⟨ 1136 ⟩ PACKAGING— UNIT-OF-USE

INTRODUCTION

This chapter provides guidance in the use and application of unit-of-use packaging and is intended for use by drug manufacturers, repackagers, and pharmacists. Suppliers of packages and packaging components may find the information useful, as well.

The *General Notices* defines a unit-of-use container as one that contains a specific quantity of a drug product that is intended to be dispensed as such without further modification except for the addition of appropriate labeling.

Unit-of-use packaging, when provided by the manufacturer, offers some of the following attractive advantages. (1) A dosage form can be dispensed to a patient in the manufacturer's original container, a practice that recognizes that the suitability of the container has been established on the basis of the manufacturer's stability studies. (2) The counting and repackaging of dosage units in the pharmacy is eliminated, thereby reducing the possibility of human error. (3) The pharmacist is able to affix the label for the patient onto the unit-of-use package and is free to use the manufacturer's expiration date as the beyond-use date. (4) The number of dosage units in a single unit-of-use package may be determined on a case-by-case basis. (5) Patient compliance is improved. (6) The unit-of use package can protect against countertfeiting because traceability of product is ensured through bar coding techniques and NDC numbers.

Unit-of-use packaging, when provided by repackagers, offers the same attractive advantages as those offered by the manufacturer. However, unit-of-use repackagers should conform to all requirements as presented in *Good Repackaging Practices* ⟨ 1178 ⟩ . There are a number of reasons why repackagers produce unit-of-use packaging: for example, (1) requests from institutions, (2) better inventory control, (3) reduced dispensing times, and (4) variations in some drug therapies.

The packaging of a unit-of-use system may be a multiple container or a single-unit container. A unit-of-use system may contain a drug product in a liquid, semisolid, or solid dosage form (see also *FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics*). [NOTE—The terms "unit-of-use package" and "unit-of-use container" may be used interchangeably.]

The Poison Prevention Packaging Act (PPPA) of 1970 requires in certain cases the use of special packaging—child-resistant and senior-friendly. Child-resistant packaging protects children from serious injury or illness resulting from ingesting or handling hazardous products including drugs.

Because drugs packaged in unit-of-use packaging are intended to be dispensed to the consumer without repackaging by the pharmacist, the manufacturer or repackager is responsible for the special packaging of PPPA-regulated substances in unit-of-use containers (l6 CFR 1701.1).

TYPES OF CONTAINERS FOR UNIT-OF-USE

Unit-of-use containers are required to be child-resistant if they are intended to be dispensed directly to the patient pursuant to a prescription. Unit-of-use packaging intended for institutional or hospital use may or may not be required to be child-resistant. Unit-of-use containers that are child-resistant single-unit containers include supported blisters, such as separate,

peel, push, and tear notch, and enclosed or in-card blisters, such as pull tabs and slide packs. Blister packaging is discussed in the general chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨1146⟩. Unit-of-use containers that are multiple-unit containers include glass and plastic containers.

Single-Unit Container

A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show any evidence of tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity, and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Unit-Dose Container

A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, directly from the container.

Single-Dose Container

A single-dose container is a single-unit container for articles intended for parenteral administration only. It is labeled as such.

Multiple-Unit Container

A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

PACKAGING FABRICATION MATERIALS

Packaging fabrication materials include substances used to manufacture packaging containers such as glass, plastics (including high-density polyethylene (HDPE), low-density polyethylene (LDPE), polyethylene terephthalate, polyethylene terephthalate G and polypropylene (PP), other resins, and other materials as listed in the general test chapter *Containers* ⟨661⟩ and in the *FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics*.

Glass

Any glass packaging material used in the immediate container should meet the glass test requirements for *Limits for Glass Types* and *Chemical Resistance—Glass Containers: Powdered Glass Test, Water Attack at 121°*, and *Arsenic* under general test chapter *Containers* ⟨661⟩.

Plastic

Any plastic packaging material used in the immediate container should meet the plastic test requirements for *Plastics* in the general test chapters *Containers* ⟨661⟩ and *Containers—Permeation* ⟨671⟩. Depending on the type of plastic packaging material used, the packaging material meets the requirements for *Biological Tests—Plastics and Other Polymers, Physicochemical Tests—Plastics, Polyethylene Containers, Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles,* and *Polypropylene Containers* under general test chapter *Containers* ⟨661⟩.

The test for moisture vapor transmission may be carried out as described in the general test chapter *Containers—Permeation* ⟨671⟩ for multiple-unit and unit-dose containers.

PACKAGING CLOSURE TYPES

Reclosables and nonreclosables may be used for solid, semisolid, and liquid dosage forms. Both must be packaged in compliance with the 16 CFR 1700.15 standards.

Reclosables

Reclosables are containers with suitable closures that may incorporate tamper evidence and child-resistance capabilities. Reclosables may be used for glass or plastic containers.

Nonreclosables

Nonreclosables are containers with closures that are nonreclosable, such as blisters, sachets, strips, and other single-unit containers. Nonreclosables may include packs such as cold-formed foil blisters, foil strip packs, and PVC/Aclar combining multilayer materials that are thermo-formed or cold-formed foil blisters (see *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨ 1146 ⟩). Nonreclosables may be child resistant depending on the intended use and place of use. Household nonreclosables are subject to the PPPA as defined in 16 CFR 1700.14. However, because of some unit-dose designs, not all unit-dose packages comply with the PPPA.

LABELING

The unit-of-use containers are labeled to include expiration dates, the manufacturer's lot number, the NDC designation, and bar codes as provided in the *Labeling* section of the *General Notices and Requirements* under *Preservation, Packaging, Storage, and Labeling* and in *Good Repackaging Practices* ⟨ 1178 ⟩. Some of the advantages of having bar codes on the label include reduced medication errors, improved inventory control, and improved access to medication identity. The labeling covers information placed in the container by the manufacturer (see *General Notices and Requirements*). Acceptable labeling can range from the full labeling as for multiple-unit containers to an abbreviated labeling when the container is too small to include all the text. Full labeling may also be provided on the carton if it is not present on the immediate container.

REPACKAGING AND REPROCESSING

Unit-of-use containers are reprocessed or repackaged as instructed by the manufacturer or as directed in the general test chapter *Containers* ⟨ 661 ⟩ or in the general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨ 1146 ⟩. A unit-of-use package that is a blister package may not be reprocessed by a pharmacist once it has been deblistered from a unit-dose container (see *General Notices and Requirements* for application of the appropriate beyond-use date for a multiple-unit or unit-dose container). Deblistering is the process of removing medication from a blister-type container. However, under current Good Manufacturing Practices (cGMPs) and tight quality controls, the manufacturer or contract repackager may repackage and reprocess unit-of-use containers.

INFORMATION FROM MANUFACTURERS

The manufacturer should provide appropriate stability information that can be used to determine appropriate labeling, storage, and shipping statements that will properly inform patients and practitioners. The manufacturer may make other assurances based on product information on packaging and distribution arrangements. In the event that a product is not to be repackaged, the manufacturer may so state in the labeling. The manufacturer also includes labeling and information suitable for optimal handling by the practitioner and the patient. The labeling and information should be bar coded to eliminate medication error and promote medication traceability.

RESPONSIBILITY OF THE DISPENSER

Labeling

The labeling on a unit-of-use container also includes a label added at the dispensing stage by the pharmacist. Prior to dispensing the unit-of-use package, the dispenser shall add label(s) that provide the following information:

1. the name of the patient;
2. the name and strength, the directions for use as prescribed by a doctor or health-care provider, and the name of the prescriber; and
3. any storage instruction, beyond-use date, and other information as deemed appropriate by federal and state laws.

In the pharmacy setting, pharmacists are encouraged to use bar codes, in conjunction with computerized prescription orders, to confirm that the right drug is being dispensed to the right patient. Bar coding would minimize errors and create opportunity for medication traceability and accountability.

Information to Patient

Patients must be given information that applies to the specific prescription being dispensed.

QUALITY CONTROL OF PACKAGING SYSTEM

The packaging system shall meet the general considerations for system suitability, protection, safety, and performance characteristics as described in *FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics*, in the general test chapters *Containers* ⟨ 661 ⟩ and *Containers—Permeation* ⟨ 671 ⟩, and in the general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨ 1146 ⟩.

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d. Establishing the expiration date in the case listed in (c) is applicable for unit-dose containers, multiple-unit containers, and unit-of-use container types.

Beyond-Use Date or Discard-After Date

In the absence of stability data, where a repackager repackages a product into a unit-dose or multiple-unit container without conducting appropriate stability studies to support expiration dates used, the period of use of the product is limited by the BUD for the repackaged product, which must be less than the expiration date.

UNIT-DOSE PACKAGING

For unit-dose packaging, the following criteria should be considered.

1. The original bulk container of the drug product to be used for repackaging has not been previously opened.
2. The contents of the original bulk drug product to be repackaged are repackaged at one time.
3. The unit-dose container meets USP general test chapter ⟨ 671 ⟩ testing requirements for either Class A or Class B containers.
4. The unit-dose container meets or exceeds the manufacturer's specification for light resistance.
5. The conditions of storage meet the storage specifications provided in the *General Notices* and as described in the labeling by the manufacturer of the bulk product. Where no specific storage conditions are specified, the product should be maintained at *controlled room temperature* and in a *dry place* during repackaging.
6. The BUD used for the repackaged product does not exceed 6 months from the date of repackaging.
7. The BUD does not exceed the manufacturer's expiration date.
8. The BUD does not exceed 25% of the time between the date of repackaging and the expiration date shown on the manufacturer's bulk article container of the drug being repackaged.
9. Documentation should be in place to show that the preceding criteria (items 1–8) are met. Documentation to show the type of packaging material used and the testing for these materials is also kept on file.
10. The repackager may not repackage if the manufacturer specifically states "Do not repackage." However, the repackager may affix the repackager's labeling if it is in accordance with FDA requirements and in agreement with the manufacturer of the drug product.
11. The repackager may not use the expiration date and BUD interchangeably because they imply the presence or absence of stability testing, respectively.

MULTIPLE-UNIT PACKAGING

The *General Notices* define multiple-unit packaging as a package that contains more than one single-dosage unit. For multiple-unit packaging, the following criteria should be considered in assigning a BUD.

1. The original bulk container of drug product to be used for repackaging has not been previously opened.
2. The contents of the original bulk drug product to be packaged are repackaged at one time.
3. The conditions of storage meet the storage specifications in the *General Notices* and as described in the labeling of the manufacturer's bulk product. Where no specific storage conditions are specified, the product should be maintained at *controlled room temperature* and in a *dry place* during repackaging.
4. The type of container used for repackaging should be the same type used by the manufacturer as the market container, and the product container should comply with the requirements for containers as directed under *Containers* ⟨ 661 ⟩ and *Containers—Permeation* ⟨ 671 ⟩, as well as the requirements of 21 CFR for food additives,

or the container should be composed of an approved food contact substance. For example, if the manufacturer packages in glass, the repackager should repackage in glass of the same type used by the manufacturer or in chemical-resistant glass containers.

5. Where the original container is a material other than glass or high density polyethylene (HDPE), the repackager may use a container demonstrated to be equivalent to, or exceed, the protective properties of the manufacturer's multiple-unit market container when performing the applicable tests as described in USP general test chapters ⟨ 661 ⟩ and ⟨ 671 ⟩.
6. Where the original container is polyethylene, the repackager may repackage in a chemical-resistant glass container or a polyethylene container. These containers should meet the appropriate tests and specifications in 21 CFR and USP general test chapters ⟨ 661 ⟩ and ⟨ 671 ⟩.
7. The container meets or exceeds the test results of the manufacturer's multiple-unit market container for light transmission.
8. The container meets or exceeds the manufacturer's container in special protective features: methods used to prevent leaching of container materials or the use of desiccants to maintain low moisture content. [NOTE—Desiccants should always be packaged on top of the drug product.]
9. The container meets or exceeds the manufacturer's container test results for "tight" as provided in USP general test chapters ⟨ 661 ⟩ and ⟨ 671 ⟩.
10. For all products, if the repackager uses a container that is equivalent in MVTR to the manufacturer's container or one that has a higher barrier, then the BUD should be 12 months or the manufacturer's expiration date, whichever is less. (See *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨ 1146 ⟩ for a description of low- and high-barrier packaging.)
11. The repackager may not repackage the original bulk container of the drug product if the manufacturer specifically states "Do not repackage." However, the repackager may affix the repackager's labeling if this is in accordance with FDA requirements or the specifications of the drug product manufacturer.

MINIMUM REQUIREMENTS

The following represents the minimum requirements a repackager must meet in order to engage in repackaging drugs from their original manufacturer's container.

a. A repackager is expected to comply with cGMPs and 21 CFR 211.170(b) for retained samples of repackaged drug products. Any alteration or manipulation of the repackaging process should be documented in accordance with the requirements in 21 CFR 211.
b. A repackager is expected to repack penicillins, or products such as penicillins, in facilities separate from those facilities used for drug products as described in 21 CFR 211.42 and 21 CFR 211.46.

SHIPPING AND DISTRIBUTION

For products identified by the manufacturer as moisture- and temperature-sensitive, the repackager must follow the specifications provided by the manufacturer during repackaging, shipping, and distribution.

a. A repackager may not repackage a moisture- and temperature-sensitive product if the manufacturer so instructs, except if the repackager is only altering the labeling in accordance with FDA requirements.
b. The repackaging container should show the equivalent of, or be better in protective properties than, the manufacturer's original container. For moisture-sensitive products, a higher-barrier container should be used for

repackaging.

c. The repackager should have proper documentation in place to show the equivalency in protection of the container used.

d. The storage and handling of the drug product should meet the conditions specifically instructed by the manufacturer of the product.

e. The repackager should label the container "Contains moisture-sensitive product."

For all other products, the repackager should follow the same guidelines provided in *Good Storage and Shipping Practices* ⟨ 1079 ⟩ that are applicable to a manufacturer.

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