

## <1177> GOOD PACKAGING PRACTICES

This chapter provides general guidance on packaging considerations for Pharmacopeial preparations that may be stored, transported, and distributed. It describes procedures that should be considered to ensure that proper packaging practices are maintained. It does not affect any applicable requirements under good manufacturing practices, state laws governing pharmacy, the *USP General Notices and Requirements* or monographs, or provisions under approved labeling.

Definitions for storage conditions and packaging are provided in <659> *Packaging and Storage Requirements*. All equipment used for recording, monitoring, and maintaining these temperature and humidity conditions should be calibrated on a regular basis. This calibration should be traceable to national or international standards (see also the general information chapter *Monitoring Devices—Time, Temperature, and Humidity* <1118>).

### CONTAINERS

The monograph packaging and storage statement specifies that the container (primary package) should meet the requirements under *Containers—Glass* <660>, *Plastic Packaging Systems and their Materials of Construction* <661>, *Plastic Materials of Construction* <661.1>, *Plastic Packaging Systems for Pharmaceutical Use* <661.2>, and *Containers—Performance Testing* <671>, which include the stipulations for determining if a container is “tight” or “well-closed.” In most cases, compendial preparations are expected to be packaged in “tight” containers, especially if the article is moisture sensitive. In addition, where necessary, the packaging component should protect the preparation from light, reactive gases, solvent loss, microbial contamination, etc. “Tight” and “well-closed” containers are clearly defined in <659> *Packaging and Storage Requirements*, whereas testing protocol and moisture permeation limits to determine if the container meets either of these definitions can be found in *Containers—Glass* <660>, *Plastic Packaging Systems and their Materials of Construction* <661>, *Plastic Materials of Construction* <661.1>, *Plastic Packaging Systems for Pharmaceutical Use* <661.2>, and *Containers—Performance Testing* <671> for single-unit and multiple-unit containers.

A packaging system is composed of a container system with its closure. This system may include several layers of protection for the Pharmacopeial preparation along with any sealing devices, delivery devices, labeling, and package inserts. The *General Notices* section also provides definitions for types of packaging systems that contain and protect a Pharmacopeial preparation (e.g., single-unit containers, unit-dose containers, etc.). Stability testing is conducted on the dosage forms packaged in the container–closure system proposed for marketing.

One type of permeation test for multiple-unit containers is described in *Containers—Performance Testing* <671>. This test is intended for drug products being dispensed on prescription in vials with a container–closure system. The results of the test reflect the water vapor permeation through the container and through the closure. Limits have been established to define whether a container for dispensing has tight or well-closed characteristics with regard to water vapor permeation. FDA recommends that manufacturers perform this test on the container–closure system, although it is not specified in *USP*. In this particular test, the inner seal of the manufacturer's container–closure system is removed prior to testing.

Single-unit containers for capsules and tablets under *Containers—Performance Testing* <671> are measured for water vapor permeation according to the criteria for the four classes of containers (classes A–D).

The *USP* recognizes several official container materials that can be selected on the basis of their properties. Most containers are made of glass or plastic. Glass containers must be evaluated for chemical resistance and light transmission (if indicated) as described in *Containers—Glass* <660>. In addition, injectable medication containers should be reviewed according to the section *Packaging and Storage Requirements* <659>, *Injection Packaging*. Elastomeric closures should be evaluated separately as described in *Elastomeric Closures for Injections* <381>. Plastic containers should be assessed as described in *Plastic Packaging Systems and their Materials of Construction* <661>; *Plastic Materials of Construction* <661.1>; and *Plastic Packaging Systems for Pharmaceutical Use* <661.2>. As articulated in these sections, plastics should undergo testing for light transmission (if appropriate), water vapor permeation (see also *Containers—Performance Testing* <671>), extraction physicochemical testing, and biological testing (see also *Biological Reactivity Tests, In Vitro* <87> and *Biological Reactivity Tests, In Vivo* <88>). For example, testing water vapor permeation for a PE container is conducted by sealing the container with heat-sealed foil laminate and measuring the water permeation in a humid atmosphere. Given that water vapor does not permeate the foil laminate, this test assesses only the properties of the container. The level of protection provided by a packaging system marketed with a heat-sealed foil laminate inner seal (prior to removal of the foil) is approximated by this test. However, in the case of a PET bottle for liquid preparations, water vapor permeation testing is done by filling containers with water and measuring the water loss rate in a dry atmosphere. Additional testing may be required for certain pharmaceutical dosage forms as well.

The container–closure system for the storage or shipment of a bulk liquid drug substance is typically plastic, stainless steel, a glass-lined metal container, or an epoxy-lined metal container with a rugged, tamper-resistant closure. Qualification of the container–closure system for these types of preparations includes evaluation for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components as appropriate (see *Containers—Glass* <660>, *Plastic Packaging Systems and their Materials of Construction* <661>, *Plastic Materials of Construction* <661.1>, and *Plastic Packaging Systems for Pharmaceutical Use* <661.2>).

Other information on container–closure systems may be found in FDA's *Guidance for Industry: Container Closure System for Packaging Human Drugs and Biologics*, [www.fda.gov](http://www.fda.gov).

## PACKAGING

Packaging for Pharmacopeial articles can be divided into categories according to terminology generally accepted by industry. As mentioned earlier, the *General Notices* section provides some definitions for different types of containers classified by their characteristics and uses. In addition, the ASTM Committee D10 on packaging publishes terminology, practices, test methods, specifications, guides, and classifications for testing and evaluating packaging (see ASTM D99695, “Standard Terminology of Packaging and Distribution Environments”). Under certain rules and guidelines (e.g., such as 49 CFR, Dangerous Goods, and others), however, alternate terminology is used for the components described below. For terminology pertaining to repackaging processes, refer to *Packaging and Repackaging—Single-Unit Containers* <1136>.

### Primary Container

This container is in direct contact with the Pharmacopeial preparation. The purpose of a primary container, also referred to as an immediate container, is to protect the preparation from environmental hazards during storage and handling. In some cases, the primary container is also a specialized delivery system, such as an aerosol or a metered-dose dispenser (see *Pharmaceutical Dosage Forms* <1151>). For the majority of oral dosage forms, the primary container consists of a cap and a bottle or a blister or pouch package that can be made from many different materials, including glass, plastic, single or laminated flexible materials, and metal. All components of the primary container must meet the requirements under 21 CFR for direct food contact and, where applicable, the USP requirements under *Containers—Glass* <660>, *Plastic Packaging Systems and their Materials of Construction* <661>, *Plastic Materials of Construction* <661.1>, *Plastic Packaging Systems for Pharmaceutical Use* <661.2>, and *Containers—Performance Testing* <671>. A full description of the primary container is included under the “Container/Closure System” section of the New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or other classes of FDA submissions.

### Critical Secondary Container

This container is not in direct contact with the article, but it provides essential product stability protection. For example, a primary container may be packed inside a critical secondary container such as a pouch to provide moisture, gas, light, or microbial protection not afforded by the primary container. A description of the critical secondary container is included under the “Container/Closure System” section of the NDA, ANDA, or other classes of FDA submissions.

### Secondary Container

This container encloses one or more primary containers. A secondary container is not always present. If used, it is usually designed for the final market presentation. Secondary containers are often used simply to carry required labeling or to keep individual primary containers together with delivery systems or other add-on features. Secondary containers can also provide protection against damage in the handling and distribution system. The most common secondary container is the standard folding carton. Some products, such as syringes, may be placed in trays prior to packing in a carton. Secondary container materials are not included in the container and closure description and require neither stability studies nor prior approval when making a change in the materials used.

### Additional Packaging

A wide variety of additional packaging, such as trays and display cartons, may be used to hold primary containers.

### Unit of Sale

This may be an individual bottle, a carton containing one or more bottles, or a tray with multiple primary containers. A unit of sale may contain more than one item for individual sale. For example, a display tray may have multiples of a single article or a variety of related articles from a single manufacturer, each intended for individual sale. The individual item intended for sale is referred to as a stock-keeping-unit (SKU). SKUs are distinguished by a discrete National Drug Code (NDC). Over-the-counter (OTC) articles contain a Universal Product Code (UPC) for all SKUs. A prescription SKU may be intended for final consumer use and may not be repackaged by a pharmacy. Such packages, often called “unit of issue” or “unit of use,” require child-resistant (CR) packaging as described under 16 CFR 1700, “Poison Prevention Packaging,” except for packages exempted by the Consumer Product Safety Commission. The CR feature is typically incorporated by the manufacturer (see *Packaging and Repackaging—Single-Unit Containers* <1136>). OTC articles are regulated under the same rule, but only if they contain certain active in-

redients above specified limits. Any regulated product shipped via the United States Postal Service (USPS) must meet the USPS rules under 39 CFR 111.

### Final Exterior Package

This is typically a corrugated fiberboard box (case) or a wrapper. The shipping case label is affixed to this outermost layer and incorporates all of the bar codes required by the National Wholesale Druggists' Association (NWDA). This final package is normally shipped on pallets to distribution centers, wholesalers, and other large-volume customers. The manufacturer may or may not intend that this package enter the small-package-shipping environment as an individual unit without further protection.

Especially with fiberboard boxes, relative humidity (RH) may have a negative effect on the compression strength of the box, causing loads to shift and potentially damage the article or the outer and inner packaging. Articles stored in refrigerators or freezers, which are environments with high RH, are prone to this type of damage when stacked. The problem may be exacerbated by carton design, stacking pattern, or use of low edge-crush-test corrugated fiberboard. Computer programs are available to determine the acceptable stack height and patterns on the basis of carton weight, style, size, and material. If problems occur, the product manufacturer should be contacted. Source materials and reference information on corrugated fiberboard boxes can be found in the "Fiber Box Handbook" published by the Fiber Box Association.

A wholesaler or other reshipper should not assume that the package received from the manufacturer is suitable for reuse. Many packages are customized for very specific routes and modes of transportation and are not suitable for other applications. Like any other shipping container, insulated cartons and inner protective packaging can be damaged during transit, thus affecting package performance and possibly allowing damage to contents if reused.

### ENVIRONMENTAL ISSUES

Packaging materials are regulated by a variety of federal, state, and local rules. In general, most pharmaceutical packaging containers can be recycled within local programs. The use of recycled material in primary containers is governed by the FDA, but it is generally not allowed. Pharmaceutical manufacturers commonly follow the most current Coalition of Northeastern Governors' rules (e.g., Model Toxics in Packaging Legislation) regarding heavy metals in packaging and other environmental issues.

Certain classes of Pharmacopeial articles may require special handling. Such articles include products classified as (1) Dangerous Goods under the Department of Transportation (DOT), state, local, or carrier rules; (2) controlled drugs under the Drug Enforcement Administration (DEA); or (3) scheduled substances under state regulations.

### LABELING

The labeling of shipping containers by manufacturers must be in compliance with the pertinent sections of FDA and DOT rules.

#### Dangerous Goods

The labeling of shipments classified as *Dangerous Goods*, including all information on the bill of lading or airway bill, must follow the instructions provided by the DOT, the International Air Transport Association (IATA), and the carrier. The exterior package must carry all of the required standard symbols for the class of goods, and the shipping container must comply with the performance standards for the articles enclosed. The shipper of record is responsible for compliance with the Dangerous Goods requirements.

#### Controlled Substances

When Pharmacopeial preparations that contain DEA-scheduled controlled substances are distributed to a patient directly via the USPS, these articles must be marked and labeled in accordance with USPS Domestic Mail Manual, Regulation Article C023, Section 7.2.