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the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names*. . . .''[4]

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⟨1151⟩ PHARMACEUTICAL DOSAGE FORMS

Dosage forms are provided for most of the Pharmacopeial drug substances, but the processes for the preparation of many of them are, in general, beyond the scope of the Pharmacopeia. In addition to defining the dosage forms, this section presents the general principles involved in the manufacture of some of them, particularly on a small scale. Other information that is given bears on the use of the Pharmacopeial substances in extemporaneous compounding of dosage forms.

BIOAVAILABILITY

Bioavailability, or the extent to which the therapeutic constituent of a pharmaceutical dosage form intended for oral or topical use is available for absorption, is influenced by a variety of factors. Among the inherent factors known to affect absorption are the method of manufacture or method of compounding; the particle size and crystal form or polymorph of the drug substance; and the diluents and excipients used in formulating the dosage form, including fillers, binders, disintegrating agents, lubricants, coatings, solvents, suspending agents, and dyes. Lubricants and coatings are foremost among these. The maintenance of a demonstrably high degree of bioavailability requires particular attention to all aspects of production and quality control that may affect the nature of the finished dosage form.

STABILITY

The term ''stability,'' with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit, and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply throughout the shelf life of the product.

The stability parameters of a drug dosage form can be influenced by environmental conditions of storage (temperature, light, air, and humidity), as well as the package components. Pharmacopeial articles should include required storage conditions on their labeling. These are the conditions under which the expiration date shall apply. The storage requirements specified in the labeling for the article must be observed throughout the distribution of the article (i.e., beyond the time it leaves the manufacturer up to and including its handling by the dispenser or seller of the article to the consumer). Although labeling for the consumer should indicate proper storage conditions, it is recognized that control beyond the dispenser or seller is difficult.

Beyond-use dating information must be provided by the manufacturer in the labeling of all solid oral Pharmacopeial dosage forms intended for dispensing on prescription, unless the dosage form is packaged by the manufacturer in a container that is labeled for dispensing directly to the patient. To meet this requirement, there must be a recommendation for an appropriate dispensing container (e.g., ''tight,'' ''well-closed,'' ''light-resistant'') and, for unit-dose packaging, a recommendation for the appropriate class of package (see Class A, B, C, or D under *Results* in *Containers—Permeation* ⟨671⟩) and the length of time that is appropriate for a beyond-use date in that type of container or package. Such a beyond-use date may be based on an ''open dish'' study in which the dosage forms are found to remain stable (i.e., conform to all monograph requirements for the declared beyond-use time period). The open dish study is a study in which the dosage forms are exposed to 60% relative humidity at 25° for 30 days without any container protection: three samples of 30-unit doses from one lot are analyzed at 0 and 30 days. The dosage forms may be protected from light during the study. Beyond-use dating information supported by such ''open dish'' studies need only indicate that, other than regarding the need for light resistance, any appropriate dispensing container may be used for repackaging the dosage form. Alternatively, studies conducted in containers that are one class below (i.e., more permeable to water vapor) the class being recommended for repackaging the dosage form may be substituted for ''open dish'' studies. For example, a study conducted in Class C unit-dose containers that demonstrates stability will support a recommendation for use of a Class B, or better, package. Beyond-use dating information may be obtained by any other type of stability study including, but not limited to, accelerated stability studies. Exempt from these requirements are drugs dispensed in a container to be used within a day and drugs in container-closure systems that are known to be equivalent in protection to the marketed container system.

Stability Protocols—Stability of manufactured dosage forms must be demonstrated by the manufacturer by the use of methods adequate for the purpose. Monograph assays may be used for stability testing if they are stability-indicating (i.e., if they accurately differentiate between the intact drug molecules and their degradation products). Stability considerations should include not only the specific compendial requirements, but also changes in physical appearance of the product that would warn users that the product's continued integrity is questionable.

Stability studies on active substances and packaged dosage forms are conducted by means of ''real-time,'' long-term tests at specific temperatures and relative humidities representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned. Labeling of the packaged active substance or dosage form should reflect the effects of temperature, relative humidity, air, and light on its stability. Label temperature storage warnings will reflect both the results of the real-time storage tests and also allow for expected seasonal excursions of temperature.

Controlled room temperature (see the *Storage Temperature* section under *General Notices and Requirements—Preservation, Packaging, Storage, and Labeling*) delineates the allowable tolerance in storage circumstances at any location in the chain of distribution (e.g., pharmacies, hospitals, and warehouses). This terminology also allows patients or consumers to be counseled as to appropriate storage for the product. Products may be labeled either to store at ''Controlled room temperature'' or to store at temperatures ''up to 25°'' where labeling is supported by long-term stability studies at the designated storage condition of 25°. *Controlled room temperature* limits the permissible excursions to those consistent with the maintenance of a mean kinetic temperature calculated to be not more than 25°. See *Mean Kinetic Temperature*. The common international guideline for long-term stability studies specifies 25 ± 2° at 60 ± 5% relative humidity. Accelerated studies are specified at 40 ± 2° and at 75 ± 5% relative humidity. Accelerated studies also allow the interpretation of data and information on short-term spikes in storage conditions in addition to the excursions allowed for by controlled room temperature.

The term ''room temperature'' is used in different ways in different countries, and it is usually preferable for product labeling for products to be shipped outside the continental U.S. to refer to a maximum storage temperature or temperature range in degrees Celsius.

Mean Kinetic Temperature—Mean kinetic temperature is defined as a single calculated temperature at which the degradation of an article would be equivalent to the actual degradation that would

Table 1. International Climatic Zones.

Climatic Zone	Calculated Data °C*	°C MKT**	% RH	mbar***	Derived Data °C	% RH	mbar
I. *Temperate* United Kingdom Northern Europe Canada Russia	20.0	20.0	42	9.9	21	45	11.2
II *Mediterranean, Subtropical* United States Japan Southern Europe (Portugal-Greece)	21.6	22.0	52	13.5	25	60	19.0
III. *Hot, Dry* Iran Iraq Sudan	26.4	27.9	35	11.9	30	35	15.0
IV. *Hot, Humid* Brazil Ghana Indonesia Nicaragua Philippines	26.7	27.4	76	26.6	30	70	30.0

* Data recorded as <19° calculated as 19°.
** Calculated mean kinetic temperature.
***Partial pressure of water vapor.

culated from average storage temperatures recorded over a one-year period, with a minimum of twelve equally spaced average storage temperature observations being recorded. Average temperature may be determined using automated recording devices or as the arithmetic mean of the highest and lowest temperatures attained during the observation period as measured on a high-low thermometer. The mean kinetic temperature is calculated by the following equation (derived from the Arrhenius equation):

$$T_k = \frac{\Delta H / R}{-ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)},$$

in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144kJ·mole^{-1} (unless more accurate information is available from experimental studies); R is the universal gas constant, 8.3144×10^{-3} kJ· mole^{-1}· degree^{-1}; T_1 is the average storage temperature during the first time period (e.g., month); T_2 is the average storage temperature during the second time period; T_n is the average storage temperature during the nth time period, n being the total number of average storage temperatures recorded (minimum of twelve) during the observation period; and all temperatures (T) being absolute temperatures in degrees Kelvin (°K).

Climatic Zones—For convenience in planning for packaging and storage, and for stability studies, international practice identifies four climatic zones, which are described in Table 1. The United States, Europe, and Japan are characterized by zones I and II. The values in Table 1 are based on observed temperatures and relative humidities, both outside and in rooms, from which mean kinetic temperatures and average humidity values are calculated.[1] Derived values are based on inspection of data from individual cities and on allowances for a margin of safety in assignment of these specified conditions.

A discussion of aspects of drug product stability that are of primary concern to the pharmacist in the dispensing of medications may be found under *Stability Considerations in Dispensing Practice* ⟨1191⟩.

Inasmuch as this chapter is for purposes of general information only, no statement herein is intended to modify or supplant any of the specific requirements pertinent to pharmaceutical preparations, which are given elsewhere in this Pharmacopeia.

TERMINOLOGY

Occasionally it is necessary to add solvent to the contents of a container just prior to use, usually because of instability of some drugs in the diluted form. Thus, a solid diluted to yield a suspension is called [*DRUG*] *for Suspension;* a solid dissolved and diluted to yield a solution is called [*DRUG*] *for Solution;* and a solution or suspension diluted to yield a more dilute form of the drug is called [*DRUG*] *Oral Concentrate.* After dilution, it is important that the drug be homogeneously dispersed before administration.

AEROSOLS

Pharmaceutical aerosols are products that are packaged under pressure and contain therapeutically active ingredients that are released upon activation of an appropriate valve system. They are intended for topical application to the skin as well as local application into the nose (nasal aerosols), mouth (lingual aerosols), or lungs (inhalation aerosols). These products may be fitted with valves enabling either continuous or metered-dose delivery; hence, the terms "[DRUG] Metered Topical Aerosols," "[DRUG] Metered Nasal Aerosols," etc.

The term "aerosol" refers to the fine mist of spray that results from most pressurized systems. However, the term has been broadly misapplied to all self-contained pressurized products, some of which deliver foams or semisolid fluids. In the case of *Inhalation Aerosols*, the particle size of the delivered medication must be carefully controlled and the average size of the particles should be under 5 μm. These products are also known as metered-dose inhalers (MDIs). Other aerosol sprays may contain particles up to several hundred micrometers in diameter.

The basic components of an aerosol system are the container, the propellant, the concentrate containing the active ingredient(s), the

[1] The source of the data and information in Table 1 is the International Conference on Harmonization sponsored by the Interna-

for metered valves, delivery rate, wetness and temperature of the spray, spray pattern and velocity or plume geometry, foam density, and fluid viscosity.

Types of Aerosols

Aerosols consist of two-phase (gas and liquid) or three-phase (gas, liquid, and solid or liquid) systems. The two-phase aerosol consists of a solution of active ingredients in liquefied propellant and the vaporized propellant. The solvent is composed of the propellant or a mixture of the propellant and co-solvents such as alcohol, propylene glycol, and polyethylene glycols, which are often used to enhance the solubility of the active ingredients.

Three-phase systems consist of a suspension or emulsion of the active ingredient(s) in addition to the vaporized propellants. A suspension consists of the active ingredient(s) that may be dispersed in the propellant system with the aid of suitable excipients such as wetting agents and / or solid carriers such as talc or colloidal silicas.

A foam aerosol is an emulsion containing one or more active ingredients, surfactants, aqueous or nonaqueous liquids, and the propellants. If the propellant is in the internal (discontinuous) phase (i.e., of the oil-in-water type), a stable foam is discharged; and if the propellant is in the external (continuous) phase (i.e., of the water-in-oil type), a spray or a quick-breaking foam is discharged.

Propellants

The propellant supplies the necessary pressure within an aerosol system to expel material from the container and, in combination with other components, to convert the material into the desired physical form. Propellants may be broadly classified as liquefied or compressed gases having vapor pressures generally exceeding atmospheric pressure. Propellants within this definition include various hydrocarbons, especially halogenated derivatives of methane, ethane, and propane, low molecular weight hydrocarbons such as the butanes and pentanes, and compressed gases such as carbon dioxide, nitrogen, and nitrous oxide. Mixtures of propellants are frequently used to obtain desirable pressure, delivery, and spray characteristics. A good propellant system should have the proper vapor pressure characteristics consistent with the other aerosol components.

Valves

The primary function of the valve is to regulate the flow of the therapeutic agent and propellant from the container. The spray characteristics of the aerosol are influenced by orifice dimension, number, and location. Most aerosol valves provide for continuous spray operation and are used on most topical products. However, pharmaceutical products for oral or nasal inhalation often utilize metered-dose valves that must deliver a uniform quantity of spray upon each valve activation. The accuracy and reproducibility of the doses delivered from metering valves are generally good, comparing favorably to the uniformity of solid dosage forms such as tablets and capsules. However, when aerosol packages are stored improperly, or when they have not been used for long periods of time, valves must be primed before use. Materials used for the manufacture of valves should be inert to the formulations used. Plastic, rubber, aluminum, and stainless steel valve components are commonly used. Metered-dose valves must deliver an accurate dose within specified tolerances.

Actuators

An actuator is the fitting attached to an aerosol valve stem, which when depressed or moved, opens the valve, and directs the spray containing the drug preparation to the desired area. The actuator usually indicates the direction in which the preparation is dispensed and protects the hand or finger from the refrigerant effects of the propellant. Actuators incorporate an orifice which may vary widely in size and shape. The size of this orifice, the expansion chamber design, and the nature of the propellant and formulation influence the delivered dose as well as the physical characteristics of the spray, foam, or stream of solid particles dispensed. For inhalation aerosols, an actuator capable of delivering the medication in the

Containers

Aerosol containers usually are made of glass, plastic, or metal, or a combination of these materials. Glass containers must be precisely engineered to provide the maximum in pressure safety and impact resistance. Plastics may be employed to coat glass containers for improved safety characteristics, or to coat metal containers to improve corrosion resistance and enhance stability of the formulation. Suitable metals include stainless steel, aluminum, and tin-plated steel. Extractables or leachables (e.g., drawing oils, cleaning agents, etc.) and particulates on the internal surfaces of containers should be controlled.

Manufacture

Aerosols are usually prepared by one of two general processes. In the "cold-fill" process, the concentrate (generally cooled to a temperature below 0°) and the refrigerated propellant are measured into open containers (usually chilled). The valve-actuator assembly is then crimped onto the container to form a pressure-tight seal. During the interval between propellant addition and crimping, sufficient volatilization of propellant occurs to displace air from the container. In the "pressure-fill" method, the concentrate is placed in the container, and either the propellant is forced under pressure through the valve orifice after the valve is sealed, or the propellant is allowed to flow under the valve cap and then the valve assembly is sealed ("under-the-cap" filling). In both cases of the "pressure-fill" method, provision must be made for evacuation of air by means of vacuum or displacement with a small amount of propellant vapor. Manufacturing process controls usually include monitoring of proper formulation and propellant fill weight and pressure testing, leak testing, and valve function testing of the finished aerosol. Microbiological attributes should also be controlled.

Extractable Substances

Since pressurized inhalers and aerosols are normally formulated with organic solvents as the propellant or the vehicle, leaching of extractables from the elastomeric and plastic components into the formulation is a potentially serious problem. Thus, the composition and the quality of materials used in the manufacture of the valve components (e.g., stem, gaskets, housing, etc.) must be carefully selected and controlled. Their compatibility with formulation components should be well established so as to prevent distortion of the valve components and to minimize changes in the medication delivery, leak rate, and impurity profile of the drug product over time. The extractable profiles of a representative sample of each of the elastomeric and plastic components of the valve should be established under specified conditions and should be correlated to the extractable profile of the aged drug product or placebo, to ensure reproducible quality and purity of the drug product. Extractables, which may include polynuclear aromatics, nitrosamines, vulcanization accelerators, antioxidants, plasticizers, monomers, etc., should be identified and minimized wherever possible.

Specifications and limits for individual and total extractables from different valve components may require the use of different analytical methods. In addition, the standard USP biological testing (see the general test chapters *Biological Reactivity Tests, In Vitro* ⟨87⟩ and *Biological Reactivity Tests, In Vivo* ⟨88⟩) as well as other safety data may be needed.

Labeling

Medicinal aerosols should contain at least the following warning information on the label as in accordance with appropriate regulations.

Warning—Avoid inhaling. Avoid spraying into eyes or onto other mucous membranes.

NOTE—The statement "Avoid inhaling" is not necessary for preparations specifically designed for use by inhalation. The phrase "or other mucous membranes" is not necessary for preparations specifically designed for use on mucous membranes.

Warning—Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120° F (49° C). Keep out of reach of children.

In addition to the aforementioned warnings, the label of a drug

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