TRANSMISSION TEST

Apparatus⁵—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

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 Designation D-1003-61; “Tentative Method of Test for Luminous Reflectance, Transmittance, and Color of Materials,” ASTM E 308-66.

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. [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.]

Table 2. Limits for Plastic Classes I–VI

Nominal Size (in mL)	Maximum Percentage of Light Transmission at Any Wavelength Between 290 and 450 nm
	Closure-Sealed Containers
1	25
2	20
5	15
10	13
20	12
50	10

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. ■^{1S} (USP30)