# ⟨671⟩ CONTAINERS—PERFORMANCE TESTING

## INTRODUCTION

It is the purpose of this chapter to provide standards for the functional properties of packaging systems used for solid oral dosage forms (SODF) and liquid oral dosage forms (LODF) for pharmaceuticals and dietary supplements. Definitions that apply to this chapter are provided in *Packaging and Storage Requirements* ⟨659⟩. The tests that follow are provided to determine the moisture vapor transmission rate (water vapor permeation rate) and spectral transmission of plastic containers.

Test methods are provided to measure moisture vapor transmission rates that may be useful for pharmaceutical and dietary supplement manufacturers to determine the level of barrier protection provided by packaging systems for SODF. Additional methods are provided to determine classification of packaging systems for SODF and LODF that are repackaged by organizations or when being dispensed on prescription by pharmacists as single-unit and multiple-unit containers (*Table 1*). There may be additional packaging systems where the test methods in this section could be applied; however, any deviation should be described. If other methods are used to measure moisture vapor transmission rate, these methods should be described in sufficient detail to justify their use.

**Table 1. Moisture Vapor Transmission Test Methods for Packaging Systems**

| | Solid Oral Dosage Forms | | | Liquid Oral Dosage Forms |
|---|---|---|---|---|
| **Section Title** | Barrier Protection Determination | Classification for Multiple-Unit Containers | Classification for Single-Unit Containers and Unit-Dose Containers | Classification for Multiple-Unit Containers and Unit-Dose Containers |
| **Application** | Multiple-unit containers with seal intact or broached state and single-unit or unit dose containers | Multiple-unit containers with closure applied and seal intact or broached state | Single-unit and unit-dose containers in sealed state | Multiple- and single-unit containers |
| **Users** | Manufacturers | Manufacturers<br>Packagers<br>Repackagers<br>Pharmacies | Manufacturers<br>Packagers<br>Repackagers<br>Pharmacies | Manufacturers<br>Packagers<br>Repackagers<br>Pharmacies |

## Definitions

**Blister**—Formed, lidded, and sealed plastic or foil dome that contains the capsule or tablet (usually a single-unit or unit-dose).

**Low-barrier blister**—Blisters made from low-barrier materials formed and sealed so that the moisture vapor transmission rate when tested at 40°/75% relative humidity (RH) is greater than 1.0 mg/cavity-day.

**High-barrier blister**—Blisters made from high-barrier material, formed and sealed so that the moisture vapor transmission rate when tested at 40°/75% RH is less than 1.0 mg/cavity-day.

**Ultra-high barrier blister**—Blisters made from ultlra high-barrier material, formed and sealed so that the moisture vapor transmission rate when tested at 40°/75% RH is less than 0.01 mg/cavity-day.

**Blister card**—A contiguous group of blisters formed and sealed with lid in place. The number of blisters per card commonly ranges from one to ten but may be more. The blister card may sometimes be referred to as a packaging system.

**Cavity**—Formed, lidded, and sealed plastic or foil dome (see *Blister*).

**Moisture vapor transmission rate**—The steady state moisture vapor transmission in unit time through a packaging system, under specific conditions of temperature and humidity. These test methods use gravimetric measurement to determine the rate of weight gain as a result of water vapor transmission into the packaging system and subsequent uptake by a desiccant enclosed within the packaging system.

**Test specimen (or specimen)**—For multiple-unit containers, the bottle is the test specimen; and for single-unit or unit-dose containers, the blister card containing multiple blister cavities is the test specimen. For blisters, more than one card (or specimen) may be grouped into a test unit for conducting the test.

**Test unit**—For multiple-unit containers, the bottle is the test unit as well as being the test specimen and for single-unit or unit-dose containers, the test unit is a group of test specimens (blister cards) processed together for temperature and humidity exposure and for weighing at each time point. The purpose of the test unit for single-unit or unit-dose containers is to gain the advantage of additive weight gain resulting from more blister cavities than are present on a single card. The *test unit*, when applied to bottles, is used to maintain congruence of naming among the three test methods.

# MOISTURE VAPOR TRANSMISSION

## Barrier Protection Determination for Packaging Systems for Solid Oral Dosage Forms

This section describes moisture vapor transmission test methods for multiple-unit containers (*Method 1*), high barrier single-unit and unit-dose containers (*Method 2*), and low barrier single-unit and unit-dose containers (*Method 3*) used by pharmaceutical manufacturers to package SODF. The purpose of this test method is to obtain reliable and specific moisture vapor transmission rates that can be used to discriminate among barrier performance of packaging systems used for regulated articles; the method is based upon ASTM method D7709.[1]

This method contains the following attributes:

a. Reports a specific moisture vapor transmission value for a container rather than a classification
b. Provides sufficient sensitivity and precision to allow differentiation among moisture barrier performance for containers
c. Conditions used for testing these packaging systems are the same as those used for accelerated stability testing of the primary packaging of regulated articles (typically 40°/75% RH).

### EQUIPMENT

The following items should be available:

- A balance for weighing the test specimens that has sufficient capacity to weigh the test specimens throughout the period of the test (see *Weighing on an Analytical Balance* ⟨1251⟩). The balance shall have sensitivity adequate to measure small differences in weight from one time point to the next. The weighing uncertainty shall be smaller than 5% of the weight gain from one time point to the next. The weighing uncertainty is typically three times the balance resolution/sensitivity. As an example, a balance with a resolution of 0.1 mg is acceptable for packaging systems whose weight gain per time interval is more than or equal to 6 mg [(0.1 × 3)/5%], which is 60 times the balance sensitivity.
- A chamber capable of maintaining 40 ± 2° and 75 ± 5% RH.

### DESICCANT

**Method 1:** The desiccant is anhydrous calcium chloride in granular form. Other desiccants, such as a molecular sieve or silica gel, may be suitable. If anhydrous calcium chloride is used, pre-dry at 215 ± 5° for 7¼ ± ¼ h to ensure that any hexahydrate present is fully converted to the anhydrate. Cool the desiccant in a desiccator for at least 2 h before use.

**Methods 2 and 3:** The desiccant is silica gel molded in a form to fit the size and shape of the blister cavity used. Other desiccants may be suitable, for example, a molecular sieve. If silica gel is used, pre-dry in a circulating hot air oven at one of two conditions: 155 ± 5° for 3¼ ± ¼ h or 150 ± 5° for 4¼ ± ¼ h. If a molecular sieve is used, pre-dry in a muffle furnace at 595 ± 25°. Dry the 4A and 3A sieves for 3¼ ± ¼ h; dry the 13X sieve for 5¼ ± ¼ h. Cool the desiccant in a desiccator for at least 2 h before use. [NOTE—It has been shown[2] that anhydrous calcium chloride may contain calcium hexahydrate, which loses water only when the temperature reaches 200°.]

### PROCEDURE

**Method 1:** Use 15 multiple-unit containers and 15 closures representative of the system to be tested. Prepare the test specimens by filling each multiple-unit container two-thirds with desiccant then, for screw type closures, apply the closure using the torque that is within the range of tightness specified in *Table 2*. For other closure types, apply according to the intended method. Ensure that a proper seal has been made with the intended membrane to the land area of the bottle finish. Identify each multiple-unit container with indelible ink. Do not use a label. If there is a need to increase the precision of the method, the user can test the system without the closure as long as an impervious seal remains on the container.

If desired, weigh each multiple-unit container at ambient temperature and RH. Record this weight for time zero, but do not use it in the calculation of permeation. Place all containers in the test chamber (40°/75% RH) within 1 h of weighing. Weigh all multiple-unit containers at time intervals of 7 days ± 1 h. Weigh the multiple-unit containers at 7, 14, 21, 28, and 35 days to get steady-state data points. (The time interval from time 0 to day 7 is the period of equilibration.) Prior to weighing at each time interval, equilibrate the containers for about 30 min at the weighing temperature and RH. Limit the time out of the chamber to less than 2 h. Record the weights in an appropriate manner for later computation of the regression line.

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[1] ASTM D7709. Standard Test Methods for Measuring Water Vapor Transmission Rate (WVTR) of Pharmaceutical Bottles and Blisters published by ASTM International, 100 Barr Harbor Drive, P.O. Box C700, West Conshohocken, PA 19428-2959.

[2] Determination of water vapor transmission rate (WVTR) of HDPE bottles for pharmaceutical products. Chen, Yisheng and Yanxia Li, International Journal of Pharmaceutics, 358 (2008) 137–143.

**Table 2. Torque Applicable to Screw-Type Container**

| Closure Diameter[a] (mm) | Suggested Tightness Range with Manually Applied Torque[b] (inch-pounds) | Suggested Tightness Range with Manually Applied Torque[b] (Newton-meters) |
|---|---|---|
| 8 | 5 | 0.56 |
| 10 | 6 | 0.68 |
| 13 | 8 | 0.90 |
| 15 | 5–9 | 0.56–1.02 |
| 18 | 7–10 | 0.79–1.13 |
| 20 | 8–12 | 0.90–1.36 |
| 22 | 9–14 | 1.02–1.58 |
| 24 | 10–18 | 1.13–2.03 |
| 28 | 12–21 | 1.36–2.37 |
| 30 | 13–23 | 1.47–2.60 |
| 33 | 15–25 | 1.69–2.82 |
| 38 | 17–26 | 1.92–2.94 |
| 43 | 17–27 | 1.92–3.05 |
| 48 | 19–30 | 2.15–3.39 |
| 53 | 21–36 | 2.37–4.07 |
| 58 | 23–40 | 2.60–4.52 |
| 63 | 25–43 | 2.82–4.86 |
| 66 | 26–45 | 2.94–5.08 |
| 70 | 28–50 | 3.16–5.65 |
| 83 | 32–65 | 3.62–7.35 |
| 86 | 40–65 | 4.52–7.35 |
| 89 | 40–70 | 4.52–7.91 |
| 100 | 45–70 | 5.09–7.91 |
| 110 | 45–70 | 5.09–7.91 |
| 120 | 55–95 | 6.22–10.74 |
| 132 | 60–95 | 6.78–10.74 |

[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 905, Maumee, Ohio 43552-0905; www.secure-pak.com. 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, published by the ASTM International, 100 Barr Harbor Drive, P.O. Box C700, West Conshohocken, PA 19428-2959.

**Method 2:** Use 10 test units for this method. Provide a minimum of 10 blister cavities for each test unit. If the card contains less than 10 cavities, bundle the cards to form a single test unit of at least 10 cavities. This is required to provide sufficient weight gain at each time interval. Fill with pre-dried desiccant, and seal the blisters on equipment that is capable of correctly filling and sealing the blister. The desiccant should fill the cavity. The total weight of desiccant shall be sufficient to meet the quantity required to avoid partial saturation of the desiccant before completion of the test. Fill the blisters in a low-humidity atmosphere (as low as possible, but not greater than 50% RH). Do not expose the desiccants to room humidity for more than 30 min before sealing. Identify each test specimen with indelible ink; do not use a label. A test unit will be one or more test specimens. Bundle test speciments into test units.

Weigh each test unit at ambient temperature and RH. Record this weight for time zero. Place all test units in the test chamber (40°/75% RH) within 1 h of weighing. Weigh all test units at time intervals of 7 days ±1 h. Weigh the test units at 7, 14, 21, 28, and 35 days to get 5 steady-state data points. (The time interval from time 0 to day 7 is the period of equilibration.) Prior to weighing at each time interval, equilibrate the containers for 30 ± 5 min at the controlled weighing temperature and RH. Limit the time out of the chamber to less than 2 h. Record the weights in an appropriate manner for later computation of the regression line.

Ultra-high barrier blisters may not show the full measure of precision and sensitivity this method can provide. For ultra-high barrier blisters, test units should have more than 10 cavities, but NMT 30 cavities. Examples are foil-foil blisters or very small blisters formed from other materials. An alternative approach is to double or triple the length of weighing intervals to achieve at least a 6-mg weight gain per time interval by the test specimen.

**Method 3:** Prepare the test units as directed for *Method 2*. Place all test units in the test chamber (40°/75% RH) within 1 h of weighing. Weigh the test units at the end of 2 days (48 ± 1 h). At this time, the difference in weight (the weight gain) is divided by the number of blisters and days (2) in each test unit and this is taken as the moisture vapor transmission rate in mg/

blister/day. The number of blisters tested depends on the barrier characteristics of the material, the size of the blister, and the sensitivity of the balance used in the test. For this method, the requirement of five consecutive weighings is waived because the desiccant quickly becomes saturated when packed in a low-barrier package and stored at 40°/75% RH. [NOTE—For single-unit and unit-dose low barrier containers, the weight gain after the second day displays a curvilinear profile typical of approaching saturation of the desiccant. To obtain five weighings within 2 days is not viable and is likely to increase variability. *Methods 2* and *3* may require that the blister cards be bundled in multiples to achieve periodic weight gains of sufficient magnitude to use the balance sensitivity. When bundled, these cards or test specimens are called test units. The weight gain in each weighing period shall be 20 times the sensitivity of the balance, and the balance sensitivity is 3 times the balance precision. In other words, the minimal weight gain per time interval should be at least 60 times the balance precision.]

## CALCULATIONS

For *Methods 1* and *2*, perform the regression analysis for each test unit. Typically, the initial data point (at day 0) is not included in fitting the regression line. The slope of the regression line is the moisture vapor transmission rate of each test unit. For *Method 1*, the slope is the moisture vapor transmission rate for the corresponding multiple-unit container. For *Method 2*, the moisture vapor transmission rate of each blister cavity is calculated by dividing the slope by the number of cavities in each test unit.

For *Method 3*, calculate the weight gain in mg/day from day 0 to day 2 using the 10 test units. The moisture vapor transmission rate of each blister is calculated by dividing the weight gain by 2 (for 2 days) and the number of blisters in each test unit. Regression Equation:

$$W = I + MT$$

Calculations:

$$Slope(M) = \sum_{i=1}^{N}[(W_i - \overline{W})(T_i - \overline{T})] / \sum_{i=1}^{N}(T_i - \overline{T})^2$$

$$\text{Intercept } (I) = \overline{W} - M\overline{T}$$

where

$M$ = regression line slope
$N$ = number of data points (each point consists of a weight and a time)
$W$ = measured weight
$\overline{W}$ = overall weight mean
$T$ = time point
$\overline{T}$ = overall time point mean
$I$ = regression line intercept (point where regression line intersects the vertical axis)

$$\sum_{i=1}^{N}[(W_i - \overline{W})(T_i - \overline{T})]$$

equals sum of cross-products (for example, for each of the $N$ data points, subtract the overall weight mean from the weight value and the overall time mean from the time value and multiply the two differences to get a cross-product. Then sum all $N$ cross-products).

$$\sum_{i=1}^{N}(T - \overline{T})^2$$

equals sum of squared deviations (for example, for each of the $N$ data points, subtract the overall mean time from the time value and square the difference. Then sum all $N$ squared differences).

## RESULTS

**Method 1:** Report the moisture vapor transmission rate as the average value, in mg/day per container, and the standard deviation of the 15 slopes. Properly describe the container closure system tested.
**Method 2:** Report the moisture vapor transmission rate as the average value, in mg/day per cavity, and the standard deviation of the 10 test unit slopes. Properly describe the container closure system tested.
**Method 3:** Report the moisture vapor transmission rate as the average value from day 0 to day 2, in mg/day per blister, and the standard deviation of the 10 test unit slopes. Properly describe the container closure system tested.

## Packaging System Classification for Multiple-Unit Containers for Solid Oral Dosage Forms

The following procedure and classification scheme is provided to evaluate the moisture vapor transmission characteristics of multiple-unit containers. The information gathered should be used to make an informed judgment regarding the suitability of the packaging system for SODF.

### DESICCANT

Place a quantity of 4- to 8-mesh, anhydrous calcium chloride[3] in a shallow container, taking care to exclude any fine powder, dry at 110° for 1 h, 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 *Table 2*. 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 container immediately after adding *Desiccant*, applying the torque designated in *Table 2* when closing screw-capped containers. To each of the remaining two 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 *Table 2* when closing screw-capped containers. Record the weight of the individual containers 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% RH 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 h (14 days), record the weight of the individual containers in the same manner. Completely fill five 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 vapor transmission, in mg/day/L:

$$(1000/14V)[(T_F - T_i) - (C_F - C_i)]$$

$V$ = volume of the container (mL)
$T_F$ = final weight of each *test container* (mg)
$T_i$ = initial weight of each *test container* (mg)
$C_F$ = average final weight of the two *controls* (mg)
$C_i$ = average initial weight of the two *controls* (mg)

**Classification:** Packaging systems are *tight* if NMT 1 of the 10 *test containers* exceeds 100 mg/day/L in moisture vapor transmission, and none exceeds 200 mg/day/L. Packaging systems are *well-closed* if NMT 1 of the 10 *test containers* exceeds 2000 mg/day/L in moisture vapor transmission, and none exceeds 3000 mg/day/L.

### POLYETHYLENE AND POLYPROPYLENE CONTAINERS

Fit the containers with impervious seals obtained by heat-sealing the bottles with an aluminum foil–polyethylene laminate or other suitable seal.[4] Test as directed in the *Procedure* section.

**Classification:** High-density polyethylene containers meet the requirements if the moisture vapor transmission exceeds 10 mg/day/L in NMT 1 of the 10 test containers and exceeds 25 mg/day/L in none of them. Low-density polyethylene containers meet the requirements if the moisture vapor transmission exceeds 20 mg/day/L in NMT 1 of the 10 test containers and exceeds 30 mg/day /L in none of them.

Polypropylene containers meet the requirements if the moisture vapor transmission exceeds 15 mg/day/L in NMT 1 of the 10 test containers and exceeds 25 mg/day/L in none of them.

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[3] Suitable 4- to 8-mesh, anhydrous calcium chloride is available commercially as Item JT1313-1 from VWR International (www.vwr.com; telephone 1-800-952-5000).

[4] A suitable laminate for sealing has, as the container layer, polyethylene of NLT 0.025 mm (0.001 in) and a second layer of aluminum foil of NLT 0.018 mm (0.0007 in), with additional layers of suitable backing materials. A suitable seal can also be obtained by using glass plates and a sealing wax consisting of 60% of refined amorphous wax and 40% of refined crystalline paraffin wax.

## Packaging System Classification for Single-Unit Containers and Unit-Dose Containers for Solid Oral Dosage Forms

The following procedure and classification scheme are provided to evaluate the moisture vapor transmission characteristics of single-unit containers and unit-dose containers. The information gathered should be used to make an informed judgment regarding the suitability of the packaging system for SODF.

### DESICCANT

Dry suitable desiccant pellets[5] at 110° for 1 h prior to use, and cool in a desiccator. Use pellets weighing approximately 400 mg each and having a diameter of approximately 8 mm. [NOTE—If necessary because of 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 1:** Seal NLT 10 unit-dose containers with one 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[6] 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% RH 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-h interval, and at each multiple thereof (see *Classification*), remove the containers from the chamber, and allow them to equilibrate for 15 to 60 min 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, to two significant figures, the rate of moisture vapor transmission, in mg/day, of each container taken:

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

$N$ = number of days expired in the test period (beginning after the initial 24-h equilibration period)
$W_F$ = final weight of each test container (mg)
$W_I$ = initial weight of each test container (mg)
$C_F$ = average final weight of the controls (mg)
$C_I$ = average inital weight of the controls (mg)

[NOTE—Where the moisture vapor transmission rates measured are less than 5 mg/day, and where the controls are observed to reach equilibrium within 7 days, the individual moisture vapor transmission rates 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 *Classification*) would be NLT 28 days following the initial 7-day equilibration period (a total of 35 days).]

**Method 2:** 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 NLT four packs and a total of NLT 10 unit-dose containers or blisters filled with one 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% RH 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 h, and at each multiple thereof (see *Classification*), remove the packs from the chamber, and allow them to equilibrate for about 45 min. 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, to two significant figures, the average rate of moisture vapor transmission, in mg/day, for each unit-dose container or blister in each pack taken:

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

$N$ = number of days expired in the test period (beginning after the initial 24-h equilibration period)
$X$ = number of separately sealed units per pack
$W_F$ = final weight of each test pack (mg)

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[5] Suitable moisture-indicating desiccant pellets are available commercially from sources such as Unit Dose Supply, P.O. Box 104, Ringoes, NJ 08551-0104 (www.unitdose.net; telephone 609-310-1456), as Indicating Desiccant Pellets, Item No. TK-1002.

[6] 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.

$W_i$ = initial weight of each test pack (mg)
$C_F$ = final weight of the control packs (mg)
$C_i$ = initial weight of the control packs (mg)

Using the *Desiccant* stated for *Method 1* and *Method 2*, the test and control containers or packs are weighed after every 24 h and after suitable test intervals for the final weighings. $W_F$ and $C_F$, are as follows: 24 h for *Class D*; 48 h for *Class C*; 7 days for *Class B*; and NLT 28 days for *Class A*.

**Classification:** The individual unit-dose containers as tested in *Method 1* are designated as follows: *Class A* if not more than 1 of 10 containers tested exceeds 0.5 mg/day in moisture vapor transmission rate and none exceeds 1 mg/day; *Class B* if NMT 1 of 10 containers tested exceeds 5 mg/day and none exceeds 10 mg/day; *Class C* if NMT 1 of 10 containers tested exceeds 20 mg/day and none exceeds 40 mg/day; and *Class D* if the containers tested meet none of the moisture vapor transmission rate requirements.

The packs as tested in *Method 2* are designated as follows: *Class A* if no pack tested exceeds 0.5 mg/day in average blister moisture vapor transmission rate; *Class B* if no pack tested exceeds 5 mg/day in average blister moisture vapor transmission rate; *Class C* if no pack tested exceeds 20 mg/day in average blister moisture vapor transmission rate; and *Class D* if the packs tested meet none of the above average blister moisture vapor transmission rate requirements.

### Packaging System Classification for Multiple-Unit Containers and Unit-Dose Containers for Liquid Oral Dosage Forms

The following procedure and classification scheme are provided to evaluate the moisture vapor transmission characteristics of multiple-unit containers. The information gathered should be used to make an informed judgment regarding the suitability of the packaging system for LODF. [NOTE—Determine the weights of individual container–closure systems (bottle, inner seal, 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 two containers with glass beads, to the same weight as the filled test containers. If using screw closures, apply a torque that is within the range specified in *Table 2*, and store the sealed containers at a temperature of 25 ± 2° and a relative humidity of 40 ± 2%. After 336 ± 1 h (14 days), record the weight of the individual containers, and calculate the water weight loss rate, in percent per year, for each bottle taken:

$$[(W_{1i} - W_T) - (W_{14i} - W_T) - (W_{C1} - W_{C14})] \times 365 \times \{[100/(W_{1i} - W_T)] \times 14\}$$

$W_{1i}$ = initial weight of each individual bottle ($i$)
$W_T$ = tare weight
$W_{14i}$ = weight of each individual bottle ($i$) at 14 days
$W_{C1}$ = initial weight of the control container at day 1
$W_{C14}$ = weight of the control container at 14 days

**Classification:** The packaging system meets the requirements for *tight* if the percentage of water weight loss does not exceed 2.5% per year in NMT 1 of the 10 test containers and does not exceed 5.0% per year in any of them.

## SPECTRAL TRANSMISSION

### Apparatus[7]

Use a spectrophotometer of suitable sensitivity and accuracy, adapted for measuring the amount of light transmitted by 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.

[7] For further details regarding apparatus and procedures, reference may be made to the following publications of ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428-2959: "Standard Test Method of Test for Haze and Luminous Transmittance of Transparent Plastics", ASTM Method D1003-11e1; "Standard Practice for Computing the Colors of Objects by Using the CIE System", ASTM Method E308-08.

## 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 290–450 nm.

## Limits

The observed spectral transmission does not exceed the limits given in *Table 3* for containers intended for parenteral use. The observed spectral transmission for plastic containers for products intended for oral or topical administration does not exceed 10% at any wavelength in the range 290–450 nm.

**Table 3. Limits for Plastic Classes I to VI**

| Nominal Size (in mL) | Maximum Percentage of Spectral Transmission at Any Wavelength between 290 and 450 nm |
|---|---|
| 1 | 50 |
| 2 | 45 |
| 5 | 40 |
| 10 | 35 |
| 20 | 30 |
| 50 | 15 |

[NOTE—Any container of a size intermediate to those listed above exhibits a spectral transmission not greater than that of the next larger size container listed in *Table 3*. For containers larger than 50 mL, the limits for 50 mL apply.]