

quence specificity. This liquid phase facilitates the formation of reaction complexes that contain DNA, streptavidin, and urease. During the *second* step the sample is filtered through a biotinylated membrane that binds to the streptavidin and captures the complexes on the membrane, which is washed to remove any reagents that are not bound to the membrane. During the *third* step the membrane is inserted into a sensor on the instrument, where the urease in the DNA complex reacts with a urea solution in the sensor, producing ammonia and a change in pH that is detected using a light-addressable potentiometric sensor (LAPS). The change in pH directly correlates with the amount of DNA in the sample. In the *fourth* step the raw data from the instrument are analyzed using the appropriate software to determine the residual DNA content of the sample.

QUANTITATIVE PCR-BASED RESIDUAL DNA ASSAY

Real-time q-PCR is a procedure that is well-adapted to fast sample throughput and has applications in many areas of biopharmaceutical manufacture (e.g., copy number detection, virus detection). The technique can quantify the amount of a nucleic acid target sequence in DNA from a variety of samples. The DNA probe used in the analysis is the key to the procedure. The probe has a reporter dye attached to one end and a quencher dye attached to the other end. A DNA primer is also added to the reaction. During the amplification reaction, DNA polymerase I attaches where the DNA primer binds to the single-stranded sample (template) DNA and moves along the sample DNA synthesizing new complementary DNA. While following the template DNA, DNA polymerase I cleaves any complementary DNA in the path. If DNA polymerase I encounters the labeled DNA probe it will cleave the reporter dye from the probe. The reporter dye is released into solution and, in the absence of the quencher dye, can be quantitated as a fluorescent measurement. Repeating the reaction cycle results in an amplification of the fluorescent signal. The number of cycles required for the fluorescent measurement to exceed a threshold value correlates to the amount of starting residual DNA in the sample. By comparing with a standard curve the fluorescence obtained from a sample, analysts can quantify the residual DNA in the sample.

PRACTICAL APPLICATIONS OF RESIDUAL DNA TESTING

Analysts choosing hybridization, DNA-binding protein, or q-PCR techniques for residual DNA analysis should consider how the assay will be used, the structure of the DNA available (e.g., fragment length), and regulatory issues. The cost of analysis can be significant and should be considered when evaluating an assay format. Traditionally, hybridization assays were performed using ^{32}P -labeled DNA and autoradiography. Because ^{32}P decays quickly, probes prepared with ^{32}P have a limited shelf life, and the precautions necessary for handling radioactive material can be cumbersome.

These issues with ^{32}P labeling may make fluorescence labeling of the hybridization probe a more desirable option. If the hybridization assay is assessed visually, this represents a semiquantitative assay, but if the intensity of the spots is determined using a densitometer or other image system, the results can be quantitative. DNA-binding protein assays and q-PCR give quantitative results. Quantitative assays are typically preferred instead of semiquantitative assays because the results are considered more accurate and precise, which allows better process monitoring and control.

Due to sample interference, a sample pretreatment step is often required to obtain accurate and reproducible results. Pretreatment steps can influence the recovery of DNA, so it is often necessary to design the assay with a spike-recovery

control and an acceptance criterion to ensure assay performance. Commercial sources of host cell and vector DNA are typically not available to prepare in-house controls. In-house controls are usually prepared in the laboratory and quantified by UV spectroscopy, using standard techniques employed in molecular biology, to determine the DNA content and purity. Additionally, it is a good practice to evaluate in-house residual DNA controls by agarose gel electrophoresis to demonstrate that the DNA is of a proper size for the assay employed and has not degraded.

The hybridization assay uses genomic and/or vector DNA, labeled randomly throughout the DNA, as the hybridization probe reagent. For this reason the hybridization assay is specific for the source of DNA but is not specific for a given sequence. A synthesized probe, specific for a specific sequence, can be prepared and used in the hybridization assay if this level of specificity is desirable. The DNA-binding protein residual DNA assay is not sequence-specific and hence not specific for the host DNA. Therefore, laboratory personnel should avoid contaminating samples for this assay with environmental DNA before denaturing the DNA; otherwise the DNA result may be falsely elevated. The q-PCR probe is sequence-specific, which creates some special challenges for development of a q-PCR residual DNA assay. The q-PCR-specific sequence must be a stable sequence within a highly conserved region of DNA. The recovery of the probe target sequence must consistently represent the recovery of all the residual DNA. As a guideline, for a DNA fragment to be detected by hybridization, q-PCR, and DNA-binding protein assays, it must have no fewer than 50, 150, and 600 base pairs, respectively. A bioprocess typically may have operations that shear DNA into smaller fragments, and this must be taken into consideration when selecting an assay. Procedures exist to determine whether the DNA fragments in a sample are too small for adequate residual DNA recovery with a given assay. As noted, residual DNA assays are extremely sensitive. Detection limits as low as <1, 3, and 6 pg of DNA per sample have been reported for q-PCR, DNA-binding protein, and hybridization assays, respectively.

Although safety concerns regarding residual DNA impurities are not as prominent as they once were, the levels of residual DNA in any bioprocess remain a key quality attribute and help define the process.

(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 counterfeiting 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 (16 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—Glass* (660), *Containers—Plastics* (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—Glass* (660).

Plastic

Any plastic packaging material used in the immediate container should meet the plastic test requirements for *Plastics* in the general test chapters *Containers—Plastics* (661) and *Containers—Performance Testing* (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—Plastic* (661).

The test for moisture vapor transmission may be carried out as described in the general test chapter *Containers—Performance Testing* (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 chapters *Containers—Glass* (660) and *Containers—Plastics* (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 repack 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—Glass* (660), *Containers—Plastics* (661), and *Containers—Performance Testing* (671), and in the general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* (1146).

(1146) PACKAGING PRACTICE— REPACKAGING A SINGLE SOLID ORAL DRUG PRODUCT INTO A UNIT-DOSE CONTAINER

INTRODUCTION

Repackaging of solid oral drug products, such as tablets and capsules, into unit-dose configurations is common practice both for the pharmacy that is dispensing drugs pursuant to a prescription and for the pharmaceutical repackaging firm. This general chapter contains minimum standards to be used as a guideline for repackaging practices. This guideline is not intended to replace or supplant the requirements of regulatory agencies.

Repackaging preparations into unit-dose configurations is an important aspect of pharmaceutical care and of optimization of patient compliance. For purposes of this chapter, there are two types of repackaging: the first involves pharmacies that dispense prescription drugs; the second concerns commercial pharmaceutical repackaging firms.

NOMENCLATURE AND DEFINITIONS

DISPENSER—A dispenser is a licensed or registered practitioner who is legally responsible for providing a preparation for patient use, with a specific patient label, pursuant to a prescription or a medication order. In addition, dispensers may prepare limited quantities in anticipation of a prescription or medication order from a physician. Dispensers are governed by the board of pharmacy of the individual state.