# Technical Bulletin

## Extemporaneous Unit-Dose Packaging of Oral Solids

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Solid Packaging Terminology</td>
<td>2</td>
</tr>
<tr>
<td>Characteristics of a Blister Package</td>
<td>2</td>
</tr>
<tr>
<td>Expiration Date and Beyond Use</td>
<td>3</td>
</tr>
<tr>
<td>Other Important Unit Dose Packaging Considerations</td>
<td>3-4</td>
</tr>
<tr>
<td>USP Testing</td>
<td>4</td>
</tr>
<tr>
<td>USP Class Ratings</td>
<td>5</td>
</tr>
<tr>
<td>HCL Package Testing</td>
<td>5</td>
</tr>
<tr>
<td>USP Test Method Employed</td>
<td>5-6</td>
</tr>
<tr>
<td>Determination of Results for HCL Packaging Products</td>
<td>7</td>
</tr>
<tr>
<td>Blister Packaging Accessories</td>
<td>7</td>
</tr>
<tr>
<td>Summary</td>
<td>8</td>
</tr>
</tbody>
</table>
Not all oral solid dose pharmaceuticals come packaged from the original manufacturer in unit-of-use; or unit-dose packaging. As a result the pharmacist in many instances has to rely on the extemporaneous packaging of oral solids and is faced with decisions as to the type of packaging/containers to be used; the reliability of the container/closure system with respect to stability and moisture permeation; its ability to protect the integrity of the drug; and ultimately the assignment of expiration dating to the product.

Fortunately the USP and ASHP have provided definitions, tools and guidelines to aid in these important packaging decisions.

This HCL Technical Bulletin is intended, in a concise and comprehensible manner to:

i. **define** terms associated with oral solid packaging
ii. **detail** a USP testing procedure used to determine package rating of HCL’s products
iii. **discuss** associated security and record keeping issues
iv. **serve** as a decision making resource regarding choice of suitable packaging materials and the assignment of expiration dating

**ORAL SOLID PACKAGING TERMINOLOGY**

**Containers**: The container is that which holds the article and is or may be in direct contact with the article. The immediate container is that which is in direct contact with the article at all times. The closure is part of the container.

**Tight Containers**: A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight re-closure.

**Well-Closed Container**: A well-closed container protects the contents from extraneous solids and from loss of the article under ordinary or customary conditions of handling, shipment, storage, and distribution.

**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 evidence of any 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, direct from the container.

**Unit-of-Use Container**: A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

**CHARACTERISTICS OF A BLISTER PACKAGE**

A blister package should have the following characteristics:

i. have an opaque and nonreflective backing (flat upper surface of package) for printing

ii. have a blister (dome or bubble) of a transparent material that is, preferably, flat bottomed

iii. be easily peelable and provide evidence of entry

iv. if containing a controlled substance, be numbered sequentially for accountability purposes.
EXPIRATION DATE AND BEYOND USE

The USP provides guidelines for the beyond-use (expiration) dating of repackaged Unit-dose containers: (USP 25 <Section 661>).

The label of an official drug product, nutritional or dietary supplement shall bear an expiration date. An official dosage form is required to bear on its label an expiration date. This date is to be assigned for the particular product and package. The expiration date identifies the time during which the article may be expected to meet the requirement of the Pharmacopeial monograph provided it is kept under the prescribed storage conditions. This expiration date limits the time during which the article may be dispensed or used.

The beyond-use date is the date after which an article must not be used. The dispenser shall place on the label of the container a suitable beyond-use date to limit the use of the article based on any information supplied by the manufacturer. The beyond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

Bulk containers of drug products direct from the manufacturer have pre-determined dating based on the particular container and drug product and the required testing performed by the manufacturer. This dating may not be applicable to the product when it has been repackaged in a different container. It is therefore necessary to take other precautions to preserve the strength, quality and purity of the drug product being repackaged.

It is the responsibility of the dispenser, taking into account the nature of the drug repackaged, the characteristics of the container and the storage conditions to which it may be subjected, to determine a suitable beyond-use (expiration date) to be placed on the label of the repackage product.

It is the responsibility of the dispenser in addition to any other relevant factors, to take into account the nature of the drug repackaged; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the new or patient's container; if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy or put-up.

Repackaged dosage forms must bear on their labels beyond-use dates as determined from information in the product labeling. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such beyond use date shall be not later than

a. the expiration date on the manufacturer's container,
   or
b. one year from the date the drug is dispensed, whichever is earlier.

Each single-unit or unit-dose blister must bear a separate label indicating such expiration date.

Based on the drug product to be packaged, the estimated time until use of the product; manufacturer's expiry dating on the original bulk container and pharmacy specific economic factors one has the ability to pick the appropriate HCL packaging offerings that can meet specific packaging decision criteria.

OTHER IMPORTANT UNIT DOSE PACKAGING CONSIDERATIONS

Light Transmission

The integrity of certain drug products is challenged because of their sensitivity to light. A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material which it is composed, including any coating applied to it. Where it is directed to "protect from light" in an individual monograph, preservation in a light resistant container is intended. Amber colored plastic blisters are available that provide excellent light protection in the critical 290 to 450 nanometer range.

Tamper Evidency

Packages should show evidence of entry or tampering. Essentially, these are packages that when sealed the contents cannot be used without obvious destruction of the seal, as such they are not re-sealable.
Record Keeping

During the repackaging process care should be taken to assure accountability and lot number traceability of the repackaged product. Data should be collected in a log book that specifies the drug product repackaged; the lot number and expiration date from the original manufacturer’s container; the number of doses repackaged; the internal lot number and expiration date assigned to the repackaged product and its disposition.

Labeling Requirements

Each single-unit or unit-dose container should bear a separate label. It is recommended that current federal labeling requirements be adhered to, with particular attention given to the following items:

- Nonproprietary name (and proprietary name, if to be shown)
- Dosage Form (if special or other than oral)
- Strength
- Strength of Dose and Total Contents Delivered (e.g., number of tablets and their total dose)
- Special Notes & Storage Requirements (e.g., refrigerate)
- Expiration Date
- Control or Lot Number
- Patient Specific Packaging

In addition, if the package is meant to be patient specific (as one intended for use in a long term care facility); it should also bear an over label stating:

1. the name of the patient
2. a package/prescription specific serial number
3. the directions for use and cautionary statements
4. the name of the prescriber
5. the name, address, and telephone number of the dispenser

Storage Requirements

After repackaging and while still in the pharmacy, storage of unit-dose or single-unit containers should be in a humidity-controlled environment and at the temperature specified in the individual monograph or in the product labeling. The dispenser must maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than 25°C. The plastic material used in packaging the dosage forms must afford better protection than poly vinyl chloride, which does not provide adequate moisture permeation. Records must be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

USP TESTING

Because of differences in packaging materials, packaging procedures, personnel and techniques used in the process of packaging, the moisture-permeation characteristics of the packaging system to be utilized in the pharmacy are most important and need to be determined.

This testing is performed to permit an informed judgement regarding the suitability of the package for a particular type of product.

The USP provides tests (USP 25 <Section 671>) to determine the moisture permeability of containers utilized for drugs being dispensed on prescription. This USP section "Single-unit Containers and Unit-dose Containers for Capsules and Tablets" applies to single-unit and unit-dose containers for non-sterile solid dosage forms.

The term "container" refers to the entire system comprising, usually the container itself (blister), the liner (if used), the closure (the foil and blister in single-unit and unit-dose containers).
USP CLASS RATINGS

* **Class "A"**: if not more than 1 of 10 samples exceeds 0.5m per day in moisture permeation rate and none exceeds 1mg per day. (testing times equals at least 28 days)

* **Class "B"**: if not more than 1 of 10 samples exceeds 5mg per day in moisture permeation and none exceeds 10mg per day. (testing times equals 7 days)

* **Class "C"**: if not more than 1 of 10 samples exceeds 20mg per day moisture permeation and none exceeds 40mg per day (testing times equals at least 48 hr.)

* **Class "D"**: if the samples meet none of the above.

These class ratings now provide the pharmacist with a professional tool. They are used to judge whether or not a specific unit-dose package (blister and foil label) has the ability to prevent moisture from entering the sealed unit during its storage period. A determination can be made from day of packaging to date of use or to the final expiration day and to what magnitude it protects the integrity of the drug product.

HCL PACKAGE TESTING

In order to test the performance of the unit-dose packaging sold by Health Care Logistics USP testing was commissioned.

The USP Standard Test Method I from Section 671 - Containers-Permeation was used in the testing.

Desiccant tablets were dried at 110°C for one (1) hour prior to use. The desiccant tablets used were (Item TK-1002) from Medical Packaging, Inc.

These tablets indicate a change in moisture content through a weight gain over time and a change in color (from blue to pink) when saturated. The tablets weigh approximately 400mg and have an approximate diameter of 8mm.

The major point in this testing procedure is to maintain a constant weight and a uniform pellet size for the respective unit-dose blister over time.

USP Test Method Employed

A. **Blister Assembly**

Two strips of ten (10) single-unit-dose blisters were assembled.

One (1) desiccant tablet was placed into each blister of the first strip of ten (10).

The second strip of ten (10) was used as a "control". No desiccant tablet was included in the control.

B. **Sealing of the Blister**

Plastic or foam trays with pre-formed individual compartments that accept the various sizes of blisters, are used to perform the sealing task. The following is the method that was used to seal the blisters during USP testing and is the recommended method used for sealing any of HCL's blisters:

1. The blister strip is placed in the tray.
2. The drug product is placed in the blister.
3. The pre-labeled lidding material is then affixed by hand to the strip.
4. Moderate pressure is applied to the package using a sealing roller.
C. Labeling and Weighing of Samples

Each sample was numbered and identified in a manner as to determine the packaging material, lot number and manufacturer’s information (i.e., date of manufacture; type of adhesive, etc).

The weighing of samples and controls are carried out by using an electrical analytical balance that can record values to 4 decimal places. This permits more precise characterization between daily weighing of samples and control and allows for shorter test periods (usually 7 to 10 days). “Class A” containers require test periods in excess of 28 days.

The weights of each sample and of the control were logged as the initial weights for the start of the test procedure.

The control is weighed as a single strip of ten and the recorded weight divided by ten to determine the average weight for each control sample. This expedites the weighing procedure.

D. Storage Parameters and Test Period

The ten (10) samples and controls are stored in a constant humidity tank at 75 ± 3% relative humidity and at a temperature of 23°± 2°C for a period of 30 days.

Temperature and humidity gauges are used both in and outside the tank for monitoring. Room temperature is held between 68 - 72°F with a relative humidity of 55 ± 3%.

Weighing continues at 24-hour intervals, the samples and the control are removed from the humidity tank and allowed to equilibrate to one hour at room temperature. Sample weights and the control weight are recorded as previously noted. Intervals greater than 24 hours may be used, however, they must be multiples of 24 hours.

As the daily weighing continues, if any desiccant tablets turn pink during the procedure, the test is terminated. If the pellet weight increases greater than 10% during any one 24-hour period, the test must also be terminated.

E. Calculations

To calculate the moisture permeation, the following USP formula was used to determine the mg gained per day:

\[
\text{Moisture Permeation} = \frac{1}{N} \left[ (W_f - W_i) - (C_f - C_i) \right]
\]

Where:

- \(N\) is the number of days (24 hr increments) expired during the test.
- \(W_f - W_i\) is the mg difference between the final weight and the initial weight on each sample.
- \(C_f - C_i\) is the average mg difference between the final and initial weight of the control.

The result [Moisture Permeation] is then expressed in “mg/day” of moisture gain.

The testing is to be taken through its completion through a 30 day testing period.

If a desiccant tablet turns pink during the course of the 30 days testing is terminated. If a tablet weight in any of the test groups increases greater than 10% in any one 24-hour period the test is also terminated.
Determination of Results For HCL Packaging Products

Health Care Logistics carries a wide range of unit-dose packaging materials - blisters and lidding (labels). This range of packaging materials provides users with the ability to pick the appropriate packaging components that meet their specific packaging decision criteria.

Health Care Logistics utilizes the earlier described USP Test Procedure to test all of its packaging materials. Based upon the test data collected during testing and the resultant calculations after applying the USP formula; the following represents the recommended combinations of blisters and labels given different levels of drug product protection:

1. HCL recommends the use of it's new "Extra High Barrier Blisters" with its "High Barrier Foil Labels". These "Extra High Barrier Blisters" are made from a new to HCL Aclar® plastic laminate to keep pace with the latest USP packaging recommendations. This combination of blister and label affords the highest in moisture barrier protection properties - "Class A".

2. HCL recommends the use of it's amber or clear "High Barrier Blisters" with its "High Barrier Foil labels".

   The "High Barrier Blister" is a PVC (poly vinyl chloride) plastic. Based upon the USP Test Procedure this combination of blisters and labels meets USP "Class B" package requirements. This combination is used to provide protection to a drug product or when packaging drugs for periods of up to 6-months time.

3. In situations where rapid drug inventory turnover is experienced Health Care Logistics "Budget Blisters" in combination with its "Paper" labels are often used. They provide minimal storage protection and are classified as a USP "Class D" package, which is for 30 days from the date of packaging.

   These "Budget Blisters" are made from a thinner mil PVC (poly vinyl chloride) plastic and are moderately priced in comparison to the "High Barrier" and "Extra High Barrier" blisters which provide increasingly more protection for drug products.

   All of Health Care Logistics amber blisters meet the USP light transmission standards for light sensitive drugs.

   Depending upon the drug product to be packaged; the estimated time until use of the product; the manufacturer's expiry dating on the original bulk container and pharmacy specific economic factors; HCL has packaging combinations that provide the ability to choose the one that's most appropriate and can meet the site-specific packaging decision criteria.

Blister Packaging Accessories

Health Care Logistics has a wide variety of blister packaging accessories that fully complement the blister and label product line and are used in conjunction with the extemporary packaging task.

These include filling trays and templates that accommodate various sizes of tablets and capsules as well as the various sizes of blisters from "compact" to "extra large". These trays and templates are designed to facilitate and speed the filling and packaging of the unit dose blisters.

Other accessories include:
- sealing rollers
- label shields
- packaging recording sheets
- stenciling kits for labeling
- lidding materials that are compatible with ink-jet and laser printers for labeling purposes
- beyond use auxiliary labels

All of these accessories can be purchased separately or in kits. Whether one is looking for an inexpensive way to get started with unit-dose packaging or just a dependable and economical manual alternative to existing systems for short runs, HCL has the packaging accessories needed to accomplish this important task.

Aclar® is a registered trademark of Honeywell International, Inc.
SUMMARY

Drug packaging is an important consideration. The package should protect its contents from deleterious environmental effects. Protect its contents from deterioration from handling such as breakage and contamination. Identify its contents completely and precisely and permit its contents to be used quickly, easily and safely.

Utilizing the guidelines made available by the USP and the American Society of Health Systems Pharmacists this Technical Bulletin has attempted to pull together the important information and criteria necessary to aid the pharmacist in making the right decisions to assure the integrity of all products dispensed by the pharmacy.

References

The United States Pharmacopeia, USP 25
* Section <661> Containers
* Section <671> Containers/Permeation

The Pharmacopeial Forum 27 No. 4
ASHP Technical Assistance Bulletin on Single Unit and Unit Dose Packages of Drugs Moisture Permeation Studies Commissioned by Health Care Logistics and Manufacturer's Product Specifications (data available upon request)

(NOTE: As this bulletin goes to press new standards are being developed by the USP and there appears to be some confusion related to extemporaneous packaging guidelines.

The general guidelines appear in the official USP (latest of which is USP 25). Newer guidelines that are being developed are published in the Pharmacopeial Forum (the Journal of Standards Development and Official Compendia Revision also published by the USP).

The USP acknowledges that PVC is the most commonly used blister material. They also indicate that this material provides a nominal or zero barrier to moisture and is used when the product does not require effective moisture protection. PVC is available in a range of gauges. USP is now recommending newer plastic laminates that provide increasingly higher moisture barrier properties.

HCL is still performing the Classic USP Package Testing as described above in this bulletin. HCL acknowledges that the final package is both a combination of the blister material and the lidding stock that is applied to make the final packaged blister. The testing performed, keeping this combination in mind, classifies our packaging materials in this fashion.

HCL uses a thin gauge mil PVC for its Budget Blisters and a thicker gauge for its "High Barrier Blisters". HCL also has added a new "Extra High Barrier Blister" made of an Aclar® laminate to its product line. These product offerings provide a range in product protection. We will continue to provide this selection of materials that offers this range.

The dispenser should always make sure that in taking on the extemporaneous packaging task, that they should refer to the latest guidelines and exercise proper professional judgement that keeps them in compliance.)