⟨ 671 ⟩ CONTAINERS—PERMEATION

The tests that follow are provided to determine the moisture permeability of containers utilized for drugs being dispensed on prescription. The section *Multiple-Unit Containers for Capsules and Tablets* applies to multiple-unit containers (see *Preservation, Packaging, Storage, and Labeling* under *General Notices and Requirements*). The section *Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets* applies to single-unit and unit-dose containers (see *Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms* under Containers ⟨ 661 ⟩). 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 single-unit and unit-dose containers.

Where the manufacturer's unopened multiple-unit, single-unit, or unit-dose packages are used for dispensing the drug, such containers are exempt from the requirements of this test.

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 one 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 one of the 10 *test containers* exceeds 2000 mg per day per L in moisture permeability, and none exceeds 3000 mg per day per L.

Torque Applicable to Screw-Type Container

Closure Diameter[1] (mm)	Suggested Tightness Range with Manually Applied Torque;[2] (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] 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.

[2] A suitable apparatus is available from Owens-Illinois, Toledo, OH 43666. (Model 25 torque tester is used for testing between 0 and 25; Model 50 for testing between 0 and 50; and Model 100 for testing between 0 and 100 inch-pounds of torque.) The torque values refer to application, not removal, of the closure. 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 D3198-97, published by the American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103.

Closure Diameter[1] (mm)	Suggested Tightness Range with Manually Applied Torque;[2] (inch-pounds)
120	55–95
132	60–95

[1] 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.

[2] A suitable apparatus is available from Owens-Illinois, Toledo, OH 43666. (Model 25 torque tester is used for testing between 0 and 25; Model 50 for testing between 0 and 50; and Model 100 for testing between 0 and 100 inch-pounds of torque.) The torque values refer to application, not removal, of the closure. 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 D3198-97, published by the American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103.

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[2] 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[3] 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*.

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[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.

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[2] 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.

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[3] 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.

Auxiliary Information— *Staff Liaison* : Desmond G. Hunt, Ph.D., Senior Scientific Associate
Expert Committee : (PS05) Packaging and Storage 05
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