

## BRIEFING

**(1151) Pharmaceutical Dosage Forms**, *USP* 32 page 663. This general information chapter is being revised in its entirety to represent current compendial thinking with respect to official preparations. The proposed revision incorporates concepts outlined in a Stimuli to the Revision Process article, *Development of a Compendial Taxonomy and Glossary for Pharmaceutical Dosage Forms*, authored by an Ad Hoc Committee composed of the chairs of the Pharmaceutical Dosage Forms Expert Committee, Biopharmaceutics Expert Committee, Nomenclature and Labeling Expert Committee, and the Council of Experts for the revision cycle, 2000–2005, and published in *PF* 29(5). The Stimuli article proposed a tiered categorization for pharmaceutical dosage forms proceeding from route of administration to physical form and ultimately release pattern. This proposed general information chapter emphasizes the second tier of the compendial taxonomy, the physical dosage form, rather than the route of administration, with the intention of avoiding redundancy for dosage forms given by multiple routes.

The proposed revision is organized into four sections providing discussion of general considerations, product quality tests, dosage form monographs, and a glossary. General considerations include dose uniformity, stability, bioavailability, manufacture, and route of administration. The discussion of product quality tests reflects the universally applied as well as dosage form specific testing that help assure safety and efficacy from manufacture through shelf life. The dosage form monographs provide general descriptions, discussion of general principles of their manufacturing or compounding, and recommendations for proper use and storage. The glossary is intended to provide guidance in selection of official names for official articles but also as a resource to provide definitions beyond those used in official names for dosage forms. The glossary clearly distinguishes preferred from not preferred terminology.

The revised general information chapter presents current concepts relating to the naming of dosage forms. Outdated forms such as elixirs, spirits, tinctures, and syrups are herein recognized as solutions. Lotions are defined as emulsions typically for topical use. While inserts are defined as solid dosage forms for placement within body cavities, suppositories are differentiated as only for placement within the rectum.

This general information chapter is intended to be supplemented by more detailed discussion of characteristics, quality tests, and other considerations based on route of administration. Early drafts of such concepts relating to topical and transdermal dosage forms are presented in *PF* 35(3) [May–June 2009]. Proposed general test chapter (3) *Topical and Transdermal Drug Products—Product Quality Tests*, providing quality testing procedures, complements the performance testing proposed in (725) *Topical and Transdermal Drug Products—Product Performance Tests*. Additional revision proposals of similar standards for the oral (gastro-intestinal), mucosal, by inhalation, and by injection routes are planned.

(BPC: W. Brown.)     RTS—C69686

**Change to read:**

## (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.

### 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  $\mu\text{m}$ . 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 valve, and the actuator. The nature of these components determines such characteristics as particle size distribution, uniformity of dose 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 cosolvents 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 that 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 proper particle size range and with the appropriate spray pattern and plume geometry is utilized.

## 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°C) 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 packaged in an aerosol container in which the propellant consists in whole or in part of a halocarbon or hydrocarbon shall, where required under regulations of the FDA, bear either of the following warnings:

**Warning**—Do not inhale directly; deliberate inhalation of contents can cause death.

**Warning**—Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

## BOLUSES

Boluses are large elongated tablets intended for administration to animals (see *Tablets*).

## CAPSULES

Capsules are solid dosage forms in which the drug is enclosed within either a hard or soft soluble container or “shell.” The shells are usually formed from gelatin; however, they also may be made from starch or other suitable substances. Hard shell capsule sizes range from No. 5, the smallest, to No. 000, which is the largest, except for veterinary sizes. However, size No. 000 generally is the largest size acceptable to patients. Size 0 hard gelatin capsules having an elongated body (known as size 0E) also are available, which provide greater fill capacity without an increase in diameter. Hard gelatin capsules consist of two, telescoping cap and body pieces. Generally, there are unique grooves or indentations molded into the cap and body portions to provide a positive closure when fully engaged, which helps prevent the accidental separation of the filled capsules during shipping and handling. Positive closure also may be affected by spot fusion (“welding”) of the cap and body pieces together through direct thermal means or by application of ultrasonic energy. Factory filled hard gelatin capsules may be completely sealed by banding, a process in which one or more layers of gelatin are applied over the seam of the cap and body, or by a liquid fusion process wherein the filled capsules are wetted with a hydroalcoholic solution that penetrates into the space where the cap overlaps the body, and then dried. Hard shell capsules made from starch consist of two, fitted cap and body pieces. Since the two pieces do not telescope or interlock positively, they are sealed together at the time of filling to prevent their separation. Starch capsules are sealed by the application of a hydroalcoholic solution to the recessed section of the cap immediately prior to its being placed onto the body.

The banding of hard shell gelatin capsules or the liquid sealing of hard shell starch capsules enhances consumer safety by making the capsules difficult to open without causing visible, obvious damage, and may improve the stability of contents by limiting O<sub>2</sub> penetration. Industrially filled hard shell capsules also are often of distinctive color and shape or are otherwise marked to identify them with the manufacturer. Additionally, such capsules may be printed axially or radially with strengths, product codes, etc. Pharmaceutical grade printing inks are usually based on shellac and employ FDA approved pigments and lake dyes.

In extemporaneous prescription practice, hard shell capsules may be hand filled; this permits the prescriber a latitude of choice in selecting either a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility gives hard shell capsules an advantage over compressed tablets and soft shell capsules as a dosage form. Hard shell capsules are usually formed from gela-

tins having relatively high gel strength. Either type may be used, but blends of pork skin and bone gelatin are often used to optimize shell clarity and toughness. Hard shell capsules also may be formed from starch or other suitable substances. Hard shell capsules may also contain colorants, such as D&C and FD&C dyes or the various iron oxides, opaquing agents such as titanium dioxide, dispersing agents, hardening agents such as sucrose, and preservatives. They normally contain between 10% and 15% water.

Hard gelatin capsules are made by a process that involves dipping shaped pins into gelatin solutions, after which the gelatin films are dried, trimmed, and removed from the pins, and the body and cap pieces are joined. Starch capsules are made by injection molding a mixture of starch and water, after which the capsules are dried. A separate mold is used for caps and bodies, and the two parts are supplied separately. The empty capsules should be stored in tight containers until they are filled. Since gelatin is of animal origin and starch is of vegetable origin, capsules made with these materials should be protected from potential sources of microbial contamination.

Hard shell capsules typically are filled with powder, beads, or granules. Inert sugar beads (nonpareils) may be coated with active ingredients and coating compositions that provide extended release profiles or enteric properties. Alternatively, larger dose active ingredients themselves may be suitably formed into pellets and then coated. Semisolids or liquids also may be filled into hard shell capsules; however, when the latter are encapsulated, one of the sealing techniques must be employed to prevent leakage.

In hard gelatin capsule filling operations, the body and cap of the shell are separated prior to dosing. In hard starch shell filling operations, the bodies and caps are supplied separately and are fed into separate hoppers of the filling machine. Machines employing various dosing principles may be employed to fill powders into hard shell capsules; however, most fully automatic machines form powder plugs by compression and eject them into empty capsule bodies. Accessories to these machines generally are available for the other types of fills. Powder formulations often require adding fillers, lubricants, and glidants to the active ingredients to facilitate encapsulation. The formulation, as well as the method of filling, particularly the degree of compaction, may influence the rate of drug release. The addition of wetting agents to the powder mass is common where the active ingredient is hydrophobic. Disintegrants also may be included in powder formulations to facilitate deaggregation and dispersal of capsule plugs in the gut. Powder formulations often may be produced by dry blending; however, bulky formulations may require densification by roll compaction or other suitable granulation techniques.

Powder mixtures that tend to liquefy may be dispensed in hard shell capsules if an absorbent such as magnesium carbonate, colloidal silicon dioxide, or other suitable substance is used. Potent drugs are often mixed with an inert diluent before being filled into capsules. Where two mutually incompatible drugs are prescribed together, it is sometimes possible to place one in a small capsule and then enclose it with the second drug in a larger capsule. Incompatible drugs also can be separated by placing coated pellets or tablets, or soft shell capsules of one drug into the capsule shell before adding the second drug.

Thixotropic semisolids may be formed by gelling liquid drugs or vehicles with colloidal silicas or powdered high molecular weight polyethylene glycols. Various waxy or fatty compounds may be used to prepare semisolid matrices by fusion.

Soft shell capsules made from gelatin (sometimes called soft-gels) or other suitable material require large scale production methods. The soft gelatin shell is somewhat thicker than that of hard shell capsules and may be plasticized by the addition of a polyol such as sorbitol or glycerin. The ratio of dry plasticizer to dry gelatin determines the “hardness” of the shell and may be varied to accommodate environmental conditions as well as the nature of the contents. Like hard shells, the shell composition may include approved dyes and pigments, opaquing agents such as titanium dioxide, and preservatives. Flavors may be added and up to 5% sucrose may be included for its sweetness and to produce a chewable shell. Soft gelatin shells normally contain 6% to 12% water. Soft shell capsules

also may be printed with a product code, strength, etc. In most cases, soft shell capsules are filled with liquid contents. Typically, active ingredients are dissolved or suspended in a liquid vehicle. Classically, an oleaginous vehicle such as a vegetable oil was used; however, nonaqueous, water-miscible liquid vehicles such as the lower molecular weight polyethylene glycols are more common today due to fewer bioavailability problems.

Available in a wide variety of sizes and shapes, soft shell capsules are both formed, filled, and sealed in the same machine; typically, this is a rotary die process, although a plate process or reciprocating die process also may be employed. Soft shell capsules also may be manufactured in a bubble process that forms seamless spherical capsules. With suitable equipment, powders and other dry solids also may be filled into soft shell capsules.

Liquid-filled capsules of either type involve similar formulation technology and offer similar advantages and limitations. For instance, both may offer advantages over dry-filled capsules and tablets in content uniformity and drug dissolution. Greater homogeneity is possible in liquid systems, and liquids can be metered more accurately. Drug dissolution may benefit because the drug may already be in solution or at least suspended in a hydrophilic vehicle. However, the contact between the hard or soft shell and its liquid content is more intimate than exists with dry-filled capsules, and this may enhance the chances for undesired interactions. The liquid nature of capsule contents presents different technological problems than dry-filled capsules in regard to disintegration and dissolution testing. From formulation, technological, and biopharmaceutical points of view, liquid-filled capsules of either type have more in common than liquid-filled and dry-filled capsules having the same shell composition. Thus, for compendial purposes, standards and methods should be established based on capsule contents rather than on whether the contents are filled into hard or soft shell capsules.

#### DELAYED-RELEASE CAPSULES

Capsules may be coated, or, more commonly, encapsulated granules may be coated to resist releasing the drug in the gastric fluid of the stomach where a delay is important to alleviate potential problems of drug inactivation or gastric mucosal irritation. The term "delayed release" is used for Pharmacopeial monographs on enteric-coated capsules that are intended to delay the release of medication until the capsule has passed through the stomach, and the individual monographs include tests and specifications for *Drug release* (see *Drug Release* (724)) or *Disintegration* (see *Disintegration* (701)).

#### EXTENDED-RELEASE CAPSULES

Extended-release capsules are formulated in such manner as to make the contained medication available over an extended period of time following ingestion. Expressions such as "prolonged action," "repeat action," and "sustained release" have also been used to describe such dosage forms. However, the term "extended release" is used for Pharmacopeial purposes and requirements for *Drug release* (see *Drug Release* (724)) typically are specified in the individual monographs.

#### CONCENTRATE FOR DIP

Concentrate for Dip is a preparation containing one or more active ingredients usually in the form of a paste or solution. It is used to prepare a diluted suspension, emulsion, or solution of the active ingredient(s) for the prevention and treatment of ectoparasitic infestations of animals. The diluted preparation (Dip) is applied by complete immersion of the animal or, where appropriate, by spraying. Concentrate for Dip may contain suitable antimicrobial preservatives.

#### CREAMS

Creams are semisolid dosage forms containing one or more drug substances dissolved or dispersed in a suitable base. This term has traditionally been applied to semisolids that possess a relatively fluid consistency formulated as either water-in-oil (e.g., *Cold Cream*) or oil-in-water (e.g., *Fluocinolone Acetonide Cream*) emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water-washable and more cosmetically and aesthetically acceptable. Creams can be used for administering drugs via the vaginal route (e.g., *Triple Sulfate Vaginal Cream*).

#### ELIXIRS

See *Solutions*.

#### EMULSIONS

Emulsions are two-phase systems in which one liquid is dispersed throughout another liquid in the form of small droplets. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets and, ultimately, into a single separated phase. Emulsifying agents (surfactants) do this by concentrating in the interface between the droplet and external phase and by providing a physical barrier around the particle to coalescence. Surfactants also reduce the interfacial tension between the phases, thus increasing the ease of emulsification upon mixing.

Natural, semisynthetic, and synthetic hydrophilic polymers may be used in conjunction with surfactants in oil-in-water emulsions as they accumulate at interfaces and also increase the viscosity of the aqueous phase, thereby decreasing the rate of formation of aggregates of droplets. Aggregation is generally accompanied by a relatively rapid separation of an emulsion into a droplet-rich and droplet-poor phase. Normally the density of an oil is lower than that of water, in which case the oil droplets and droplet aggregates rise, a process referred to as creaming. The greater the rate of aggregation, the greater the droplet size and the greater the rate of creaming. The water droplets in a water-in-oil emulsion generally sediment because of their greater density.

The consistency of emulsions varies widely, ranging from easily pourable liquids to semisolid creams. Generally oil-in-water creams are prepared at high temperature, where they are fluid, and cooled to room temperature, whereupon they solidify as a result of solidification of the internal phase. When this is the case, a high internal phase volume to external phase volume ratio is not necessary for semisolid character, and, for example, stearic acid creams or vanishing creams are semisolid with as little as 15% internal phase. Any semisolid character with water-in-oil emulsions generally is attributable to a semisolid external phase.

All emulsions require an antimicrobial agent because the aqueous phase is favorable to the growth of microorganisms. The presence of a preservative is particularly critical in oil-in-water emulsions where contamination of the external phase occurs readily. Since fungi and yeasts are found with greater frequency than bacteria, fungistatic as well as bacteriostatic properties are desirable. Bacteria have been shown to degrade nonionic and anionic emulsifying agents, glycerin, and many natural stabilizers such as tragacanth and guar gum.

Complications arise in preserving emulsion systems, as a result of partitioning of the antimicrobial agent out of the aqueous phase where it is most needed, or of complexation with emulsion ingredients that reduce effectiveness. Therefore, the effectiveness of the preservative system should always be tested

in the final product. Preservatives commonly used in emulsions include methyl-, ethyl-, propyl-, and butyl parabens, benzoic acid, and quaternary ammonium compounds.

See also *Creams and Ointments*.

## EXTRACTS AND FLUIDEXTRACTS

Extracts are concentrated preparations of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with suitable menstrua, by evaporation of all or nearly all of the solvent, and by adjustment of the residual masses or powders to the prescribed standards.

In the manufacture of most extracts, the drugs are extracted by percolation. The entire percolates are concentrated, generally by distillation under reduced pressure in order to subject the drug principles to as little heat as possible.

Fluidextracts are liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, and so made that, unless otherwise specified in an individual monograph, each mL contains the therapeutic constituents of 1 g of the standard drug that it represents.

A fluidextract that tends to deposit sediment may be aged and filtered or the clear portion decanted, provided the resulting clear liquid conforms to the Pharmacopeial standards.

Fluidextracts may be prepared from suitable extracts.

## GELS

Gels (sometimes called jellies) are semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (e.g., *Aluminum Hydroxide Gel*). In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma (e.g., *Bentonite Magma*). Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation. They should be shaken before use to ensure homogeneity and should be labeled to that effect. (See *Suspensions*.)

Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules (e.g., *Carbomer*) or from natural gums (e.g., *Tragacanth*). The latter preparations are also called mucilages. Although these gels are commonly aqueous, alcohols and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.

Gels can be used to administer drugs topically or into body cavities (e.g., *Phenylephrine Hydrochloride Nasal Jelly*).

## IMPLANTS (PELLETS)

Implants or pellets are small sterile solid masses consisting of a highly purified drug (with or without excipients) made by compression or molding. They are intended for implantation in the body (usually subcutaneously) for the purpose of providing continuous release of the drug over long periods of time. Implants are administered by means of a suitable special injector or surgical incision. This dosage form has been used to administer hormones such as testosterone or estradiol. They are packaged individually in sterile vials or foil strips.

## INFUSIONS, INTRAMAMMARY

Intramammary infusions are suspensions of drugs in suitable oil vehicles. These preparations are intended for veterinary use only, and are administered by instillation via the teat canals into the udders of milk-producing animals.

## INHALATIONS

Inhalations are drugs or solutions or suspensions of one or more drug substances administered by the nasal or oral respiratory route for local or systemic effect.

Solutions of drug substances in sterile water for inhalation or in sodium chloride inhalation solution may be nebulized by use of inert gases. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles. Nebulized solutions may be breathed directly from the nebulizer or the nebulizer may be attached to a plastic face mask, tent, or intermittent positive pressure breathing (IPPB) machine.

Another group of products, also known as metered dose inhalers (MDIs) are propellant driven drug suspensions or solutions in liquified gas propellant with or without a cosolvent and are intended for delivering metered doses of the drug to the respiratory tract. An MDI contains multiple doses, often exceeding several hundred. The most common single dose volumes delivered are from 25 to 100  $\mu\text{L}$  (also expressed as mg) per actuation.

Examples of MDIs containing drug solutions and suspensions in this pharmacopeia are *Epinephrine Inhalation Aerosol* and *Iso-*proterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol*, respectively.*

Powders may also be administered by mechanical devices that require manually produced pressure or a deep inhalation by the patient (e.g., *Cromolyn Sodium for Inhalation*).

A special class of inhalations termed inhalants consists of drugs or combination of drugs, that by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant generally is administered is known as an inhaler.

## INJECTIONS

An Injection is a preparation intended for parenteral administration or for constituting or diluting a parenteral article prior to administration (see *Injections* (-1)).

Each container of an Injection is filled with a volume in slight excess of the labeled "size" or that volume that is to be withdrawn. The excess volumes recommended in the accompanying table are usually sufficient to permit withdrawal and administration of the labeled volumes.

Labeled Size	Recommended Excess Volume	
	For Mobile Liquids	For Viscous Liquids
0.5 mL	0.10 mL	0.12 mL
1.0 mL	0.10 mL	0.15 mL
2.0 mL	0.15 mL	0.25 mL
5.0 mL	0.30 mL	0.50 mL
10.0 mL	0.50 mL	0.70 mL
20.0 mL	0.60 mL	0.90 mL
30.0 mL	0.80 mL	1.20 mL
50.0 mL or more	2%	3%

## IRRIGATIONS

Irrigations are sterile solutions intended to bathe or flush open wounds or body cavities. They are used topically, never parenterally. They are labeled to indicate that they are not intended for injection.

## LOTIONS

See *Solutions or Suspensions*.

## LOZENGES

Lozenges are solid preparations, that are intended to dissolve or disintegrate slowly in the mouth. They contain one or more medicaments, usually in a flavored, sweetened base. They can be prepared by molding (gelatin and/or fused sucrose or sorbitol base) or by compression of sugar based tablets. Molded lozenges are sometimes referred to as pastilles while compressed lozenges are often referred to as troches. They are usually intended for treatment of local irritation or infections of the mouth or throat but may contain active ingredients intended for systemic absorption after swallowing.

## OINTMENTS

Ointments are semisolid preparations intended for external application to the skin or mucous membranes.

Ointment bases recognized for use as vehicles fall into four general classes: the hydrocarbon bases, the absorption bases, the water removable bases, and the water soluble bases. Each therapeutic ointment possesses as its base a representative of one of these four general classes.

### Hydrocarbon Bases

These bases, which are known also as "oleaginous ointment bases," are represented by *White Petrolatum* and *White Ointment*. Only small amounts of an aqueous component can be incorporated into them. They serve to keep medicaments in prolonged contact with the skin and act as occlusive dressings. Hydrocarbon bases are used chiefly for their emollient effects, and are difficult to wash off. They do not "dry out" or change noticeably on aging.

### Absorption Bases

This class of bases may be divided into two groups: the first group consisting of bases that permit the incorporation of aqueous solutions with the formation of a water in oil emulsion (*Hydrophilic Petrolatum* and *Lanolin*), and the second group consisting of water in oil emulsions that permit the incorporation of additional quantities of aqueous solutions (*Lanolin*). Absorption bases are useful also as emollients.

### Water-Removable Bases

Such bases are oil in water emulsions, e.g., *Hydrophilic Ointment*, and are more correctly called "creams." (See *Creams*.) They are also described as "water washable," since they may be readily washed from the skin or clothing with water, an attribute that makes them more acceptable for cosmetic reasons. Some medicaments may be more effective in these bases than in hydrocarbon bases. Other advantages of the water removable bases are that they may be diluted with water and that they favor the absorption of serous discharges in dermatological conditions.

### Water-Soluble Bases

This group of so-called "greaseless ointment bases" comprises water soluble constituents. *Polyethylene Glycol Ointment* is the only Pharmacopeial preparation in this group. Bases of this type offer many of the advantages of the water removable bases and, in addition, contain no water insoluble substances such as petrolatum, anhydrous lanolin, or waxes. They are more correctly called "Gels." (See *Gels*.)

**Choice of Base**—The choice of an ointment base depends upon many factors, such as the action desired, the nature of the medicament to be incorporated and its bioavailability and stability, and the requisite shelf life of the finished product. In some

cases, it is necessary to use a base that is less than ideal in order to achieve the stability required. Drugs that hydrolyze rapidly, for example, are more stable in hydrocarbon bases than in bases containing water, even though they may be more effective in the latter.

## OPHTHALMIC PREPARATIONS

Drugs are administered to the eyes in a wide variety of dosage forms, some of which require special consideration. They are discussed in the following paragraphs.

### Ointments

Ophthalmic ointments are ointments for application to the eye. Special precautions must be taken in the preparation of ophthalmic ointments. They are manufactured from sterilized ingredients under rigidly aseptic conditions and meet the requirements under *Sterility Tests* (71). If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described under *Sterility Tests* (71), along with aseptic manufacture, may be employed. Ophthalmic ointments must contain a suitable substance or mixture of substances to prevent growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use, unless otherwise directed in the individual monograph, or unless the formula itself is bacteriostatic (see *Added Substances* under *Ophthalmic Ointments* (71)). The medicinal agent is added to the ointment base either as a solution or as a micronized powder. The finished ointment must be free from large particles and must meet the requirements for *Leakage* and for *Metal Particles* under *Ophthalmic Ointments* (71). The immediate containers for ophthalmic ointments shall be sterile at the time of filling and closing. It is mandatory that the immediate containers for ophthalmic ointments be sealed and tamper proof so that sterility is assured at time of first use.

The ointment base that is selected must be nonirritating to the eye, permit diffusion of the drug throughout the secretions bathing the eye, and retain the activity of the medicament for a reasonable period under proper storage conditions.

Petrolatum is mainly used as a base for ophthalmic drugs. Some absorption bases, water removable bases, and water soluble bases may be desirable for water soluble drugs. Such bases allow for better dispersion of water soluble medicaments, but they must be nonirritating to the eye.

### Solutions

Ophthalmic solutions are sterile solutions, essentially free from foreign particles, suitably compounded and packaged for instillation into the eye. Preparation of an ophthalmic solution requires careful consideration of such factors as the inherent toxicity of the drug itself, isotonicity value, the need for buffering agents, the need for a preservative (and, if needed, its selection), sterilization, and proper packaging. Similar considerations are also made for nasal and otic products.

#### ISOTONICITY VALUE

Lacrimal fluid is isotonic with blood, having an isotonicity value corresponding to that of a 0.9% sodium chloride solution. Ideally, an ophthalmic solution should have this isotonicity value; but the eye can tolerate isotonicity values as low as that of a 0.6% sodium chloride solution and as high as that of a 2.0% sodium chloride solution without marked discomfort.

Some ophthalmic solutions are necessarily hypertonic in order to enhance absorption and provide a concentration of the active ingredient(s) strong enough to exert a prompt and effective action. Where the amount of such solutions used is small, dilution with lacrimal fluid takes place rapidly so that discomfort from the hypertonicity is only temporary. However, any adjust-

ment toward isotonicity by dilution with tears is negligible where large volumes of hypertonic solutions are used as collyria to wash the eyes; it is, therefore, important that solutions used for this purpose be approximately isotonic.

#### BUFFERING

Many drugs, notably alkaloidal salts, are most effective at pH levels that favor the undissociated free bases. At such pH levels, however, the drug may be unstable so that compromise levels must be found and held by means of buffers. One purpose of buffering some ophthalmic solutions is to prevent an increase in pH caused by the slow release of hydroxyl ions by glass. Such a rise in pH can affect both the solubility and the stability of the drug. The decision whether or not buffering agents should be added in preparing an ophthalmic solution must be based on several considerations. Normal tears have a pH of about 7.4 and possess some buffer capacity. The application of a solution to the eye stimulates the flow of tears and the rapid neutralization of any excess hydrogen or hydroxyl ions within the buffer capacity of the tears. Many ophthalmic drugs, such as alkaloidal salts, are weakly acidic and have only weak buffer capacity. Where only 1 or 2 drops of a solution containing them are added to the eye, the buffering action of the tears is usually adequate to raise the pH and prevent marked discomfort. In some cases pH may vary between 3.5 and 8.5. Some drugs, notably pilocarpine hydrochloride and epinephrine bitartrate, are more acid and overtax the buffer capacity of the lacrimal fluid. Ideally, an ophthalmic solution should have the same pH, as well as the same isotonicity value, as lacrimal fluid. This is not usually possible since, at pH 7.4, many drugs are not appreciably soluble in water. Most alkaloidal salts precipitate as the free alkaloid at this pH. Additionally, many drugs are chemically unstable at pH levels approaching 7.4. This instability is more marked at the high temperatures employed in heat sterilization. For this reason, the buffer system should be selected that is nearest to the physiological pH of 7.4 and does not cause precipitation of the drug or its rapid deterioration.

An ophthalmic preparation with a buffer system approaching the physiological pH can be obtained by mixing a sterile solution of the drug with a sterile buffer solution using aseptic technique. Even so, the possibility of a shorter shelf life at the higher pH must be taken into consideration, and attention must be directed toward the attainment and maintenance of sterility throughout the manipulations.

Many drugs, when buffered to a therapeutically acceptable pH, would not be stable in solution for long periods of time. These products are lyophilized and are intended for reconstitution immediately before use (e.g., *Acetylcholine Chloride for Ophthalmic Solution*).

#### STERILIZATION

The sterility of solutions applied to an injured eye is of the greatest importance. Sterile preparations in special containers for individual use on one patient should be available in every hospital, office, or other installation where accidentally or surgically traumatized eyes are treated. The method of attaining sterility is determined primarily by the character of the particular product (see *Sterilization and Sterility Assurance of Compendial Articles* (1211)).

Whenever possible, sterile membrane filtration under aseptic conditions is the preferred method. If it can be shown that product stability is not adversely affected, sterilization by autoclaving in the final container is also a preferred method.

Buffering certain drugs near the physiological pH range makes them quite unstable at high temperature.

Avoiding the use of heat by employing a bacteria retaining filter is a valuable technique, provided caution is exercised in the selection, assembly, and use of the equipment. Single filtration, presterilized disposable units are available and should be utilized wherever possible.

#### PRESERVATION

Ophthalmic solutions may be packaged in multiple dose containers when intended for the individual use of one patient and where the ocular surfaces are intact. It is mandatory that the immediate containers for ophthalmic solutions be sealed and tamper proof so that sterility is assured at time of first use. Each solution must contain a suitable substance or mixture of substances to prevent the growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use.

Where intended for use in surgical procedures, ophthalmic solutions, although they must be sterile, should not contain antibacterial agents, since they may be irritating to the ocular tissues.

#### THICKENING AGENT

A pharmaceutical grade of methylcellulose (e.g., 1% if the viscosity is 25-centipoises, or 0.25% if 4000-centipoises) or other suitable thickening agents such as hydroxypropyl methylcellulose or polyvinyl alcohol occasionally are added to ophthalmic solutions to increase the viscosity and prolong contact of the drug with the tissue. The thickened ophthalmic solution must be free from visible particles.

### Suspensions

Ophthalmic suspensions are sterile liquid preparations containing solid particles dispersed in a liquid vehicle intended for application to the eye (see *Suspensions*). It is imperative that such suspensions contain the drug in a micronized form to prevent irritation and/or scratching of the cornea. Ophthalmic suspensions should never be dispensed if there is evidence of caking or aggregation.

### Strips

Fluorescein sodium solution should be dispensed in a sterile, single use container or in the form of a sterile, impregnated paper strip. The strip releases a sufficient amount of the drug for diagnostic purposes when touched to the eye being examined for a foreign body or a corneal abrasion. Contact of the paper with the eye may be avoided by leaching the drug from the strip onto the eye with the aid of sterile water or sterile sodium chloride solution.

### PASTES

Pastes are semisolid dosage forms that contain one or more drug substances intended for topical application. One class is made from a single phase aqueous gel (e.g., *Carboxymethylcellulose Sodium Paste*). The other class, the fatty pastes (e.g., *Zinc Oxide Paste*), consists of thick, stiff ointments that do not ordinarily flow at body temperature, and therefore serve as protective coatings over the areas to which they are applied.

The fatty pastes appear less greasy and more absorptive than ointments by reason of a high proportion of drug substance(s) having an affinity for water. These pastes tend to absorb serous secretions, and are less penetrating and less macerating than ointments, so that they are preferred for acute lesions that have a tendency towards crusting, vesiculation, or oozing.

A dental paste is intended for adhesion to the mucous membrane for local effect (e.g., *Triamcinolone Acetonide Dental Paste*). Some paste preparations intended for administration to animals are applied orally. The paste is squeezed into the mouth of the animal, generally at the back of the tongue, or is spread inside the mouth.

## PELLETS

See *Implants*.

## POWDERS

Powders are intimate mixtures of dry, finely divided drugs and/or chemicals that may be intended for internal (Oral Powders) or external (Topical Powders) use. Because of their greater specific surface area, powders disperse and dissolve more readily than compacted dosage forms. Children and those adults who experience difficulty in swallowing tablets or capsules may find powders more acceptable. Drugs that are too bulky to be formed into tablets or capsules of convenient size may be administered as powders. Immediately prior to use, oral powders are mixed in a beverage or apple sauce.

Often, stability problems encountered in liquid dosage forms are avoided in powdered dosage forms. Drugs that are unstable in aqueous suspensions or solutions may be prepared in the form of granules or powders. These are intended to be constituted by the pharmacist by the addition of a specified quantity of water just prior to dispensing. Because these constituted products have limited stability, they are required to have a specified expiration date after constitution and may require storage in a refrigerator.

Oral powders may be dispensed in doses premeasured by the pharmacist, i.e., divided powders, or in bulk. Traditionally, divided powders have been wrapped in materials such as bond paper and parchment. However, the pharmacist may provide greater protection from the environment by sealing individual doses in small cellophane or polyethylene envelopes.

Granules for veterinary use may be administered by sprinkling the dry powder on animal feed or by mixing it with animal food.

Bulk oral powders are limited to relatively nonpotent drugs such as laxatives, antacids, dietary supplements, and certain analgesics that the patient may safely measure by the teaspoonful or capful. Other bulky powders include douche powders, tooth powders, and dusting powders. Bulk powders are best dispensed in tight, wide mouth glass containers to afford maximum protection from the atmosphere and to prevent the loss of volatile constituents.

Dusting powders are impalpable powders intended for topical application. They may be dispensed in sifter top containers to facilitate dusting onto the skin. In general, dusting powders should be passed through at least a 100 mesh sieve to assure freedom from grit that could irritate traumatized areas (see *Powder Fineness* (811)).

## PREMIXES

Premixes are mixtures of one or more drug substances with suitable vehicles. Premixes are intended for admixture to animal feedstuffs before administration. They are used to facilitate dilution of the active drug components with animal feed. Premixes should be as homogeneous as possible. It is essential that materials of suitable fineness be used and that thorough mixing be achieved at all stages of premix preparation. Premixes may be prepared as powder, pellets, or in granulated form. The granulated form is free flowing and free from aggregates.

## SOLUTIONS

Solutions are liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents. Since molecules in solutions are uniformly dispersed, the use of solutions as dosage forms generally provides for the assurance of uniform dosage upon administration, and good accuracy when diluting or otherwise mixing solutions.

Substances in solutions, however, are more susceptible to chemical instability than the solid state and dose for dose, generally require more bulk and weight in packaging relative to sol-

id dosage forms. For all solutions, but particularly those containing volatile solvents, tight containers, stored away from excessive heat, should be used. Consideration should also be given to the use of light resistant containers when photolytic chemical degradation is a potential stability problem. Dosage forms categorized as "Solutions" are classified according to route of administration, such as "Oral Solutions" and "Topical Solutions," or by their solute and solvent systems, such as "Spirits," "Tinctures," and "Waters." Solutions intended for parenteral administration are officially entitled "Injections" (see *Injections* (1)).

## Oral Solutions

Oral Solutions are liquid preparations, intended for oral administration, that contain one or more substances with or without flavoring, sweetening, or coloring agents dissolved in water or cosolvent water mixtures. Oral Solutions may be formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration. It is important to recognize that dilution with water of Oral Solutions containing cosolvents, such as alcohol, could lead to precipitation of some ingredients. Hence, great care must be taken in diluting concentrated solutions when cosolvents are present. Preparations dispensed as soluble solids or soluble mixtures of solids, with the intent of dissolving them in a solvent and administering them orally, are designated "for Oral Solution" (e.g., *Potassium Chloride for Oral Solution*).

Oral Solutions containing high concentrations of sucrose or other sugars traditionally have been designated as Syrups. A near saturated solution of sucrose in purified water, for example, is known as Syrup or "Simple Syrup." Through common usage the term, syrup, also has been used to include any other liquid dosage form prepared in a sweet and viscid vehicle, including oral suspensions.

In addition to sucrose and other sugars, certain polyols such as sorbitol or glycerin may be present in Oral Solutions to inhibit crystallization and to modify solubility, taste, mouth feel, and other vehicle properties. Antimicrobial agents to prevent the growth of bacteria, yeasts, and molds are generally also present. Some sugarless Oral Solutions contain sweetening agents such as sorbitol or aspartame, as well as thickening agents such as the cellulose gums. Such viscid sweetened solutions, containing no sugars, are occasionally prepared as vehicles for administration of drugs to diabetic patients.

Many oral solutions, that contain alcohol as a cosolvent, have been traditionally designated as Elixirs. However, many others designated as Oral Solutions also contain significant amounts of alcohol. Since high concentrations of alcohol can produce a pharmacologic effect when administered orally, other cosolvents, such as glycerin and propylene glycol, should be used to minimize the amount of alcohol required. To be designated as an Elixir, however, the solution must contain alcohol.

## Topical Solutions

Topical Solutions are solutions, usually aqueous but often containing other solvents, such as alcohol and polyols, intended for topical application to the skin, or as in the case of *Lidocaine Oral Topical Solution*, to the oral mucosal surface. The term "lotion" is applied to solutions or suspensions applied topically.

## Otic Solutions

Otic Solutions, intended for instillation in the outer ear, are aqueous, or they are solutions prepared with glycerin or other solvents and dispersing agents (e.g., *Antipyrine and Benzocaine Otic Solution* and *Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution*).

## Ophthalmic Solutions

See *Ophthalmic Preparations*.

## Spirits

Spirits are alcoholic or hydroalcoholic solutions of volatile substances prepared usually by simple solution or by admixture of the ingredients. Some spirits serve as flavoring agents while others have medicinal value. Reduction of the high alcoholic content of spirits by admixture with aqueous preparations often causes turbidity.

Spirits require storage in tight, light resistant containers to prevent loss by evaporation and to limit oxidative changes.

## Tinctures

Tinctures are alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances.

The proportion of drug represented in the different chemical tinctures is not uniform but varies according to the established standards for each. Traditionally, tinctures of potent vegetable drugs essentially represent the activity of 10 g of the drug in each 100 mL of tincture, the potency being adjusted following assay. Most other vegetable tinctures represent 20 g of the respective vegetable material in each 100 mL of tincture.

### PROCESS P

Carefully mix the ground drug or mixture of drugs with a sufficient quantity of the prescribed solvent or solvent mixture to render it evenly and distinctly damp, allow it to stand for 15 minutes, transfer it to a suitable percolator, and pack the drug firmly. Pour on enough of the prescribed solvent or solvent mixture to saturate the drug, cover the top of the percolator, and, when the liquid is about to drip from the percolator, close the lower orifice and allow the drug to macerate for 24 hours or for the time specified in the monograph. If no assay is directed, allow the percolation to proceed slowly, or at the specified rate, gradually adding sufficient solvent or solvent mixture to produce 1000 mL of tincture, and mix (for definitions of flow rates, see under *Extracts and Fluidextracts*). If an assay is directed, collect only 950 mL of percolate, mix this, and assay a portion of it as directed. Dilute the remainder with such quantity of the prescribed solvent or solvent mixture as calculation from the assay indicates is necessary to produce a tincture that conforms to the prescribed standard, and mix.

### PROCESS M

Macerate the drug with 750 mL of the prescribed solvent or solvent mixture in a container that can be closed, and put in a warm place. Agitate it frequently during 3 days or until the soluble matter is dissolved. Transfer the mixture to a filter, and when most of the liquid has drained away, wash the residue on the filter with a sufficient quantity of the prescribed solvent or solvent mixture, combining the filtrates, to produce 1000 mL of tincture, and mix.

Tinctures require storage in tight, light resistant containers, away from direct sunlight and excessive heat.

## Waters, Aromatic

Aromatic waters are clear, saturated aqueous solutions (unless otherwise specified) of volatile oils or other aromatic or volatile substances. Their odors and tastes are similar, respectively, to those of the drugs or volatile substances from which they are prepared, and they are free from empyreumatic and other for-

eign odors. Aromatic waters may be prepared by distillation or solution of the aromatic substance, with or without the use of a dispersing agent.

Aromatic waters require protection from intense light and excessive heat.

## SUPPOSITORIES

Suppositories are solid bodies of various weights and shapes, adapted for introduction into the rectal, vaginal, or urethral orifice of the human body. They usually melt, soften, or dissolve at body temperature. A suppository may act as a protectant or palliative to the local tissues at the point of introduction or as a carrier of therapeutic agents for systemic or local action. Suppository bases usually employed are cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol.

The suppository base employed has a marked influence on the release of the active ingredient incorporated in it. While cocoa butter melts quickly at body temperature, it is immiscible with body fluids and this inhibits the diffusion of fat soluble drugs to the affected sites. Polyethylene glycol is a suitable base for some antiseptics. In cases where systemic action is expected, it is preferable to incorporate the ionized rather than the non-ionized form of the drug, in order to maximize bioavailability. Although nonionized drugs partition more readily out of water-miscible bases such as glycerinated gelatin and polyethylene glycol, the bases themselves tend to dissolve very slowly and thus retard release in this manner. Oleaginous vehicles such as cocoa butter are seldom used in vaginal preparations because of the nonabsorbable residue formed, while glycerinated gelatin is seldom used rectally because of its slow dissolution. Cocoa butter and its substitutes (Hard Fat) are superior for allaying irritation, as in preparations intended for treating internal hemorrhoids.

## Cocoa Butter Suppositories

Suppositories having cocoa butter as the base may be made by means of incorporating the finely divided medicinal substance into the solid oil at room temperature and suitably shaping the resulting mass, or by working with the oil in the melted state and allowing the resulting suspension to cool in molds. A suitable quantity of hardening agents may be added to counteract the tendency of some medicaments such as chloral hydrate and phenol to soften the base. It is important that the finished suppository melt at body temperature.

The approximate weights of suppositories prepared with cocoa butter are given below. Suppositories prepared from other bases vary in weight and generally are heavier than the weights indicated here.

*Rectal Suppositories* for adults are tapered at one or both ends and usually weigh about 2 g each.

*Vaginal Suppositories* are usually globular or oviform and weigh about 5 g each. They are made from water soluble or water-miscible vehicles such as polyethylene glycol or glycerinated gelatin.

Suppositories with cocoa butter base require storage in well-closed containers, preferably at a temperature below 30° (controlled room temperature).

## Cocoa Butter Substitutes

Fat type suppository bases can be produced from a variety of vegetable oils, such as coconut or palm kernel, which are modified by esterification, hydrogenation, and fractionation to obtain products of varying composition and melting temperatures (e.g., *Hydrogenated Vegetable Oil* and *Hard Fat*). These products can be so designed as to reduce rancidity. At the same time, desired characteristics such as narrow intervals between melt-

ing and solidification temperatures, and melting ranges to accommodate various formulation and climatic conditions, can be built in.

### Glycerinated Gelatin Suppositories

Medicinal substances may be incorporated into glycerinated gelatin bases by addition of the prescribed quantities to a vehicle consisting of about 70 parts of glycerin, 20 parts of gelatin, and 10 parts of water.

Glycerinated gelatin suppositories require storage in tight containers, preferably at a temperature below 35°.

### Polyethylene Glycol Base Suppositories

Several combinations of polyethylene glycols having melting temperatures that are above body temperature have been used as suppository bases. Inasmuch as release from these bases depends on dissolution rather than on melting, there are significantly fewer problems in preparation and storage than exist with melting type vehicles. However, high concentrations of higher molecular weight polyethylene glycols may lengthen dissolution time, resulting in problems with retention. Labels on polyethylene glycol suppositories should contain directions that they be moistened with water before inserting. Although they can be stored without refrigeration, they should be packaged in tightly closed containers.

### Surfactant Suppository Bases

Several nonionic surface active agents closely related chemically to the polyethylene glycols can be used as suppository vehicles. Examples of such surfactants are polyoxyethylene sorbitan fatty acid esters and the polyoxyethylene stearates. These surfactants are used alone or in combination with other suppository vehicles to yield a wide range of melting temperatures and consistencies. One of the major advantages of such vehicles is their water dispersibility. However, care must be taken with the use of surfactants, because they may either increase the rate of drug absorption or interact with drug molecules, causing a decrease in therapeutic activity.

### Tableted Suppositories or Inserts

Vaginal suppositories occasionally are prepared by the compression of powdered materials into a suitable shape. They are prepared also by encapsulation in soft gelatin.

## SUSPENSIONS

Suspensions are liquid preparations that consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble. Dosage forms officially categorized as "Suspensions" are designated as such if they are not included in other more specific categories of suspensions, such as Oral Suspensions, Topical Suspensions, etc. (see these other categories). Some suspensions are prepared and ready for use, while others are prepared as solid mixtures intended for constitution just before use with an appropriate vehicle. Such products are designated "for Oral Suspension", etc. The term "Milk" is sometimes used for suspensions in aqueous vehicles intended for oral administration (e.g., *Milk of Magnesia*). The term "Magma" is often used to describe suspensions of inorganic solids such as clays in water, where there is a tendency for strong hydration and aggregation of the solid, giving rise to gel like consistency and thixotropic rheological behavior (e.g., *Bentonite Magma*). The term "Lotion" has been used to categorize many topical suspensions and emulsions intended for application to the skin (e.g., *Calamine Lotion*). Some suspensions are prepared in sterile form and are used as Injectables, as well as for ophthalmic and

otic administration. These may be of two types, ready to use or intended for constitution with a prescribed amount of Water for Injection or other suitable diluent before use by the designated route. Suspensions should not be injected intravenously or intrathecally.

Suspensions intended for any route of administration should contain suitable antimicrobial agents to protect against bacteria, yeast, and mold contamination (see *Emulsions* for some consideration of antimicrobial preservative properties that apply also to Suspensions). By its very nature, the particular matter in a suspension may settle or sediment to the bottom of the container upon standing. Such sedimentation may also lead to caking and solidification of the sediment with a resulting difficulty in redispersing the suspension upon agitation. To prevent such problems, suitable ingredients that increase viscosity and the gel state of the suspension, such as clays, surfactants, polyols, polymers, or sugars, should be added. It is important that suspensions always be shaken well before use to ensure uniform distribution of the solid in the vehicle, thereby ensuring uniform and proper dosage. Suspensions require storage in tight containers.

### Oral Suspensions

Oral Suspensions are liquid preparations containing solid particles dispersed in a liquid vehicle, with suitable flavoring agents, intended for oral administration. Some suspensions labeled as "Milks" or "Magmas" fall into this category.

### Topical Suspensions

Topical Suspensions are liquid preparations containing solid particles dispersed in a liquid vehicle, intended for application to the skin. Some suspensions labeled as "Lotions" fall into this category.

### Otic Suspensions

Otic Suspensions are liquid preparations containing micronized particles intended for instillation in the outer ear.

### Ophthalmic Suspensions

See *Ophthalmic Preparations*.

## SYRUPS

See *Oral Solutions*.

## SYSTEMS

In recent years, a number of dosage forms have been developed using modern technology that allows for the uniform release or targeting of drugs to the body. These products are commonly called delivery systems. The most widely used of these are Transdermal Systems.

### Transdermal Systems

Transdermal drug delivery systems are self contained, discrete dosage forms that, when applied to intact skin, are designed to deliver the drug(s) through the skin to the systemic circulation. Systems typically comprise an outer covering (barrier), a drug reservoir, which may have a rate controlling membrane, a contact adhesive applied to some or all parts of the system and the system/skin interface, and a protective liner that is removed before applying the system. The activity of

these systems is defined in terms of the release rate of the drug(s) from the system. The total duration of drug release from the system and the system surface area may also be stated.

Transdermal drug delivery systems work by diffusion: the drug diffuses from the drug reservoir, directly or through the rate-controlling membrane and/or contact adhesive if present, and then through the skin into the general circulation. Typically, modified release systems are designed to provide drug delivery at a constant rate, such that a true steady-state blood concentration is achieved and maintained until the system is removed. At that time, blood concentration declines at a rate consistent with the pharmacokinetics of the drug.

Transdermal drug delivery systems are applied to body areas consistent with the labeling for the product(s). As long as drug concentration at the system/skin interface remains constant, the amount of drug in the dosage form does not influence plasma concentrations. The functional lifetime of the system is defined by the initial amount of drug in the reservoir and the release rate from the reservoir.

**NOTE**—Drugs for local rather than systemic effect are commonly applied to the skin embedded in glue on a cloth or plastic backing. These products are defined traditionally as plasters or tapes.

### Ocular System

Another type of system is the ocular system, which is intended for placement in the lower conjunctival fornix from which the drug diffuses through a membrane at a constant rate (e.g., *Pilocarpine Ocular System*).

### Intrauterine System

An intrauterine system, based on a similar principle but intended for release of drug over a much longer period of time, e.g., one year, is also available (e.g., *Progesterone Intrauterine Contraceptive System*).

## TABLETS

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets.

The vast majority of all tablets manufactured are made by compression, and compressed tablets are the most widely used dosage form in this country. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granulations. Tablets can be produced in a wide variety of sizes, shapes, and surface markings, depending upon the design of the punches and dies. Capsule-shaped tablets are commonly referred to as caplets. Boluses are large tablets intended for veterinary use, usually for large animals.

Molded tablets are prepared by forcing dampened powders under low pressure into die cavities. Solidification depends upon crystal bridges built up during the subsequent drying process, and not upon the compaction force.

Tablet triturates are small, usually cylindrical, molded or compressed tablets. Tablet triturates were traditionally used as dispensing tablets in order to provide a convenient, measured quantity of a potent drug for compounding purposes. Such tablets are rarely used today. Hypodermic tablets are molded tablets made from completely and readily water-soluble in-

gredients and formerly were intended for use in making preparations for hypodermic injection. They are employed orally, or where rapid drug availability is required such as in the case of *Nitroglycerin Tablets*, sublingually.

Buccal tablets are intended to be inserted in the buccal pouch, and sublingual tablets are intended to be inserted beneath the tongue, where the active ingredient is absorbed directly through the oral mucosa. Few drugs are readily absorbed in this way, but for those that are (such as nitroglycerin and certain steroid hormones), a number of advantages may result.

Soluble, effervescent tablets are prepared by compression and contain, in addition to active ingredients, mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water. They are intended to be dissolved or dispersed in water before administration. Effervescent tablets should be stored in tightly closed containers or moisture-proof packs and labeled to indicate that they are not to be swallowed directly.

### Chewable Tablets

Chewable tablets are formulated and manufactured so that they may be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste. These tablets have been used in tablet formulations for children, especially multivitamin formulations, and for the administration of antacids and selected antibiotics. Chewable tablets are prepared by compression, usually utilizing mannitol, sorbitol, or sucrose as binders and fillers, and containing colors and flavors to enhance their appearance and taste.

### Preparation of Molded Tablets

Molded tablets are prepared from mixtures of medicinal substances and a diluent usually consisting of lactose and powdered sucrose in varying proportions. The powders are dampened with solutions containing high percentages of alcohol. The concentration of alcohol depends upon the solubility of the active ingredients and fillers in the solvent system and the desired degree of hardness of the finished tablets. The dampened powders are pressed into molds, removed, and allowed to dry. Molded tablets are quite friable and care must be taken in packaging and dispensing.

### Formulation of Compressed Tablets

Most compressed tablets consist of the active ingredient and a diluent (filler), binder, disintegrating agent, and lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide), flavors, and sweetening agents may also be present. Diluents are added where the quantity of active ingredient is small or difficult to compress. Common tablet fillers include lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose. Chewable tablets often contain sucrose, mannitol, or sorbitol as a filler. Where the amount of active ingredient is small, the overall tableting properties are in large measure determined by the filler. Because of problems encountered with bioavailability of hydrophobic drugs of low water solubility, water-soluble diluents are used as fillers for these tablets.

Binders give adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They add to the cohesive strength already available in the diluent. While binders may be added dry, they are more effective when added out of solution. Common binders include acacia, gelatin, sucrose, povidone, methylcellulose, carboxymethylcellulose, and hydrolyzed starch pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression.

A disintegrating agent serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegrating agent is starch. Chemically modified starches and cellulose, alginic acid, microcrystalline cellulose, and cross-linked povidone, are also used for this purpose. Effervescent mixtures are used in soluble tablet systems as disintegrating agents. The concentration of the disintegrating agent, method of addition, and degree of compaction play a role in effectiveness.

Lubricants reduce friction during the compression and ejection cycle. In addition, they aid in preventing adherence of tablet material to the dies and punches. Metallic stearates, stearic acid, hydrogenated vegetable oils, and talc are used as lubricants. Because of the nature of this function, most lubricants are hydrophobic, and as such tend to reduce the rates of tablet disintegration and dissolution. Consequently, excessive concentrations of lubricant should be avoided. Polyethylene glycols and some lauryl sulfate salts have been used as soluble lubricants, but such agents generally do not possess optimal lubricating properties, and comparatively high concentrations are usually required.

Glidants are agents that improve powder fluidity, and they are commonly employed in direct compression where no granulation step is involved. The most effective glidants are the colloidal pyrogenic silicas.

Colorants are often added to tablet formulations for esthetic value or for product identification. Both D&C and FD&C dyes and lakes are used. Most dyes are photosensitive and they fade when exposed to light. The Federal Food and Drug Administration regulates the colorants employed in drugs.

## Manufacturing Methods

Tablets are prepared by three general methods: wet granulation, dry granulation (roll compaction or slugging), and direct compression. The purpose of both wet and dry granulation is to improve flow of the mixture and/or to enhance its compressibility.

Dry granulation (slugging) involves the compaction of powders at high pressures into large, often poorly formed tablet compacts. These compacts are then milled and screened to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of both heat and moisture in the processing. Dry granulations can be produced also by extruding powders between hydraulically operated rollers to produce thin cakes which are subsequently screened or milled to give the desired granule size.

Excipients are available that allow production of tablets at high speeds without prior granulation steps. These directly compressible excipients consist of special physical forms of substances such as lactose, sucrose, dextrose, or cellulose, which possess the desirable properties of fluidity and compressibility. The most widely used direct compaction fillers are microcrystalline cellulose, anhydrous lactose, spray dried lactose, compressible sucrose, and some forms of modified starches. Direct compression avoids many of the problems associated with wet and dry granulations. However, the inherent physical properties of the individual filler materials are highly critical, and minor variations can alter flow and compression characteristics so as to make them unsuitable for direct compression.

Physical evidence of poor tablet quality is discussed under *Stability Considerations in Dispensing Practice* (1191).

### WEIGHT VARIATION AND CONTENT UNIFORMITY

Tablets are required to meet a weight variation test (see *Uniformity of Dosage Units* (905)) where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. Weight variation is not an adequate indication of content uniformity where the drug substance comprises a relatively minor portion of the tablet, or where the tablet is sugar coated. Thus, the Pharmacopeia generally requires that coated tablets and tablets containing 50 mg or less of active ingredient, comprising less than 50% by weight of the dosage form unit, pass a content uniformity test (see *Uniformity of Dosage Units* (905)), wherein individual tablets are assayed for actual drug content.

### DISINTEGRATION AND DISSOLUTION

Disintegration is an essential attribute of tablets intended for administration by mouth, except for those intended to be chewed before being swallowed and for some types of extended release tablets. A disintegration test is provided (see *Disintegration* (701)), and limits on the times in which disintegration is to take place, appropriate for the types of tablets concerned, are given in the individual monographs.

For drugs of limited water solubility, dissolution may be a more meaningful quality attribute than disintegration. A dissolution test (see *Dissolution* (711)) is required in a number of monographs on tablets. In many cases, it is possible to correlate dissolution rates with biological availability of the active ingredient. However, such tests are useful mainly as a means of screening preliminary formulations and as a routine quality control procedure.

## Coatings

Tablets may be coated for a variety of reasons, including protection of the ingredients from air, moisture, or light, masking of unpleasant tastes and odors, improvement of appearance, and control of the site of drug release in the gastrointestinal tract.

### PLAIN COATED TABLETS

Classically, tablets have been coated with sugar applied from aqueous suspensions containing insoluble powders such as starch, calcium carbonate, talc, or titanium dioxide, suspended by means of acacia or gelatin. For purposes of identification and esthetic value, the outside coatings may be colored. The finished coated tablets are polished by application of dilute solutions of wax in solvents such as chloroform or powdered mix. Water protective coatings consisting of substances such as shellac or cellulose acetate phthalate are often applied out of nonaqueous solvents prior to application of sugar coats. Excessive quantities should be avoided. Drawbacks of sugar coating include the lengthy time necessary for application, the need for waterproofing, which also adversely affects dissolution, and the increased bulk of the finished tablet. These factors have resulted in increased acceptance of film coatings. Film coatings consist of water soluble or dispersible materials such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, and mixtures of cellulose acetate phthalate and polyethylene glycols applied out of nonaqueous or aqueous solvents. Evaporation of the solvents leaves a thin film that adheres directly to the tablet and allows it to retain the original shape, including grooves or identification codes.

~~DELAYED-RELEASE TABLETS~~

~~Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach. The term "delayed release" is used for Pharmacopeial purposes, and the individual monographs include tests and specifications for *Drug release* (see *Drug Release* (724)) or *Disintegration* (see *Disintegration* (701)).~~

~~EXTENDED-RELEASE TABLETS~~

~~Extended-release tablets are formulated in such manner as to make the contained medicament available over an extended period of time following ingestion. Expressions such as "prolonged action," "repeat action," and "sustained release" have also been used to describe such dosage forms. However, the term "extended release" is used for Pharmacopeial purposes, and requirements for *Drug release* typically are specified in the individual monographs.~~

**GENERAL CONSIDERATIONS**

This chapter provides general descriptions of and definitions for drug products, or dosage forms, commonly used to administer the drug substance [active pharmaceutical ingredient (API)]. It discusses general principles involved in the manufacture or compounding of these dosage forms, and recommendations for proper use and storage. A glossary is provided as a resource on nomenclature.

A dosage form is a combination of drug substances and excipients to facilitate dosing, administration, and delivery of the medicine to the patient. The design and testing of all dosage forms target drug product quality.<sup>1</sup>

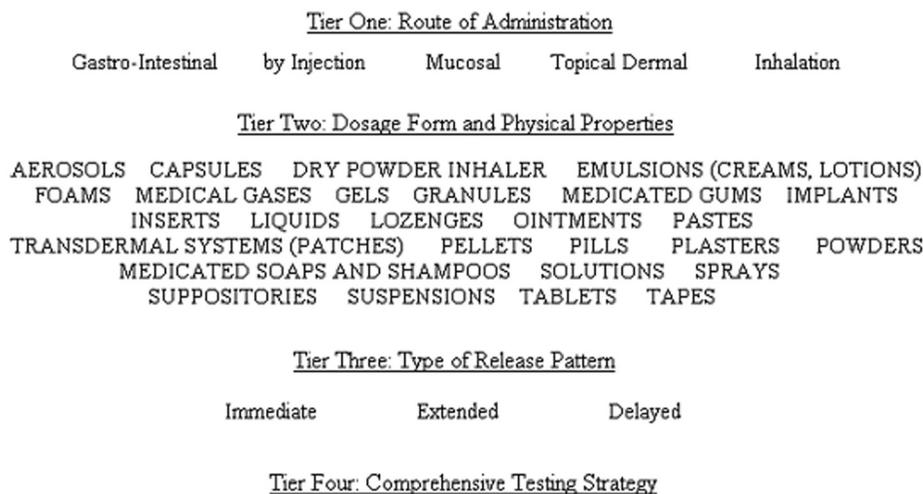
A testing protocol must consider not only the physical, chemical, and biological properties of the dosage form as appropriate but also the administration route and desired dosing regimen. The interrelationships of dosage forms and routes of administration have been summarized in the compendial taxonomy for pharmaceutical dosage forms (*Figure 1*).<sup>2</sup> The organization of this general information chapter is by the physical attributes of each particular dosage form (*Tier Two*), generally without specific reference to route of administration. Information specific to route of administration is given when needed.

Tests to ensure compliance with pharmacopeial standards for dosage form performance fall into one of the following areas.

<sup>1</sup> In the United States, a drug with a name recognized in *USP–NF* must comply with compendial identity standards or be deemed adulterated, misbranded, or both. To avoid being deemed adulterated, such drugs also must comply with compendial standards for strength, quality, or purity, unless labeled to show all respects in which the drug differs. See the Federal Food, Drug, and Cosmetic Act (FDCA), Sections 501(b) and 502(e)(3)(b), and Food and Drug Administration (FDA) regulations at 21 CFR 299.5. In addition, to avoid being deemed misbranded, drugs recognized in *USP–NF* also must comply with compendial standards for packing and labeling, FDCA Section 502(g). "Quality" is used herein as suitable shorthand for all such compendial requirements. This approach also is consistent with U.S. and FDA participation in the International Conference on Harmonization (ICH). The ICH guideline on specifications, Q6A, notes that "specifications are chosen to confirm the quality of the drug substance and drug product. . ." and defines "quality" as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as identity, strength, and purity."

<sup>2</sup> Marshall K, Foster TS, Carlin HS, Williams RL. Development of a compendial taxonomy and glossary for pharmaceutical dosage forms. *Pharm Forum*. 2003;29(5):1742–1752.

**Figure 1. Compendial Taxonomy for Pharmaceutical Dosage Forms**



**Dose Uniformity** (see also *Uniformity of Dosage Units* (905))—Consistency in dosing for a patient or consumer requires that the variation in the drug substance content of each dosage unit be accurately controlled throughout the manufactured batch or compounded lot of drug product. Uniformity of dosage units typically is demonstrated by one of two procedures: content uniformity or weight variation. The procedure for content uniformity requires the assay of drug substance content of individual units, and that for weight variation uses the weight of the individual units to estimate their content. Weight variation may be used where the underlying distribution of drug substance in the blend is presumed to be uniform and well-controlled, as in solutions. In such cases the content of drug substance may be adequately estimated by the net weight. Content uniformity does not rely on the assumption of blend uniformity and can be applied in all cases. Tablets and capsules are assigned a limit below which the weight variation procedure is not applicable. Successful development and manufacture of dosage

forms requires careful evaluation of drug substance particle or droplet size, incorporation techniques, and excipient properties.

**Stability** (see also *Pharmaceutical Stability* (1150))—Drug product stability involves the evaluation of chemical stability, physical stability, and performance over time. The chemical stability of the drug substance in the dose form matrix must support the expiration dating for the commercially prepared dosage forms and a beyond-use date for a compounded dosage form. Test procedures for potency must be stability indicating (see *Validation of Compendial Procedures* (1225)). Degradation products should be quantified. In the case of dispersed or emulsified systems, consideration must be given to the potential for settling or separation of the formulation components. Any physical changes to the dosage form must be easily reversed (e.g., by shaking) prior to dosing or administration. In vitro release test procedures such as dissolution and disintegration provide a measure of continuing consistency in performance over time (see *Dissolution* (711), *Disintegration* (701), and *Drug Release* (724)).

**Bioavailability** (see also *In Vitro and In Vivo Evaluation of Dosage Forms* <1088>, and *Assessment of Drug Product Performance—Bioavailability, Bioequivalence, and Dissolution* <1090>)—Bioavailability is influenced by factors such as the method of manufacture or compounding, particle size, crystal form (polymorph) of the drug substance, the properties of the excipients used to formulate the dosage form, and physical changes as the drug product ages. Assurance of consistency in bioavailability over time (bioequivalence) requires close attention to all aspects of the production (or compounding) and testing of the dosage form. In vitro release (disintegration and dissolution) testing is commonly used as a surrogate to demonstrate consistent availability of the API from the formulated dosage.

**Manufacture**—Although detailed instructions about the manufacture of any of these dosage forms are beyond the scope of this general information chapter, general manufacturing principles have been included, as well as suggested testing for proper use and storage. Further information relative to extemporaneous compounding of dosage forms can be found in *Pharmaceutical Compounding—Nonsterile Preparations* <795> and *Pharmaceutical Compounding—Sterile Preparations* <797>.

**Route of Administration**—The primary routes of administration for pharmaceutical dosage forms can be defined as mucosal, oral, parenteral (by injection), inhalation, and topical/dermal, and each has subcategories as needed. Many tests employed to ensure quality generally are applied across all of the administration routes, but some tests are specific for individual routes. For example, products intended for injection must be evaluated for *Sterility* <71> and *Pyrogen Test* <151>, and the manufacturing process (and sterilization technique) employed for parenterals (by injection) should ensure compliance with these tests. Tests for particulate matter may be required for solution dosage forms depending on the

route of administration (e.g., by injection—*Particulate Matter in Injections* <788>, or mucosal—*Particulate Matter in Ophthalmic Solutions* <789>). Additionally, dosage forms intended for the inhalation route of administration must be monitored for particle size and spray pattern (for a metered-dose inhaler or dry-powder inhaler) and drop-let size (for nasal sprays). Further information regarding administration routes and suggested testing can be found in the *Guide to General Chapters, Charts 4–8 and 10–13*.

An appropriate manufacturing process and testing regimen help ensure that a dosage form can meet the appropriate quality attributes for the intended route of administration.

### PRODUCT QUALITY TESTS, GENERAL

ICH Guidance Q6A (available at [www.ich.org](http://www.ich.org)) recommends specifications (list of tests, references to analytical procedures, and acceptance criteria) to ensure that commercialized drug products are safe and effective at the time of release and over their shelf life. Tests that are universally applied to ensure safety and efficacy (and strength, quality, and purity) include description, identification, assay, and impurities.

**Description**—According to the ICH guidance a qualitative description (size, shape, color, etc.) of the dosage form should be provided. The acceptance criteria should include the final acceptable appearance. If any of these characteristics change during manufacturing or storage, a quantitative procedure may be appropriate. It specifies the content or the label claim of the article. This parameter is not part of the USP dosage form monograph because it is product specific. USP monographs define the product by specifying the range of acceptable assayed content of the active substance(s) present in the dosage form, together with any additional information about the presence or absence of other components, excipients, or adjuvants.

**Identification**—Identification tests are discussed in the *General Notices and Requirements*. Identification tests should establish the identity of the drug or drugs present in the drug product and should discriminate between compounds of closely related structure that are likely to be present. Identification tests should be specific for the drug substances. The most conclusive test for identity is the infrared absorption spectrum (see *Spectrophotometry and Light-Scattering* (851) and *Spectrophotometric Identification Tests* (197)). If no suitable infrared spectrum can be obtained, other analytical methods can be used. Near-infrared (NIR) or Raman spectrophotometric methods also could be acceptable as the sole identification method of the drug product formulation (see *Near-infrared Spectrophotometry* (1119) and *Raman Spectroscopy* (1120)). Identification by a chromatographic retention time from a single procedure is not regarded as specific. The use of retention times from two chromatographic procedures for which the separation is based on different principles or a combination of tests in a single procedure can be acceptable (see *Chromatography* (621) and *Thin-Layer Chromatographic Identification Test* (201)).

**Assay**—A specific and stability-indicating test should be used to determine the strength (API content) of the drug product. Some examples of these procedures are *Antibiotics—Microbial Assays* (81), *Chromatography* (621), or *Assay for Steroids* (351). In cases when the use of a nonspecific assay is justified, e.g., *Titrimetry* (541), other supporting analytical procedures should be used to achieve specificity. When evidence of excipient interference with a nonspecific assay exists, a procedure with demonstrated specificity should be used.

**Impurities**—Process impurities, synthetic by-products, and other inorganic and organic impurities may be present in the API and excipients used in the manufacture of the drug product. These impurities are

evaluated by tests in API and excipients monographs. Impurities arising from degradation of the drug substance or from the drug-product manufacturing process should be monitored. *Residual Solvents* (467) is applied to all products where relevant.

In addition to the universal tests listed above, the following tests may be considered on a case-by-case basis.

**Physicochemical Properties**—Examples include *pH* (791), *Viscosity* (911), and *Specific Gravity* (841).

**Particle Size**—For some dosage forms, particle size can have a significant effect on dissolution rates, bioavailability, therapeutic outcome, and stability. Procedures such as *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* (601), and *Particle Size Distribution Estimation by Analytical Sieving* (786) could be used.

**Uniformity of Dosage Units**—See discussion of dose uniformity above.

**Water Content**—A test for water content is included when appropriate (see *Water Determination* (921)).

**Microbial Limits**—The type of microbial test(s) and acceptance criteria are based on the nature of the drug substance, method of manufacture, and the route of administration (see *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* (61) and *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* (62)).

**Antimicrobial Preservative Content**—Acceptance criteria for preservative content in multidose products should be established. They are based on the levels of antimicrobial preservative necessary to maintain the product's microbiological quality at all stages throughout its proposed usage and shelf life (see *Antimicrobial Effectiveness Testing* (51)).

**Antioxidant Preservative Content**—If antioxidant preservatives are present in the drug product, tests of their content should be performed.

**Sterility**—Depending on the route of administration—e.g., ophthalmic preparations, implants, and solutions for injection—sterility of the product is demonstrated as appropriate (see *Sterility Tests* ⟨71⟩).

**Dissolution**—A test to measure release of the drug substance(s) from the drug product normally is included for dosage forms such as tablets, capsules, suspensions, granules for suspensions, implants, transdermal delivery systems, and medicated chewing gums. Single-point measurements typically are used for immediate-release dosage forms. For modified-release dosage forms, appropriate test conditions and sampling procedures are established as needed (see *Dissolution* ⟨711⟩ and *Drug Release* ⟨724⟩). In some cases, dissolution testing may be replaced by disintegration testing (see *Disintegration* ⟨701⟩).

**Hardness and Friability**—These parameters are evaluated as in-process controls. Acceptance criteria depend on packaging, supply chain, and intended use (see *Tablet Friability* ⟨1216⟩ and *Tablet Breaking Force* ⟨1217⟩).

**Extractables**—When evidence exists that extractables from the container-closure systems (e.g., rubber stopper, cap liner, or plastic bottle) have an impact on the safety or efficacy of the drug product, a test is included to evaluate the presence of extractables and leachables.

Depending on the type and composition of the dosage form, other tests such as alcohol content, redispersibility, particle size distribution, rheological properties, reconstitution time, endotoxins/pyrogens, particulate matter, functionality testing of delivery systems, and osmolarity may be necessary.

## DOSAGE FORMS

### Aerosols

Aerosols are preparations packaged under pressure and contain therapeutic agent(s) and a propellant that are released upon activation of an appropriate valve system. Upon activation of the valve system, the drug substance is released as a plume of fine particles or droplets. Only one dose is released from the preparation upon activation of a metered valve. In the case of topical products, activation of the valve results in a continuous release of the formulation.

In this chapter, the aerosol dosage form refers only to those products packaged under pressure that release a fine mist of particles or droplets when activated (see *Glossary*). Other products that produce dispersions of fine droplets or particles will be covered in subsequent sections (e.g., *Dry Powder Inhalers* and *Sprays*).

#### TYPICAL COMPONENTS

Typical components of aerosols are the formulation containing one or more drug substances and propellant, the container, the valve, and the actuator. Each component plays a role in determining various characteristics of the emitted plume, such as droplet or particle size distribution, uniformity of delivery of the therapeutic agent, delivery rate, and plume velocity and geometry. The metering valve and actuator act in tandem to generate the plume of droplets or particles. The metering valve allows measure of an accurate volume of the liquid formulation under pressure within the container. The activator directs the metered volume to a small orifice that is open to the atmosphere. Upon activation, the formulation is forced through the opening, forming the fine mist of particles that are directed to the site of administration.

Aerosol preparations may consist of either a two-phase (gas and liquid) or a three-phase (gas, liquid, and solid or liquid) formulation. The two-phase formulation consists of drug(s) dissolved in liquefied propellant. Liquid co-solvents, such as alcohol, propylene glycol, and polyethylene glycols often are added to enhance the solubility of the drug substance(s). Three phase inhalation and nasal aerosol systems consist of a suspension or emulsion of the drug substance(s) [i.e., API(s)] in addition to the vaporizable propellants. The suspension or emulsion of the finely divided drug substance typically is dispersed in the liquid propellant with the aid of suitable biocompatible surfactants or other excipients.

Propellants for aerosol formulations are typically low molecular weight hydrofluorocarbons or hydrocarbons that are liquid when constrained in the container, exhibit a suitable vapor pressure at room temperature, and are biocompatible and nonirritating. Compressed gases do not supply a constant pressure over use and typically are not employed as propellants.

Metal containers can withstand the vapor pressure produced by the propellant and reduce the opportunity that leachable components will enter the formulation. Excess formulation may be added to the container to ensure that the full number of labeled doses can be accurately administered. The container and closure must be able to withstand the pressures anticipated under normal use conditions as well as when the system is exposed to elevated temperatures.

#### TYPES OF AEROSOL DOSAGE FORMS

Aerosol dosage forms can be delivered via various routes. The design of the container and metering valve, as well as the formulation, are designed to target the site of administration.

*Inhalation aerosols* are intended to produce fine particles or droplets for inhalation through the mouth and deposition in the pulmonary tree. The design of the delivery system releases one dose with each actuation. These products are commonly known as metered-dose inhalers.

*Nasal aerosols* produce fine particles or droplets for inhalation through the nasal vestibule and deposition in the nasal cavity. One dose is released with each activation of the valve.

*Lingual aerosols* are intended to produce fine particles or droplets for deposition in the mouth. The design of the delivery system releases one dose with each actuation.

*Topical aerosols* produce fine particles or droplets for application to the skin. Formulations that are intended for inhalation, nasal, or lingual administration are typically aqueous based, but topical aerosols may utilize nonaqueous solvents to achieve rapid drying or disinfectant action for abraded skin surfaces.

#### PACKAGING

The accuracy of a system's delivered dose is demonstrated at the range of pressures likely to be encountered as a result of ambient temperature variations or storage in a refrigerator. As an alternative, the system should include clear instructions for use to ensure the container and contents have been equilibrated to room temperature prior to use.

#### LABELING FOR PROPER USE

Typical warning statements include:

- Contents under pressure. Do not puncture or incinerate container.
- Do not expose to heat or store at temperatures above 49°.

- Keep out of the reach of children unless otherwise prescribed.
- Use only as directed; intentional misuse by deliberate concentration and inhaling of the contents can be harmful or fatal.

Many experts recommend the addition of a statement indicating that patients and/or consumers should seek advice and instruction from a health care professional about the proper use of the device.

### Capsules

Capsules are solid dosage forms in which the API and excipients are enclosed within a soluble container or shell. The shells may be composed of two pieces, a body and a cap, or they may be composed of a single piece. Two-piece capsules are commonly referred to as hard-shell capsules, and one-piece capsules are often referred to as soft-shell capsules. This distinction, although it is imprecise, reflects differing levels of plasticizers in the two compositions and the fact that one-piece capsules typically are more pliable than two-piece capsules.

The shells of capsules usually are made from gelatin. However, they also may be made from cellulose polymers or other suitable material. Most capsules are designed for oral administration.

**Two-Piece or Hard-Shell Capsules**—Two-piece capsules consist of two telescoping cap and body pieces in a range of standard sizes.

**One-Piece or Soft-Shell Capsules**—One-piece capsules typically are used to deliver an API as a solution or suspension. Liquid formulations placed into one-piece capsules may offer advantages by comparison with dry-filled capsules and tablets in achieving content uniformity of potent APIs or acceptable dissolution of APIs with poor aqueous solubility. Because the contact between the shell wall and its liquid contents is more intimate than

in dry-filled capsules, undesired interactions may be more likely to occur (including gelatin crosslinking and pellicle formation).

**Modified-Release Capsules**—The release of APIs from capsules can be modified in several ways, including coating the filled capsule shells or the contents in the case of dry-filled capsules.

**Delayed-Release Capsules**—Capsules sometimes are formulated to include enteric-coated granules to protect acid-labile APIs from the gastric environment or to prevent adverse events such as irritation. Enteric-coated multiparticulate capsule dosage forms may reduce variability in bioavailability associated with gastric emptying times for larger particles (i.e., tablets) and to minimize the likelihood of a therapeutic failure when coating defects occur during manufacturing.

### PREPARATION

**Two-Piece Capsules**—Two-piece gelatin capsules usually are formed from blends of gelatins that have relatively high gel strength in order to optimize shell clarity and toughness or from hypromellose. They also may contain colorants such as D&C and FD&C dyes<sup>3</sup> or various iron oxides, opaquing agents such as titanium dioxide, dispersing agents, and preservatives. Gelatin capsule shells normally contain between 12% and 16% water.

<sup>3</sup> In 1960 Congress enacted the Color Additive Amendments, requiring FDA to regulate dyes, pigments, or other coloring agents in foods, drugs, and cosmetics separately from food additives. Under the law, color additives are deemed unsafe unless they are used in compliance with FDA regulations. The law provides a framework for the listing and certification of color additives. See FDCA section 721; see FDA regulations at 21 CFR Part 70. Colors must also be listed in pertinent FDA regulations for specific uses; the list of color additives for drugs that are exempt from certification is published at 21 CFR Part 73, Subpart B. FDA also conducts a certification program for batches of color additives that are required to be certified before sale; see 21 CFR Part 74 (Subpart B re: drugs). Regulations regarding certification procedures, general specifications, and the listing of certified provisionally listed colors, are at 21 CFR Part 80. FDA maintains a color additives website, with links to various legal and regulatory resources, at: <http://www.cfsan.fda.gov/~dms/col-toc.html>

The shells are manufactured in one set of operations and later filled in a separate manufacturing process. Two-piece shell capsules are made by a process that involves dipping shaped pins into gelatin or hypromellose solutions, followed by drying, cutting, and joining steps.

Powder formulations for two-piece gelatin capsules generally consist of the API and at least one excipient. Both the formulation and the method of filling can affect release of the API. In the filling operation, the body and cap of the shell are separated before filling. Following the filling operation, the machinery rejoins the body and cap and ensures satisfactory closure of the capsule by exerting appropriate force on the two pieces. The joined capsules can be sealed after filling by a band at the joint of the body and cap or by other suitable means. In compounding prescription practice, two-piece capsules may be hand-filled. This permits the prescriber the choice of selecting either a single API or a combination of APIs at the exact dose level considered best for an individual patient.

**One-Piece Capsules**—One-piece shell capsules are formed, filled, and sealed in a single process on the same machine and are available in a wide variety of sizes, shapes, and colors. The most common type of one-piece capsule is that produced by a rotary die process that results in a capsule with a seam. The soft gelatin shell is somewhat thicker than that of two-piece capsules and is plasticized by the addition of polyols such as glycerin, sorbitol, or other suitable material. The ratio of the plasticizer to the gelatin can be varied to change the flexibility of the shell depending on the nature of the fill material, its intended usage, or environmental conditions.

In most cases, one-piece capsules are filled with liquids. Typically, APIs are dissolved or suspended in a liquid vehicle. Classically, an oleaginous vehicle such as a vegetable oil was used. However, nonaqueous, water-miscible liquid vehicles such as the lower molecular weight poly-

ethylene glycols now are more common. The physicochemical properties of the vehicle can be chosen to ensure stability of the API as well as to influence the release profile from the capsule shell.

### Dry Powder Inhalers

The dry powder inhaler (DPI) consists of a mixture of drug(s) and carrier, and all components exist in a finely divided solid state packaged as a unit dose. The dose is released from the packaging by an appropriate mechanism and is mobilized into a fine mist only upon oral inhalation by the patient.

#### TYPICAL COMPONENTS

The basic components of the DPI are the formulation consisting of the drug(s) and carrier, both in the dry state; packaging that contains an amount equivalent to a unit dose; and a mechanism designed to open the unit-dose container and permit mobilization of the powders by the patient inhaling through the built-in mouthpiece. Typically, the unit-dose container is either a capsule made of gelatin or other suitable non-animal-derived material (e.g., hypromellose or starch), or the container may consist of a series of unit doses in foil-lined blisters arranged in a strip. When the drug is contained in a capsule, release of the medication takes place when the capsule is pierced. As a consequence of this release mechanism, the device is designed to minimize the generation of capsule fragments that might subsequently be inhaled. When the drug is contained in a blister pack, the mechanism is designed to advance an unused blister to a platform where the foil lining can be peeled back to expose the powder mixture to an air stream created when the patient inhales. To facilitate dosing compliance, some delivery devices incorporate dosing administration information such as number of doses remaining.

## PACKAGING

For drug contained in blister-pack strips, the packs must be designed to allow individual blister cavities to be opened without compromising the seal of adjacent cavities. Package components must provide acceptable protection from humidity, light, and/or oxygen as appropriate. Containers for DPIs typically are made of plastic, but metal may be suitable. Packaging for the encapsulated drug must provide protection from humidity extremes to ensure that capsule breakage will occur in the desired fashion.

## LABELING AND USE

Typical warning statements include:

- Keep out of the reach of children unless otherwise prescribed.
- Do not attempt to disassemble mechanism. Discard the device after all doses have been administered.
- Keep the device level while in use.
- Do not breathe into the device.

Many experts recommend the addition of a statement indicating that patients and/or consumers should seek advice and instruction from a health care professional about the proper use of the device.

**Emulsions (Creams and Lotions)**

**Creams**—Creams are semisolid emulsion dosage forms. They often contain more than 20% water and volatiles and typically contain less than 50% hydrocarbons, waxes, or polyols as the vehicle for the API. Creams generally are intended for external application to the skin or to the mucous membranes. Creams have a relatively soft, spreadable consistency and can be formulated as either a water-in-oil emulsion (e.g., *Cold Cream* or *Fatty Cream* as in the *European Pharmacopoeia*) or as an oil-in-water emulsion (e.g., *Betamethasone Valerate Cream*). Creams

generally are described as either nonwashable or washable, reflecting the fact that an emulsion with an aqueous external continuous phase is more easily removed than one with a nonaqueous external phase (water-in-oil emulsion). Where the term “cream” is used without qualification, a water-washable product is generally inferred.

**Lotions**—Lotions are an emulsified liquid dosage form generally intended for external application to the skin. Historically, some topical suspensions such as calamine lotion have been called lotions but that nomenclature is not currently preferred. Lotions share many characteristics with creams. The distinguishing factor is that they are more fluid than semisolid and thus pourable. Due to their fluid character, lotions are more easily applied to large skin surfaces than semisolid preparations. Lotions may contain antimicrobial agents as preservatives.

## PREPARATION

*Pharmaceutical Compounding—Nonsterile Preparations* (795) provides general information regarding the preparation of emulsions.

**Creams**—Creams may be formulated from a variety of oils, both mineral and vegetable, and from fatty alcohols, fatty acids, and fatty esters. The solid excipients are melted at the time of preparation. Emulsifying agents include nonionic surfactants, detergents, and soaps. Soaps are usually formed from a fatty acid in the oil phase hydrolyzed by a base dissolved in the aqueous phase in situ during the preparation of creams.

Preparation usually involves separating the formula components into two portions: lipid and aqueous. The lipid portion contains all water-insoluble components and the aqueous portion the water-soluble components. Both phases are heated to a temperature above the melting point of the highest melting component. The phases then are mixed and the mixture is stirred until reaching

ambient temperature or the mixture has congealed. Mixing generally is continued during the cooling process to promote uniformity. Traditionally, the aqueous phase is added to the lipid phase, but comparable results have been obtained with the reverse procedure. High-shear homogenation may be employed to reduce particle or droplet size and improve the physical stability of the resultant dosage form.

The API(s) can be added to the phase in which it is soluble at the beginning of the manufacturing process, or it can be added after the cream is prepared by a suitable dispersion process such as levigation or milling with a roller mill. Creams usually require the addition of a preservative(s) unless they are compounded immediately prior to use and intended to be consumed in a relatively short period of time.

**Lotions**—Lotions usually are prepared by dissolving or dispersing the API into the more appropriate phase (oil or water), adding the appropriate emulsifying or suspending agents, and mixing the oil and water phases to form a uniform fluid emulsion.

#### LABELING AND PACKAGING

Some products may require labeling directions indicating to shake well prior to application and to avoid freezing. Storage limits must be specifically indicated to prevent melting of semisolid components. Instructions to ensure proper dosing and administration must accompany the product. Tight containers are used for preparation and storage to prevent loss by evaporation.

#### Feed Additives

Feed additives are preparations used in veterinary medicine to deliver the API(s) via the water or food given to animals. The feed additive may be either a solid or liquid and sometimes is called a premix. Feed additives are further subdivided into three types.

#### TYPE A MEDICATED ARTICLES

Type A medicated articles are products containing one or more animal APIs, and that are sold to licensed feed mills or producers and are intended to be further diluted by mixing into food or water prior to consumption by the animals. Because these preparations are not actually dosed to animals, they are not considered dosage forms.

#### TYPE B MEDICATED FEEDS

Type B medicated feeds are products that contain a type A medicated article, or another type B medicated feed, plus a substantial quantity of nutrients (not less than 25% of the total weight). Like type A medicated articles, type B medicated feeds are intended for mixture with food or water and additional nutrients, are not to be fed directly to the animals, and are not considered dosage forms.

#### TYPE C MEDICATED FEEDS

Type C medicated feeds are made from type A medicated articles or type B medicated feeds and are prepared at concentrations of the API appropriate for administration to animals by mixing in food or water. Administration of type C medicated feeds can be accomplished by blending directly into the feed; top-dressing the preparation onto the animal's normal daily rations; or heating, steaming, and extruding into pellets that are mixed or top-dressed onto the animal's food. Another form of type C medicated feeds is compressed or molded blocks from which animals receive the API or nutrients via licking the block.

## PREPARATION

Type A medicated articles that are liquids are produced by mixing the API(s) with a suitable solvent (e.g., water or propylene glycol). The API(s) is usually dissolved to produce a solution, but suspension products also could be produced.

Type A medicated articles that are solids are produced by blending the API with excipients to provide a uniform dosage form when mixed with the animal's feed. Often the API is first mixed with an excipient (e.g., starch or sodium aluminosilicate) that has a similar particle size and can help distribute the API uniformly throughout the final drug product. This pre-blend is then mixed with bulking excipients (e.g., calcium carbonate or soybean hulls). Mineral oil may be added to aid uniform distribution, to prevent particle segregation during shipping, and to minimize formation of airborne API particles during production of type B or C medicated feeds.

Type B or C medicated feeds are produced at licensed feed mills or by farm producers. Type A medicated articles are added to the feeds (e.g., ground corn or oats) during the milling process of making feeds. Liquid type A medicated articles often are sprayed in at set rates, and solid type A medicated articles are added slowly to aid in creating uniform distribution in the feeds. Liquid type A medicated articles can also be mixed in with bulk water sources at prescribed amounts.

## LABELING AND PACKAGING

Type A medicated articles or type B medicated feeds include special labeling to indicate that they should be used in the manufacture of animal feeds or added to the drinking water. The labels indicate that they are not to be fed directly to animals. Also included is a statement indicating "Not for Human Use". Type A medicated articles or type B medicated feeds are packaged either in pa-

per bags, often with polyethylene liners, for solids and in plastic containers for liquids. Typical sizes are 50-lb bags or several-gallon containers.

**Foams**

Medicated foams are emulsions containing a dispersed phase of gas bubbles in a liquid continuous phase containing the API. Medicated foams are packaged in pressurized containers or special dispensing devices and are intended for application to the skin or mucous membranes. The medicated foam is formed at the time of application. Surfactants are used to ensure the dispersion of the gas and the two phases. Medicated foams have a fluffy, semisolid consistency and can be formulated to break to a liquid quickly or to remain as foam to ensure prolonged contact.

Medicated foams intended to treat severely injured skin or open wounds must be sterile.

## PREPARATION

A foam may contain one or more APIs, surfactants, aqueous or nonaqueous liquids, and the propellants. If the propellant is in the internal (discontinuous) phase (i.e., is of the oil-in-water type), a stable foam is discharged. If the propellant is in the external (continuous) phase (i.e., is of the water-in-oil type), a spray or a quick-breaking foam is discharged. Quick-breaking foams formulated with alcohol create a cooling sensation when applied to the skin and may have disinfectant properties.

## LABELING AND USE

Foams formulated with flammable components should be appropriately labeled. Labeling indicates that prior to dispensing, a foam drug product is shaken well to ensure uniformity. The instructions for use must clearly note spe-

cial precautions that are necessary to preserve sterility. In the absence of a metering valve, delivered volume may be variable.

### Medical Gases (Inhalation Materials)

Medical gases are products that are administered directly as a gas. A medical gas has a direct pharmacological action or acts as a diluent for another medical gas. Gases employed as excipients for administration of aerosol products, as an adjuvant in packaging, or produced by other dosage forms, are not included in this definition.

**Components**—Medical gases may be single components or defined mixtures of components. Mixtures also can be extemporaneously prepared at the point of use.

**Administration**—Medical gases may be administered to the patient via the pulmonary route or via extracorporeal methods. The dose of medical gas typically is metered by a volume rate of flow under ambient temperature and pressure conditions. Administration of a highly compressed gas generally requires a regulator to decrease the pressure, a variable-volume flow controller, and suitable tubing to conduct the gas to the patient. For pulmonary administration, the gas flow will be directed to the nose or mouth by a suitable device or into the trachea through a mechanical ventilator. When medical gases are administered chronically, provision for humidification is common. Care should be exercised to avoid microbial contamination.

#### STORAGE

Medical gases are stored in a compressed state in cylinders or other suitable containers. The containers must be constructed of materials that can safely withstand the expected pressure and must be impact resistant. In some cases each container holds a single defined dose (e.g., general anesthetics), but in other cases the container holds sufficient gas for extended administration.

#### SPECIAL CONSIDERATIONS

The container and system fittings should be appropriate for the medical gas. Adaptors should not be used to connect containers to patient-use supply system piping or equipment. Large quantities of gases such as oxygen or nitrogen can be stored in the liquid state in a cryogenic container and converted into a gas, as needed, by evaporation. Additional rules concerning the construction and use of cryogenic containers are promulgated by governmental agencies (e.g., U.S. Department of Commerce).

Containers, tubing, and administration masks employed for gases containing oxygen are free of any compound that would be sensitive to oxidation or that would be irritating to the respiratory tract.

A significant fraction of the dose of a medical gas may be released into the general vicinity of the patient due to incomplete absorption. Adequate ventilation may be necessary to protect health care workers and others from exposure to the gas (e.g., nitrous oxide).

#### LABELING

Warning statements to be placed on pressurized containers include:

- Contents under pressure.
- Do not puncture or incinerate container.
- Do not expose to heat or store at temperatures above 49°.
- Keep out of the reach of children unless otherwise prescribed.
- Use only as directed; intentional misuse may be harmful or fatal.

If required under the individual monograph, label to indicate method of manufacture (such as oxygen via air liquefaction). When piped directly from the storage container to the point of use, the gas must be labeled for content at each outlet.

When oxygen is in use, a posted warning should indicate the necessity of extinguishing smoking materials and avoiding the use of open flames or other potential ignition sources.

### Gels

Gels (sometimes called jellies) are semisolid systems consisting either of suspensions of small inorganic particles or of organic molecules interpenetrated by a liquid. Gels can be classed either as single-phase or two-phase systems.

A two-phase gel consists of a network of small discrete particles (e.g., *Aluminum Hydroxide Gel* or *Psyllium Hemicellulose*). In a two-phase system the gel mass sometimes is referred to as a magma (e.g., *Bentonite Magma*) if the particle size of the suspended material is large. Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation. They should be shaken before use to ensure homogeneity and should be so labeled (see *Suspensions*).

Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from natural or synthetic macromolecules (e.g., *Carbomer*, *Hydroxypropyl Methylcellulose*, or *Starch*) or natural gums (e.g., *Tragacanth*). The latter preparations are also called mucilages. Although these gels commonly are aqueous, alcohols and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.

Gels can be administered by the topical or mucosal routes. Gels containing antibiotics administered by teat infusion are often the dosage form used in veterinary medicine to treat mastitis.

### PREPARATION

See *Pharmaceutical Compounding—Nonsterile Preparations* (795) for general procedures. Also see the information contained under *Dosage Forms, Suspensions* for the formulation and manufacture of gels containing inorganic components or APIs in the solid phase. See *Pharmaceutical Compounding—Sterile Preparations* (797) for general procedures for the preparation of sterile gels such as *Lidocaine Hydrochloride Jelly*.

Gels formed with large organic molecules may be formed by dispersing the molecule in the continuous phase (e.g., by heating starch), by cross-linking the dispersed molecules by changing the pH (as for *Carbomer Copolymer*), or by reducing the continuous phase (as for jellies formed with sucrose).

Care should be taken to ensure uniformity of the APIs by dispersing them by vigorous mixing or milling or by shaking if the preparation is less viscous.

### PACKAGING AND STORAGE

Store in tight containers to prevent water loss. Avoid freezing.

### Granules

Granules are solid dosage forms that are composed of agglomerations of smaller particles. These multicomponent compositions are prepared for oral administration and are used to facilitate flexible dosing regimens, address stability challenges, allow taste masking, or facilitate flexibility in administration (for instance, to pediatric patients, geriatric patients, or animals). Granular dosage forms may be formulated for direct oral administration and may facilitate compounding of multiple APIs by allowing compounding pharmacists to blend various granular compositions in the retail or hospital pharmacy. More commonly, granules are reconsti-

tuted to a suspension by the addition of water or a supplied liquid diluent immediately prior to delivery to the patient. Effervescent granules are formulated to liberate gas (carbon dioxide) upon addition of water. Common examples of effervescent granules include antacid and potassium supplementation preparations. Common therapeutic classes formulated as granule dosage forms include antibiotics, certain laxatives (such as senna extract products), electrolytes, and various cough and cold remedies that contain multiple APIs.

Granular dosages also are employed in veterinary medicine when they are often placed on top of or mixed with an animal's food. They are frequently provided with a measuring device to allow addition to feeds. The resultant mix facilitates dosing.

#### PREPARATION

Granules often are the precursors used in tablet compression or capsule filling. Although this application represents a pharmaceutical intermediate and not a final dosage form, numerous commercial products are based on granules. In the typical manufacture of granules, the API is blended with excipients (processing aids) and wetted with an appropriate pharmaceutical solvent or blend of solvents to promote agglomeration. This composition is dried and sized to yield the desired material properties.

Frequently, granules are used because the API is unstable in aqueous environments and cannot be exposed to water for periods sufficient to accommodate manufacture, storage, and distribution in a suspension. Preparation of the liquid dosage form from the granules immediately prior to dispensing allows acceptable stability for the duration of use. Granules manufactured for this purpose are packaged in quantities sufficient for a limited time period—usually one course of therapy that typically does not exceed 2 weeks. In addition to the API, other ingredients may be added to ensure acceptable stability

(e.g., buffers, antioxidants, or chelating agents) or to provide color, sweetness, flavor, and for suspensions, acceptable viscosity to ensure adequate suspension of the particulate to enable uniform dosing.

Effervescent granules typically are formulated from sodium or potassium bicarbonate and an acid such as citric or tartaric acid. To prevent untimely generation of carbon dioxide, manufacturers should take special precautions to limit residual water in the product due to manufacture and to select packaging that protects the product from moisture. The manufacture of effervescent granules can require specialized facilities designed to maintain very low humidity (approximately 10% relative humidity). Effervescent powder mixtures are purposely formed into relatively coarse granules to reduce the rate of dissolution and provide a more controlled effervescence.

#### PACKAGING AND STORAGE

Granules for reconstitution may be packaged in unit-of-use containers or in containers with sufficient quantities to accommodate a typical course of therapy (frequently 10 days to 2 weeks with antibiotic products). Packaging should provide suitable protection from moisture. This is particularly true for effervescent granules. Granules may be stored under controlled room temperature conditions unless other conditions are specifically noted.

Many granule products specify refrigerated storage following reconstitution and direct the patient to discard unused contents after a specified date that is based on the stability of the API in the reconstituted preparation.

#### LABELING AND USE

Effervescent granules (and tablets) are labeled to indicate that they are not to be swallowed directly.

Reconstitution of granules must ensure complete wetting of all ingredients and sufficient time and agitation to allow the soluble components to dissolve. Specific instructions for reconstitution provided by the manufacturer should be carefully followed.

Reconstituted suspensions should be shaken before use to re-suspend the dispersed particulates. This is especially true of suspension preparations dosed from multiple-dose containers. For particularly viscous suspensions prone to air entrapment, instructions may advise the user how to shake the preparation to re-suspend settled particulates while minimizing air entrapment.

#### SPECIAL CONSIDERATIONS

For granules reconstituted to form suspensions for oral administration, acceptable suspension of the particulate phase depends on the particle size of the dispersed phase as well as the viscosity of the vehicle. Temperature can influence the viscosity, which influences suspension properties and the ease of removal of the dose from the bottle. In addition, temperature cycling can lead to changes in the particle size of the dispersed phase via Ostwald ripening. Thus, clear instructions should be provided regarding the appropriate storage temperature for the product.

#### Medicated Gums

Medicated gum is a semisolid confection that is designed to be chewed rather than swallowed. Medicated gums release the API(s) into the saliva. Medicated gums can deliver therapeutic agents for local action in the mouth (such as antibiotics to control gum disease) or for systemic absorption via the buccal or gastrointestinal routes (e.g., nicotine or aspirin). Most medicated gums are manufactured using the conventional melting process derived from the confectionary industry or alternatively may be directly compressed from gum powder.

Medicated gums are formulated from insoluble synthetic gum bases such as polyisoprene, polyisobutylene, isobutyleneisoprene copolymer, styrene butadiene rubber, polyvinyl acetate, polyethylene, ester gums, or polyterpenes. Plasticizers and softeners such as propylene glycol, glycerin, oleic acid, or processed vegetable oils are added to keep the gum base pliable and to aid incorporation of the API(s), sweeteners, and flavoring agents. Sugars as well as artificial sweeteners and flavorings are incorporated to improve taste, and dyes may be used to enhance appearance. Some medicated gums are coated with magnesium stearate to reduce tackiness and improve handling during packaging. A preservative may be added.

#### PREPARATION

**Melted Gum**—The gum base is melted at a temperature of about 115° until it has the viscosity of thick syrup and at that point is filtered through a fine-mesh screen. This molten gum base is transferred to mixing tanks where the sweeteners, plasticizers, and typically the API are added and mixed. Colorings, flavorings, and preservatives are added and mixed while the melted gum is cooling. The cooled mixture is shaped by extrusion or rolling and cutting. Dosage units of the desired shape and potency are packaged individually. Additional coatings such as powder coatings to reduce tackiness or film or sugar coatings may be added to improve taste or facilitate bulk packaging.

**Directly Compressed Gum**—The gum base is supplied in a free-flowing granular powder form. The powder gum base is then dry blended with sweeteners, flavors, the API, and lubricant. The blend is then processed through a conventional tablet press and tableted into desired shapes. The resulting medicated gum tablets

can be further coated with sugar or sugar-free excipients. These tablets can be packaged in blisters or bottles as needed.

#### SPECIAL CONSIDERATIONS

Medicated gums are typically dispensed in unit-dose packaging. The patient instructions also may include a caution to avoid excessive heat.

### Implants

Implants are long-acting dosage forms that provide continuous release of the API for periods of months to years. They are administered by the parenteral route. For systemic delivery they may be placed subcutaneously, or for local delivery they can be placed in a specific region in the body.

Several types of implants are available. Pellet implants are small, sterile, solid masses composed of an API with or without excipients. They are usually administered by means of a suitable special injector (e.g., trocar) or by surgical incision. Release of the API from pellets typically is controlled by diffusion and dissolution kinetics. The size of the pellets and rate of erosion will influence the release rate, which typically follows first-order kinetics. Drug release from pellets for periods of 6 months or more is possible. Pellet implants have been used to provide extended delivery of hormones such as testosterone or estradiol.

Resorbable microparticles are a type of implants that provide extended release of drug over periods varying from a few weeks to months. They can be administered subcutaneously or intramuscularly for systemic delivery, or they may be deposited in a desired location in the body for site-specific delivery. Injectable resorbable microparticles (or microspheres) generally range from 20 to 100  $\mu\text{m}$  in diameter. They are composed of a drug dispersed within a biocompatible, bioresorbable polymeric

excipient (matrix). Poly(lactide-co-glycolide) polymers have been used frequently. These excipients typically resorb by hydrolysis of ester linkages. The microparticles are administered by suspension in an aqueous vehicle followed by injection with a conventional syringe and needle. Release of the drug from the microparticles begins after physiological fluid enters the polymer matrix, dissolving some of the drug that then is released by a diffusion-controlled process. Drug release also can occur as the matrix erodes.

Polymer implants can be formed as a single shaped mass such as a cylinder. The polymer matrix must be biocompatible, but it can be either biodegradable or non-biodegradable. Shaped polymer implants are administered by means of a suitable special injector. Release kinetics typically are not zero-order, but zero-order kinetics are possible. Drug release can be controlled by the diffusion of the API from the bulk polymer matrix or by the properties of a rate-limiting polymeric membrane coating. Polymer implants are used to deliver potent small molecules like steroids (e.g., estradiol for cattle) and large molecules like peptides [e.g., luteinizing hormone-releasing hormone (LHRH)]. Example durations of drug release are 2 and 3 months for biodegradable implants and 1 year for non-biodegradable implants. An advantage of biodegradable implants is that they do not require removal after release of all drug content. Non-biodegradable polymer implants can be removed before or after drug release is complete or may be left in situ. An implant can have a tab with a hole in it to facilitate suturing it in place, e.g., for an intravitreal implant for local ocular delivery. Such implants may provide therapeutic release for periods as long as 2.5 years.

Some implants are designed to form as a mass in situ. These implants are initially prepared as liquid formulations comprising polymer, API, and solvent for the polymer. The polymer solvent can be water or an organic solvent. After administration of the liquid formulation

to a patient by subcutaneous or intramuscular administration, it forms a gel or a solid polymeric matrix that traps the API and extends the API release for days or months. In situ-forming implants also are used for local delivery of the API to treat periodontal disease. The implant is formed within the periodontal pocket.

Another type of implant can be fabricated from a metal such as titanium and plastic components. These implants are administered by means of a suitable injector or by surgical installation. A solution of API inside the implant, like an LHRH solution, is released via an osmotically driven pump inside the implant. Duration of release may be as long as 1 year or more. Release kinetics are zero order. After the drug is delivered, metal-based implants are removed.

Drug-eluting stents combine the mechanical effect of the stent to maintain arterial patency with the prolonged pharmacologic effect of the incorporated API (to reduce restenosis, inhibit clot formation, or combat infection). As an example, a metal stent can be coated with a non-biodegradable or biodegradable polymer-containing API. The resultant coating is a polymeric matrix that controls the extended release of the API.

#### PREPARATION

Pellet implants are made by API compression or molding. Cylindrical polymeric implants typically are made by melt extrusion of a blend of API and polymer, resulting in a rod that is cut into shorter lengths. Polymer implants also can be made by injection molding. Still other implants are assembled from metal tubes and injection-molded plastic components.

Sterility can be achieved by terminal sterilization or by employing aseptic manufacturing procedures.

#### PACKAGING AND STORAGE

All implants are individually packaged (typically in their injector or for veterinary use in cartridges that are placed in the injector guns), are sterile (except for some animal health products), and conform to the appropriate standards for injection. Biodegradable implants are protected from moisture so the polymer does not hydrolyze and alter drug release kinetics before use.

#### Inserts

Inserts are solid dosage forms that are inserted into a body cavity other than the rectum (see *Suppositories*). The API is delivered in inserts for local or systemic action. Inserts applied to the eye, such as *Pilocarpine Ocular System*, typically are sterile. Vaginal inserts for humans are usually globular or oviform and weigh about 5 g each. Vaginal inserts for cattle are T-shaped, are formed of polymer, are removable, and can be used for up to 8 days. One veterinary application is for estrus synchronization. Inserts intended to dissolve in vaginal secretions usually are made from water-soluble or water-miscible vehicles such as polyethylene glycol or glycerinated gelatin. Vaginal inserts such as dinoprostone vaginal insert (e.g., see USP monograph *Dinoprostone Vaginal Suppositories*) are formulated to deliver medication to the cervix and to be removed or recovered once the API has been released. Intrauterine inserts such as *Progesterone Intrauterine Contraceptive System* are used to deliver APIs locally to achieve efficacy while reducing side effects. Some intrauterine inserts are formulated to remain in the uterus for extended periods of time. An intra-urethral insert of alprostadil is available for the treatment of erectile dysfunction.

PREPARATION

For general considerations see *Pharmaceutical Compounding—Nonsterile Preparations* (795). Inserts vary considerably in their preparation. Inserts may be molded (using technology similar to that employed to prepare lozenges, suppositories, or plastics), compressed from powders (as in tableting), or formulated as special applications of capsules (soft gelatin capsules and hard gelatin capsules have been employed for extemporaneously compounded preparations). Inserts may be formulated to melt at body temperature or disintegrate upon insertion. Design of the dosage form should take into consideration the fluid volume available at the insertion site and minimize the potential to cause local irritation. Most inserts are formulated to ensure retention at the site of administration.

STORAGE AND LABELING

Appropriate storage conditions must be clearly indicated in the labeling for all inserts, especially for those that are designed to melt at body temperature. Instructions to ensure proper dosing and administration must accompany the product.

**Liquids**

As a dosage form a liquid consists of a pure chemical in its liquid state. Examples include mineral oil, isoflurane, and ether. This dosage form term is not applied to solutions. In veterinary medicine liquids may be administered topically or diluted via mixing with drinking water or food.

STORAGE AND LABELING

Storage, packaging, and labeling consider the physical properties of the material and are designed to maintain potency and purity.

**Lotions (see *Emulsions*)**

**Lozenges**

Lozenges are solid oral dosage forms that are designed to dissolve or disintegrate slowly in the mouth. They contain one or more APIs that are slowly liberated from the flavored and sweetened base. They are frequently intended to provide local action in the oral cavity or the throat but also include those intended for systemic absorption after dissolution. The typical therapeutic categories of APIs delivered in lozenges are antiseptics, analgesics, decongestants, antitussives, and antibiotics. Molded lozenges are called cough drops or pastilles. Molded lozenges mounted on a stick are known as lollipops. Lozenges prepared by compression or by stamping or cutting from a uniform bed of paste sometimes are known as troches. Troches are often produced in a circular shape.

Lozenges can be made using sugars such as sucrose and dextrose or can provide the benefits of a sugar-free formulation that is usually based on sorbitol or mannitol. Polyethylene glycols and hypromellose sometimes are included to slow the rate of dissolution.

MANUFACTURE

Excipients used in molded lozenge manufacture include gelatin, fused sucrose, sorbitol, or another carbohydrate base.

Molded lozenges using a sucrose or sorbitol base containing APIs such as phenol, dextromethorphan, fentanyl, and dyclonine hydrochloride and menthol are

prepared by cooking the sugar (sucrose, corn syrup, and sorbitol) and water at about 150° to reduce the water content to less than 2%. The molten sugar solution is transferred to a cooling belt or cooling table, and medications, flavorings, and colorings are added and thoroughly mixed while cooling. Individual dosage units of the desired shape are formed by filling the molten mass into molds. These lozenges are quickly cooled in the molds to trap the base in the glassy state. Once formed, the lozenges are removed from the molds and packaged. Care is taken to avoid excessive moisture during storage to prevent crystallization of the sugar base.

Compressed lozenges are made using excipients that may include a filler, binder, sweetening agent, flavoring agent, and lubricant. Sugars such as sucrose, sorbitol, and mannitol often are included because they can act as filler and binder as well as serve as sweetening agents. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide) also may be present.

The manufacturing of compressed lozenges is essentially the same as that for conventional tableting, with the exception that a tablet press capable of making larger tablets and exerting greater force to produce harder tablets may be required (see *Tablets*).

The paste used to produce lozenges manufactured by stamping or cutting contains a moistening agent, sucrose, and flavoring and sweetening agents. The homogeneous paste is spread as a bed of uniform thickness, and the lozenges are cut or stamped from the bed and are allowed to dry. Some lozenges are prepared by forcing dampened powders under low pressure into mold cavities and then ejecting them onto suitable trays for drying at moderate temperatures.

#### PACKAGING AND STORAGE

Many lozenges are sensitive to moisture, and typically a monograph indicates that the package or container type is well closed and/or moisture resistant. Storage instructions may include protection from high humidity.

### Ointments

Ointments are semisolid preparations intended for external application to the skin or mucous membranes. APIs delivered in ointments are intended for local action or for systemic absorption. Ointments usually contain less than 20% water and volatiles and more than 50% hydrocarbons, waxes, or polyols as the vehicle. Ointment bases recognized for use as vehicles fall into four general classes: hydrocarbon bases, absorption bases, water-removable bases, and water-soluble bases.

**Hydrocarbon Bases**—Also known as oleaginous ointment bases, they allow the incorporation of only small amounts of an aqueous component. Ointments prepared from hydrocarbon bases act as occlusive dressings and provide prolonged contact of the API with the skin. They are difficult to remove and do not change physical characteristics upon aging.

**Absorption Bases**—Allow the incorporation of aqueous solutions. Such bases include only anhydrous components (e.g., *Hydrophilic Petrolatum*) or water-in-oil emulsions (e.g., *Lanolin*). Absorption bases are also useful as emollients.

**Water-Removable Bases**—Oil-in-water emulsions (e.g., *Hydrophilic Ointment*) and are sometimes referred to as creams (see *Emulsions*). They may be readily washed from the skin or clothing with water, making them acceptable for cosmetic reasons. Other advantages of the water-removable bases are that they can be diluted with water and that they favor the absorption of serous discharges in dermatological conditions.

**Water-Soluble Bases**—Also known as greaseless ointment bases, they are formulated entirely from water-soluble constituents. *Polyethylene Glycol Ointment* is the only official preparation in this group. They offer many of the advantages of the water-removable bases and, in addition, contain no water-insoluble substances such as petrolatum, anhydrous lanolin, or waxes. They are more correctly categorized as gels (see *Gels*).

The choice of an ointment base depends on the action desired, the characteristics of the incorporated API, and the latter's bioavailability if systemic action is desired. The product's stability may require the use of a base that is less than ideal in meeting other quality attributes. APIs that hydrolyze rapidly, for example, are more stable in hydrocarbon bases than in bases that contain water.

Ophthalmic ointments are intended for application directly to the eye or eye-associated structures such as the subconjunctival sac. They are manufactured from sterilized ingredients under aseptic conditions and meet the requirements under *Sterility Tests* (71). Ingredients meeting the requirements described under *Sterility Tests* (71) are used if they are not suitable for sterilization procedures. Ophthalmic ointments in multiple-dose containers contain suitable antimicrobial agents to control microorganisms that might be introduced during use unless otherwise directed in the individual monograph or unless the formula itself is bacteriostatic (see *Ophthalmic Ointments* (771), *Added Substances*). The finished ointment is free from large particles and must meet the requirements for *Leakage* and for *Metal Particles* under *Ophthalmic Ointments* (771). The immediate container for ophthalmic ointments is sterile at the time of filling and closing. The immediate containers for ophthalmic ointments are sealed and made tamper-proof so that sterility is ensured at time of first use.

A suitable ophthalmic ointment base is nonirritating to the eye and permits diffusion of the API throughout the secretions bathing the eye. Petrolatum is most common-

ly used as a base for ophthalmic drugs. Some absorption bases, water-removable bases, and water-soluble bases may be desirable for water-soluble APIs if the bases are nonirritating.

#### MANUFACTURE

Ointments typically are prepared by either direct incorporation into a previously prepared ointment base or by fusion (heating during the preparation of the ointment). A levigating agent is often added to facilitate the incorporation of the medicament into the ointment base by the direct incorporation procedure. In the fusion method, the ingredients are heated, often in the range of 60° to 80°. Homogenization is often necessary. The rate of cooling is an important manufacturing detail because rapid cooling can impart increased structure to the product of the fusion method.

#### PACKAGING AND STORAGE

Protect from moisture. For emulsified systems, temperature extremes can lead to physical instability of the preparation. When this is the case products should be clearly labeled to specify appropriate storage conditions. Ointments typically are packaged either in ointment jars or ointment tubes. Ointment jars are often used for more viscous ointments that do not require sterility. Ointment tubes typically are used for less viscous ointments and those such as ophthalmic ointments that require the maintenance of sterility. The package sizes for ophthalmic preparations are controlled to minimize the likelihood of contamination and loss of sterility.

## Pastes

Pastes are semisolid preparations of stiff consistency and contain a high percentage of finely dispersed solids. Pastes are intended for application to the skin, oral cavity, or mucous membranes. In veterinary practice, pastes are used for systemic delivery of APIs.

Pastes ordinarily do not flow at body temperature and thus can serve as occlusive, protective coatings. As a consequence, pastes are more often used for protective action than are ointments.

Fatty pastes that have a high proportion of hydrophilic solids appear less greasy and more absorptive than ointments. They are used to absorb serous secretions and are often preferred for acute lesions that have a tendency toward crusting, vesiculation, or oozing.

Dental pastes may be applied to the teeth, or alternatively they may be indicated for adhesion to the mucous membrane for a local effect (e.g., *Triamcinolone Acetonide Dental Paste*). Some paste preparations intended for animals are administered orally. The paste is squeezed into the mouth of the animal, generally at the back of the tongue, or is spread inside the mouth.

### PREPARATION

Pastes can be prepared by direct incorporation or by fusion (the use of heat to soften the base). The solid ingredients often are incorporated following comminution and sieving. If a levigating agent is needed, a portion of the ointment base is often employed rather than a liquid.

### LABELING AND STORAGE

Veterinary products should be labeled to ensure they are not administered to humans. Labeling should indicate the need for protection from heat.

## Transdermal Systems (Patches)

Transdermal drug delivery systems (TDSs) are discrete dosage forms that are designed to deliver the API(s) through intact skin to the systemic circulation. Typically, a TDS is composed of an outer covering (barrier), a drug reservoir (possibly covered with a rate-controlling membrane), a contact adhesive applied to some or all parts of the system (to attach the TDS to the skin surface), and a protective layer that is removed before the patch is applied. The activity of a TDS is defined in terms of the release rate of the API(s) from the system. The total duration of drug release from the system and the system surface area also may be stated.

Most TDSs can be considered either matrix-type or reservoir-type systems. Matrix-type patches are often further divided into monolithic adhesive matrix or polymer matrix types. Reservoir-type systems include liquid reservoir systems and solid-state reservoir systems. Solid-state reservoir patches also include multilaminate adhesive and multilaminate polymer matrix systems.

Drug delivery from some TDSs is controlled by diffusion kinetics. The API diffuses from the drug reservoir directly or through the rate-controlling membrane and/or contact adhesive and then through the skin into the general circulation. Modified-release systems are generally designed to provide drug delivery at a constant rate so that a true steady-state blood concentration is achieved and maintained until the system is removed. Other TDSs work by active transport of the API. For example, iontophoretic transdermal delivery uses the current between two electrodes to enhance the movement of ionized APIs through the skin.

TDSs are applied to the body areas recommended by the labeling. The API content of the system provides a reservoir that, by design, maintains a constant API concentration at the system-skin interface. The dosing interval of the system is a function of the amount of API in the reservoir and the release rate. Some API concentration

may remain in the reservoir at the end of the dosing interval, in particular for diffusion-controlled delivery mechanisms. [NOTE—Where the API is intended for local action, it may be embedded in adhesive on a cloth or plastic backing. This type of product is more correctly called a plaster or tape (see *Plasters* and *Tapes*).]

#### PREPARATION

TDSs require a backing, a means of storing the API for delivery to the skin, an adhesive to attach the system to the skin, and a removable release liner to protect the adhesive, API, and excipients before application. The backing has low moisture- and vapor-transmission rates to support product stability. The adhesive layer may contain the API and permeation enhancers in the case of matrix-type systems or multi-laminate reservoir systems for which a priming dose is desired. Adhesive may be applied to the entire patch release surface or merely to the periphery. Liquid reservoir systems are often formed–filled–sealed between the backing and release-controlling materials. For monolithic adhesive matrix systems, the API and excipients are applied as a solution or suspension either to the backing or the release liner, and the solvent is allowed to evaporate.

#### PACKAGING AND STORAGE

Storage conditions are clearly specified because extreme temperature excursions can influence the performance of some systems.

#### LABELING

The labeling should clearly indicate any performance limitations of the system (e.g., influence of application site, hydration state, hair, or other variables).

### Pellets

Pellets are dosage forms composed of small, solid particles of uniform shape sometimes called beads. Typically, pellets are nearly spherical but this is not required. Pellets may be administered by the oral (gastrointestinal) or by the injection route (see also *Implants*). Pellet formulations may provide several advantages including physical separation for chemically or physically incompatible materials, extended release of the API, or delayed release to protect an acid-labile API from degradation in the stomach or to protect stomach tissues from irritation. Extended-release pellet formulations may be designed with the API dispersed in a matrix, or the pellet may be coated with an appropriate polymer coating that modifies the drug-release characteristics. Alternatively, the pellet design may combine these two approaches. In the case of delayed-release formulations, the coating polymer is chosen to resist dissolution at the lower pH of the gastric environment but to dissolve in the higher pH intestinal environment. Injected or surgically administered pellet preparations (see *Implants*) are often used to provide continuous therapy for periods of months or years.

Pellet dosage forms may be designed as single or multiple entities. Often implanted pellets will contain the desired API content in one or several units. In veterinary practice, 4 to 8 pellets may be implanted in the ears for cattle, depending on animal size. Oral pellets typically are contained within hard gelatin capsules for administration. Although there are no absolute requirements for size, the useful size range of pellets is governed by the practical constraints of the volume of commonly used capsules and the need to include sufficient numbers of pellets in each dose to ensure uniform dosing of the API. As a result, many pellets used for oral administration fall within a size range of 8 to 24 mesh. Pellet formulations sometimes are used to minimize variability associated with larger dosage forms caused by gastric retention upon stomach emptying.

Enteric-coated (delayed-release) pellet formulations and some extended-release formulations are prepared by applying a coating to the formulated particles. The coating must be applied as a continuous film over the entire surface of each particle. Because a small population of imperfectly coated particles may be unavoidable, oral pellets are designed to require the administration of a large number in a single dose to minimize any adverse influence of imperfectly coated pellets on drug delivery.

#### PREPARATION

The desired performance characteristics determine the manufacturing method chosen. In general, pellet dosage forms are manufactured by wet extrusion processes followed by spheronization, by wet or dry coating processes, or by compression. Manufacture of pellets by wet coating usually involves the application of successive coatings upon nonpareil seeds. This manufacturing process frequently is conducted in fluid-bed processing equipment. Dry powder coating or layering processes often are performed in specialized rotor granulation equipment. The extent of particle growth achievable in wet coating processes is generally more limited than the growth that can be obtained with dry powder layering techniques, but either method allows the formulator to develop and apply multiple layers of coatings to achieve the desired release profile. The manufacture of pellets by compression is largely restricted to the production of material for subcutaneous implantation. This method of manufacture provides the necessary control to ensure dose uniformity and generally is better suited to aseptic processing requirements.

Alternatively, microencapsulation techniques can be used to manufacture pellets. Coacervation coating techniques typically produce coated particles that are much smaller than those made by other techniques.

#### PACKAGING AND STORAGE

Pellets for oral administration generally are filled into hard gelatin capsules and are placed in bottles or blister packages. The packaging provides suitable protection from moisture to ensure the stability of the pellet formulation as well as to preserve desirable moisture content of the capsule shells. Pellets for implantation are sterile and should be packaged in tight containers suitable for maintaining sterile contents. Pellets may be stored under controlled room temperature conditions unless other conditions are specifically noted.

#### LABELING AND USE

Pellets for oral administration that are formulated to provide delayed or controlled release must be swallowed intact to ensure preservation of the desired release characteristics. These products should be labeled accordingly to ensure that the material is not crushed or chewed during administration.

#### Pills

Pills are API-containing small round solid bodies intended for oral administration. At one time pills were the most extensively used oral dosage form, but they have been replaced by compressed tablets and capsules. Pills are distinguished from tablets because pills are manufactured by a wet massing and molding technique, while tablets are formed by compression.

#### PREPARATION

Excipients are selected on the basis of their ability to produce a mass that is firm and plastic. The API is triturated with powdered excipients in serial dilutions to attain a uniform mixture. Liquid excipients that act to bind and provide plasticity to the mass are subsequently added

to the dry materials. The mass is formed by kneading. The properties of firmness and plasticity are necessary to permit the mass to be worked and retain the shape produced. Cylindrical pill pipes are produced from portions of the mass. The pill pipe is cut into individual lengths corresponding to the intended pill size, and the pills are rolled to form the final shape. Pill-making machines can automate the preparation of the mass, production of pill piping, and the cutting and rolling of pills.

#### PACKAGING AND LABELING

Labeling and use instructions for pills are similar to those for tablets. Although many pills are resistant to breakage, some pills are friable. Appropriate handling guidelines should be provided in such cases in order to avoid breakage.

#### Plasters

A plaster is a semisolid substance for external application and usually is supplied on a support material. Plasters are applied for prolonged periods to provide protection, support, or occlusion (maceration).

Plasters consist of an adhesive layer that may contain active substances. This layer is spread uniformly on an appropriate support that is usually made of a rubber base or synthetic resin. Unmedicated plasters are designed to provide protection or mechanical support to the site of application. These plasters are neither irritating nor sensitizing to the skin.

Plasters are available in a range of sizes or cut to size to effectively provide prolonged contact to the site of application. They adhere firmly to the skin but can be peeled off the skin without causing injury.

One example of a plaster currently in use is salicylic acid plasters used for the removal of corns by the keratolytic action of salicylic acid.

#### PACKAGING AND STORAGE

Plasters are preserved in well-closed containers, preferably at controlled room temperature.

#### Powders

Powders are defined as a solid or a mixture of solids in a finely divided state intended for internal or external use. Powders used as pharmaceutical dosage forms may contain one or more APIs and can be mixed with water for oral administration or injection. Often pediatric antibiotics utilize a powder dosage form for improved stability. In some areas medicated powders are used for extemporaneous compounding of preparations for simultaneous administration of multiple APIs. Medicated powders also can be inhaled for pulmonary administration (see *Dry Powder Inhalers*). Aerosolized powders for the lungs typically contain processing aids to improve flow and ensure uniformity (see *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* (601)). Powders can also be used topically as a dusting powder.

Externally applied powders should have a particle size of 150  $\mu\text{m}$  or less (typically in the 50- to 100- $\mu\text{m}$  range) in order to prevent a gritty feel on the skin that could further irritate traumatized skin. Powders are grouped according to the following terms: very coarse, coarse, moderately coarse, fine, and very fine (see *Powder Finesness* (811)). The performance of powder dosage forms can be affected by the physical characteristics of the powder. Particle size can influence the dissolution rate of the particles and affect bioavailability. For dispersed delivery systems, particle size can influence the mixing and segregation behavior of the particle, which in turn affects the uniformity of the dosage form.

## PREPARATION

Powder dosage forms can be produced by the combination of multiple components into a uniform blend. This can also involve particle size reduction, a process referred to as comminution. Mills and pulverizers are used to reduce the particle size of powders when necessary. As the particle size is decreased, the number of particles and the surface area increase, which can increase the dissolution rate and bioavailability of the API.

Blending techniques for powders include those used in compounding pharmacy such as spatulation and trituration (see *Pharmaceutical Compounding Nonsterile Preparations* (795)). Industrial processes may employ sifting or tumbling the powders in a rotating container. One of the most common tumble blenders is a V-blender, which is available in a variety of scales suitable for small-scale and large-scale compounding and industrial production.

Powder flow can be influenced by both particle size and shape. Larger particles generally flow more freely than do fine particles. Powder flow is an important attribute that can affect the packaging or dispensing of a medicated powder.

## PACKAGING AND STORAGE

Powders for pharmaceutical use can be packaged in multiple- or single-unit containers. Bulk containers have been used for antacid powders and for laxative powders. In these instances the patient dissolves the directed amount in water prior to administration. This type of multiple-unit packaging is acceptable for many APIs but should not be utilized for powders that require exact dosing. Multiple-unit powders for topical application often are packaged in a container with a sifter top.

Potent APIs in a powder dosage form are dispensed in unit-of-use allocations in folded papers, cellophane envelopes, or packets. Powder boxes are often used by the dispensing pharmacist to hold multiple doses of indi-

vidual folded papers. Hygroscopic powders pose special challenges and typically are dispensed in moisture-resistant packaging.

## LABELING

Typical warning statements include:

- External powders must indicate: “External Use Only”.
- Oral powders should indicate: “For Oral Use Only”.
- Powders intended for veterinary use must indicate: “For Veterinary Use Only”.

Individual monographs specify the labeling requirements for powder dosage forms that are listed in *USP–NF*. Oral powders for reconstitution prior to dispensing typically have a limited shelf life (for example, 2 weeks), and the dispensed product should indicate a beyond-use date based on the date of the water addition. Pharmaceutical powders that are compounded indicate a beyond-use date. Compounded preparations typically are intended for immediate use and have short-term storage durations.

**Medicated Soaps And Shampoos**

Medicated soaps and shampoos are solid or liquid preparations intended for topical application to the skin or scalp followed by subsequent rinsing with water. Soaps and shampoos are emulsions or surface-active compositions that readily form emulsions or foams upon the addition of water followed by rubbing. Incorporation of APIs in soaps and shampoos combines the cleansing/degreasing abilities of the vehicle and facilitates the topical application of the API to affected areas, even large areas, of the body. The surface-active properties of the vehicle facilitate contact of the API with the skin or scalp. Medicated soap and shampoo formulations frequently contain suitable antimicrobial agents to protect against bacteria, yeast, and mold contamination.

#### PREPARATION

The preparation of medicated soaps and shampoos follows techniques frequently used for the preparation of emulsified systems. To ensure uniformity, the API(s) must be added to the vehicle prior to congealing (in the case of soaps) followed by thorough mixing. If the medication is present as a suspension, the particle size must be controlled to promote uniform distribution of the API and possibly optimize performance. Because soap manufacture frequently involves processing the ingredients at elevated temperature, care must be exercised to avoid excessive degradation of the API during processing.

#### PACKAGING AND STORAGE

Individual monographs specify the packaging and storage requirements for medicated soaps and shampoos in *USP–NF*.

#### LABELING AND USE

Medicated soaps and shampoos are clearly labeled to indicate “For External Use Only”. The preparations also clearly advise the patient to discontinue use and consult a physician/veterinarian if skin irritation or inflammation occurs or persists following application.

### Solutions

A solution is a liquid preparation that contains one or more dissolved chemical substances in a suitable solvent or mixture of mutually miscible solvents. Because molecules of a drug substance in solution are uniformly dispersed, the use of solutions as dosage forms generally provides assurance of uniform dosage upon administration and good accuracy when the solution is diluted or otherwise mixed.

Substances in solutions are more susceptible to chemical instability than they are in the solid state and dose-for-dose generally are heavier and more bulky than solid dosage forms. These factors increase the cost of packaging and shipping relative to that of solid dosage forms. Solution dosage forms can be administered by injection; inhalation; and the mucosal, topical/dermal, and gastrointestinal routes. Terminology for solutions in veterinary practice includes spot-ons or pour-ons that refer to solutions that are applied to an animal’s skin for systemic absorption, dips that refer to solutions that are used for washing and disinfection (e.g., udders, eggs, and whole animals), and drenches that include solutions that are orally administered to livestock, usually with a dosing device. Solutions administered by injection are officially titled injections (see *Injections* <1>).

Solutions intended for oral (gastrointestinal) administration usually contain flavorings and colorants to make the medication more attractive and palatable for the patient or consumer. When needed, they also may contain stabilizers to maintain chemical and physical stability and preservatives to prevent microbial growth.

#### STORAGE AND USE

Light-resistant containers should be considered when photolytic chemical degradation is a potential issue. To prevent water or solvent loss, solutions are stored in tight containers. Instructions to ensure proper dosing and administration must accompany the product

### Sprays (Nasal, Pulmonary, or Solutions For Nebulization)

A spray is a preparation that contains a therapeutic agent(s) in either the liquid or solid state and is intended for administration as a fine mist of small aqueous droplets. The droplets may be generated by means other than the use of a volatile propellant (see *Aerosols*). The mech-

anism for droplet generation and the intended use of the preparation distinguish the various classes of sprays. A spray is composed of a pump, container, valve, actuator, and nozzle in addition to the formulation containing the drug(s), solvents, and excipients. Each component plays a role in determining the critical characteristics of the mist of fine droplets. Droplet size and size distribution, uniformity of delivery of dose, plume geometry, and droplet velocity are critical parameters that influence the efficiency of drug delivery. When the preparation is supplied as a multi-dose container, the addition of a suitable antimicrobial preservative may be necessary.

Spray formulations intended for nasal or pulmonary administration have an aqueous base. Nasal preparations may be solutions, suspensions, or emulsions intended for local or systemic effect. Nasal delivery may be employed for drugs with high hepatic extraction ratios. Pulmonary preparations typically are solutions, although appropriately sized suspension formulations are permissible. Preparations are usually isotonic and may contain excipients to control pH and viscosity.

Metered-dose sprays typically require manually depressing the top of the container to activate a metered valve system. Depending on the design of the formulation and the valve system, the droplets generated may be intended for immediate inhalation through the mouth and deposition in the pulmonary tree or for inhalation into the nose and deposition in the nasal cavity. These preparations are commonly known as metered-dose sprays. The design of the pump, container, valve, actuator, nozzle, and formulation are critical to the performance of the product.

Alternatively, sprays can be generated by package designs that do not accurately control the volume of formulation delivered. These presentations release the formulation as a fine mist of droplets upon physical ma-

nipulation of the package by the patient. This generally involves squeezing the sides of the container and expelling the formulation through the nozzle of the container.

Finally, liquid sprays may be generated from solutions by nebulization. This is a method for continuous generation of a fine mist of aqueous droplets from a drug-containing solution by application of the Venturi principle, ultrasonic energy, or other suitable mechanical means. The generated mist is directed to the patient for inhalation, sometimes with the aid of an appropriate tube or face mask. Although formulations for nebulization typically are solutions, they also may be fine suspensions or emulsions.

#### PACKAGING

Containers typically are made of a rigid plastic, but metal or glass may be suitable.

The nasal spray pump is designed to allow convenient one-handed operation. The nasal spray nozzle is designed so that it fits comfortably into the vestibule of the nasal cavity and allows the plume to be directed toward the appropriate region of the cavity.

#### LABELING AND USE

Typical warning statements include:

- All inhalation sprays should indicate: "For Inhalation Administration Only. Keep out of the reach of children unless otherwise prescribed. Avoid spraying into the eyes."
- All nasal sprays indicate: "For Intranasal Administration Only".

The device should contain a statement that patients should seek advice and instruction from a health care professional about the proper use of the device. Guid-

ance should be provided about the proper care and cleaning of the device to prevent introduction of microbes into the pulmonary airways.

### Suppositories

Suppositories are dosage forms adapted for application into the rectum. They usually melt, soften, or dissolve at body temperature. A suppository may have a local protectant or palliative effect or may deliver an API for systemic or local action.

Suppository bases typically include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol. The suppository base can have a notable influence on the release of the API(s). Although cocoa butter melts quickly at body temperature, it is immiscible with body fluids and this inhibits the diffusion of fat-soluble APIs to the affected sites. Polyethylene glycol is a suitable base for some antiseptics. In cases when systemic action is desired, incorporating the ionized rather than the non-ionized form of the API may help maximize bioavailability. Although non-ionized APIs partition more readily out of water-miscible bases such as glycerinated gelatin and polyethylene glycol, the bases themselves tend to dissolve very slowly, which slows API release. Cocoa butter and its substitutes (e.g., *Hard Fat*) perform better than other bases for allaying irritation in preparations intended for treating internal hemorrhoids. Suppositories for adults are tapered at one or both ends and usually weigh about 2 g each.

#### PREPARATION

Cocoa butter suppositories have cocoa butter as the base and can be made by incorporating the finely divided API into the solid oil at room temperature and suitably shaping the resulting mass or by working with the oil in the melted state and allowing the resulting suspension to

cool in molds. A suitable quantity of hardening agents may be added to counteract the tendency of some APIs (such as chloral hydrate and phenol) to soften the base. The finished suppository melts at body temperature.

A variety of vegetable oils, such as coconut or palm kernel, modified by esterification, hydrogenation, or fractionation, are used as cocoa butter substitutes to obtain products that display varying compositions and melting temperatures (e.g., *Hydrogenated Vegetable Oil* and *Hard Fat*). These products can be designed to reduce rancidity while incorporating desired characteristics such as narrow intervals between melting and solidification temperatures and melting ranges to accommodate formulation and climatic conditions.

APIs can be incorporated into glycerinated gelatin bases by addition of the prescribed quantities to a vehicle consisting of about 70 parts of glycerin, 20 parts of gelatin, and 10 parts of water.

Several combinations of polyethylene glycols that have melting temperatures that are above body temperature are used as suppository bases. Because release from these bases depends on dissolution rather than on melting, there are significantly fewer problems in preparation and storage than is the case for melting-type vehicles. However, high concentrations of higher molecular weight polyethylene glycols may lengthen dissolution time, resulting in problems with retention.

Several non-ionic surface-active agents closely related chemically to the polyethylene glycols can be used as suppository vehicles. Examples include polyoxyethylene sorbitan fatty acid esters and the polyoxyethylene steirates. These surfactants are used alone or in combination with other suppository vehicles to yield a wide range of melting temperatures and consistencies. A notable advantage of such vehicles is their water dispersibility. However, care must be taken with the use of surfactants

because they may either increase the rate of API absorption or interact with the API to reduce therapeutic activity.

Compounding suppositories using a suppository base typically involves melting the suppository base and dissolution or dispersion of the API in the molten base (see *Pharmaceutical Compounding—Nonsterile Preparations* (795)). When compounding suppositories, the manufacturer or compounding professional prepares an excess amount of total formulation to allow the prescribed quantity to be accurately dispensed. In compounding suppositories, avoid caustic or irritating ingredients, carefully select a base that will allow the API to provide the intended effect, and in order to minimize abrasion of the rectal membranes, reduce solid ingredients to the smallest reasonable particle size. A representative number of the compounded suppositories should be weighed to confirm that none is less than 90% or more than 110% of the average weight of all units in the batch.

#### STORAGE AND USE

Suppositories typically are provided in unit-dose packaging with storage instructions to prevent melting of the suppository base. Suppositories with cocoa butter base require storage in well-closed containers, preferably at a temperature below 30° (controlled room temperature). Glycerinated gelatin suppositories require storage in tight containers, preferably at a temperature below 2°. Although polyethylene glycol suppositories can be stored without refrigeration, they should be packaged in tightly closed containers.

Include instructions about insertion procedures to ensure ease of use and absorption. Labels on polyethylene glycol suppositories should contain directions that they be moistened with water before insertion.

## Suspensions

A suspension is a biphasic preparation consisting of solid particles dispersed throughout a liquid phase. Suspension dosage forms may be formulated for specific routes of administration such as oral suspensions, topical suspensions, or suspensions for aerosols (see *Aerosols*). Some suspensions are prepared and ready for use, and others are prepared as solid mixtures intended for reconstitution with an appropriate vehicle just before use. The term “milk” is sometimes used for suspensions in aqueous vehicles intended for oral administration (e.g., *Milk of Magnesia*). The term “magma” is often used to describe suspensions of inorganic solids, such as clays in water, that display a tendency toward strong hydration and aggregation of the solid, giving rise to gel-like consistency and thixotropic rheological behavior (e.g., *Bentonite Magma*). The term “lotion” may refer to a suspension dosage although the liquid phase in these preparations is commonly an emulsion intended for application to the skin (e.g., *Calamine Topical Suspension*; see *Emulsions*). Some suspensions are prepared in sterile form and are used as injectables (see *Injections* (1)). Other sterile suspensions are for ophthalmic or otic administration. Suspensions generally are not injected intravenously, epidurally, or intrathecally unless the product labeling clearly specifies these routes of administration.

Limited aqueous solubility of the API(s) is the most common rationale for developing a suspension. Other potential advantages of a suspension include taste masking and improved patient compliance because of the more convenient dosage form. When compared to solutions, suspensions have improved chemical stability. Ideally, a suspension should contain small uniform particles that are readily suspended and easily re-dispersed following settling. Unless the dispersed solid is colloidal, the particulate matter in a suspension likely will settle to the bottom of the container upon standing. Such sedimentation may lead to caking and solidification of the

sediment and difficulty in re-dispersing the suspension upon agitation. To prevent such problems, manufacturers commonly add ingredients to increase viscosity and the gel state of the suspension or flocculation, including clays, surfactants, polyols, polymers, or sugars. Frequently, thixotropic vehicles are employed to counter particle-settling tendencies, but these vehicles must not interfere with pouring or re-dispersal. Additionally, the density of the dispersed phase and continuous phase may be modified to further control settling rate. For topical suspensions, rapid drying upon application is desirable.

The product is both chemically and physically stable throughout its shelf life. Temperature can influence the viscosity (and thus suspension properties and the ease of removing the dose from the bottle), and temperature cycling can lead to changes in the particle size of the dispersed phase via Ostwald ripening. When manufacturers conduct stability studies to establish product shelf life and storage conditions, they should cycle conditions (freeze/thaw) to investigate temperature effects.

All suspensions contain suitable antimicrobial agents to protect against bacterial, yeast, and mold contamination (see *Antimicrobial Effectiveness Testing* (51)).

Suspensions for reconstitution are dry powder or granular mixtures that require the addition of water or a supplied formulated diluent before administration. This formulation approach is frequently used when the chemical or physical stability of the API or suspension does not allow sufficient shelf life for a preformulated suspension. Typically, these suspensions are refrigerated after reconstitution to increase their shelf life. For this type of suspension, the powder blend is uniform and the powder readily disperses when reconstituted. Taste of the reconstituted suspension is also an important attribute because many suspensions are used for pediatric populations.

Injectable suspensions generally are intended for either subcutaneous or intramuscular routes of administration and should have a controlled particle size, typically in

the range of 5  $\mu\text{m}$  or smaller. The rationale for the development of injectable suspensions includes poor API solubility, improved chemical stability, prolonged duration of action, and avoidance of first-pass metabolism. Care is needed in selecting the sterilization technique because it may affect product stability or alter the physical properties of the material.

#### PREPARATION

Suspensions are prepared by adding suspending agents or other excipients and purified water or oil to solid APIs and mixing to achieve uniformity. In the preparation of a suspension, the characteristics of both the dispersed phase and the dispersion medium should be considered. During development manufacturers should define an appropriate particle size distribution for the suspended material to minimize the likelihood of particle size changes during storage.

In some instances the dispersed phase has an affinity for the vehicle and is readily wetted upon its addition. For some materials the displacement of air from the solid surface is difficult, and the solid particles may clump together or float on top of the vehicle. In the latter case, a wetting agent is used to facilitate displacement of air from the powder surface. Surfactants, alcohol, glycerin, and other hydrophilic liquids can be employed as wetting agents when an aqueous vehicle will be used as the dispersion phase. These agents function by displacing the air in the crevices of the particles and dispersing the particles. In the large-scale preparation of suspensions, wetting of the dispersed phase may be aided by the use of high-energy mixing equipment such as colloid mills or other rotor–stator mixing devices.

After the powder has been wetted, the dispersion medium (containing the soluble formulation components such as colorants, flavorings, and preservatives) is added in portions to the powder, and the mixture is thoroughly

blended before subsequent additions of the vehicle. A portion of the vehicle is used to wash the mixing equipment free of suspended material, and this portion is used to bring the suspension to final volume and ensure that the suspension contains the desired concentration of solid matter. The final product may be passed through a colloid mill or other blender or mixing device to ensure uniformity. When appropriate, preservatives are included in the formulation of suspensions to protect against bacterial and mold contamination.

Suspensions are shaken before the dose is dispensed. Because of the viscosity of many suspension vehicles, air entrainment may occur during dosing. The formulation process allows evaluation of this possibility; adjustments in vehicle viscosity or the incorporation of low levels of antifoaming agents are common approaches to minimize air entrainment. Alternatively, specific instructions for shaking the formulation may be provided to minimize air incorporation and ensure accurate dosing.

#### PACKAGING AND STORAGE

Individual monographs specify the packaging and storage requirements for suspension products. Typically, the monograph will indicate a container type such as tight, well-closed, or light-resistant and may indicate storage conditions such as controlled room temperature. For additional information about meeting packaging requirements listed in the individual monographs, refer to *Containers—Glass* (660), *Containers—Plastic* (661), *Containers—Performance Testing* (671), *Good Packaging Practices* (1177), and the *General Notices* for statements about preservation, packaging, storage, and labeling.

Acceptable suspension of the particulate phase depends on the particle size of the dispersed phase as well as the viscosity and density of the vehicle. Clear instruction is provided regarding the appropriate storage tem-

perature for the product because temperature can influence the viscosity and density (that affect suspension properties and the ease of removal of the dose from the bottle), and temperature cycling can lead to changes in particle size of the dispersed phase. Suspensions require storage in tight containers. Avoid freezing.

#### LABELING AND USE

Instructions to ensure proper dosing and administration must accompany the product. When labeling a suspension, consider any air that might be entrained in the preparation as a result of shaking, and avoid such entrainment. Compounded suspensions should indicate a beyond-use date that is calculated from the time of compounding. Suspensions are shaken well before use to ensure uniform distribution of the solid in the vehicles.

#### Tablets

Tablets are solid dosage forms in which the API is blended with excipients and compressed into the final dosage. Tablets are the most widely used dosage form in the U.S. Tablet presses use steel punches and dies to prepare compacted tablets by the application of high pressures to powder blends or granulations. Tablets can be produced in a wide variety of sizes, shapes, and surface markings. Capsule-shaped tablets are commonly referred to as caplets. Specialized tablet presses may be used to produce tablets with multiple layers or with specially formulated core tablets placed in the interior of the final dosage form. These specialized tablet presentations can delay or extend the release of the API(s) or physically separate incompatible APIs. Tablets may be coated by a variety of techniques to provide taste masking, protection of photo-labile API(s), prolonged or delayed release, or unique appearance (colors). When no deliberate effort has been made to modify the API release rate, tablets are referred to as immediate-release.

**Tablet Triturates**—Small, usually cylindrical, molded or compacted tablets. Tablet triturates traditionally were used as dispensing tablets in order to provide a convenient, measured quantity of a potent API for compounding purposes, but they are rarely used today.

**Hypodermic Tablets**—Molded tablets made from completely and readily water-soluble ingredients; formerly intended for use in making preparations for hypodermic injection. They may be administered orally or sublingually when rapid API availability is required, as in the case of *Nitroglycerin Sublingual Tablets*.

**Bolus Tablets**—Large, usually elongated, tablets intended for administration to large animals. Conventional tableting processes can be used to manufacture bolus tablets, but due to their size higher compression forces may be necessary.

**Buccal Tablets**—Intended to be inserted in the buccal pouch, where the API is absorbed directly through the oral mucosa. Few APIs are readily absorbed in this way (examples are nitroglycerin and certain steroid hormones).

**Effervescent Tablets**—Prepared by compaction and contain, in addition to the API(s), mixtures of acids (e.g., citric acid or tartaric acid) and carbonates and/or hydrogen carbonates. Upon contact with water, these formulations release carbon dioxide, producing the characteristic effervescent action.

**Hard and Soft Chewable Tablets**—Formulated and manufactured to produce a pleasant-tasting residue in the mouth and to facilitate swallowing. Hard chewable tablets are prepared by compaction, usually utilizing mannitol, sorbitol, or sucrose as binders and fillers, and contain colors and flavors to enhance their appearance and taste. Some chewable tablets may be swallowed without compromising delivery of the API. Chewable tablets are clearly labeled to indicate whether chewing is necessary to ensure reliable release of the API(s). Hard chewable tablets in veterinary medicine often have flavor

enhancers like brewers yeast or meat/fish-based flavors. Soft chewable tablets are made by a molding or extrusion process, frequently with more than 10% water to help maintain a pliable, soft product.

**Orally Disintegrating Tablets**—Intended to disintegrate rapidly within the mouth to provide a fine dispersion before the patient swallows the resulting suspension. Some of these dosage forms have been formulated to facilitate rapid disintegration and are manufactured by conventional means or by using lyophilization or molding processes.

**Sublingual Tablets**—Intended to be inserted beneath the tongue, where the API is absorbed directly through the oral mucosa. As with buccal tablets, few APIs are extensively absorbed in this way, and much of the API is swallowed and is available for gastrointestinal absorption.

#### PREPARATION

Most compacted (compressed) tablets consist of the API(s) and a number of excipients. These excipients may include fillers (diluent), binders, disintegrating agents, lubricants, and glidants. Approved FD&C and D&C dyes or lakes, flavors, and sweetening agents also may be present.

Fillers or diluents are added when the quantity of API(s) is too small or the properties of the API do not allow satisfactory compaction in the absence of other ingredients. Binders impart adhesiveness to the powder blend and promote tablet formation and maintenance of API uniformity in the tableting mixture. Disintegrating agents facilitate reduction of the tablet into small particles upon contact with water or biological fluids. Lubricants reduce friction during the compaction and ejection cycles. Glidants improve powder fluidity, powder handling proper-

ties, and tablet weight control. Colorants are often added to tablet formulations for esthetic value or for product identification.

Tablets are prepared from formulations that have been processed by one of three general methods: wet granulation, dry granulation (roll compaction or slugging), and direct compression.

**Wet Granulation**—Involves the mixing of dry powders with a granulating liquid to form a moist granular mass that is dried and sized prior to compression. It is particularly useful in achieving uniform blends of low-dose APIs and facilitating the wetting and dissolution of poorly soluble, hydrophobic APIs.

**Dry Granulations**—Can be produced by passing powders between rollers at elevated pressure (roll compaction). Alternatively, dry granulation also can be carried out by the compaction of powders at high pressures on tablet presses, a process also known as slugging. In either case the compacts are sized before compression. Dry granulation improves the flow and handling properties of the powder formulation without involving moisture in the processing.

**Direct Compression**—Tablet processing involves dry blending of the API(s) and excipients followed by compression. The simplest manufacturing technique, direct compression is acceptable only when the API and excipients possess acceptable flow and compression properties without prior process steps.

Tablets may be coated to protect the ingredients from air, moisture, or light; to mask unpleasant tastes and odors; to improve tablet appearance; and to reduce dustiness. In addition, coating may be used to protect the API from acidic pH values associated with gastric fluids or to control the rate of drug release in the gastrointestinal tract.

The most common coating in use today is a thin film coating composed of a polymer that is derived from cellulose. Sugar coating is an alternative, less common ap-

proach. Sugar-coated tablets have considerably thicker coatings that are primarily sucrose with a number of inorganic diluents. A variety of film-coating polymers are available and enable the development of specialized release profiles. These formulations are employed to protect acid-labile APIs from the acidic stomach environment as well as to prolong the release of the API to reduce dosing frequency (see *Dissolution* <711> or *Disintegration* <701>).

#### PACKAGING, STORAGE, AND LABELING

Individual monographs specify the packaging and storage requirements for tablet products. Typically, the monograph will indicate the container type such as tight, well-closed, or light-resistant. For additional information on meeting USP packaging requirements see *Containers—Glass* <660>, *Containers—Plastic* <661> and *Containers—Performance Testing* <671>. Effervescent tablets are stored in tightly closed containers or moisture-proof packs and are labeled to indicate that they should not be swallowed directly.

#### Tapes

A tape is a dosage form suitable for delivering APIs to the skin. It consists of an API(s) impregnated into a durable yet flexible woven fabric or extruded synthetic material that is coated with an adhesive agent. Typically the impregnated API is present in the dry state. The adhesive layer is designed to hold the tape securely in place without the aid of additional bandaging. Unlike transdermal patches, tapes are not designed to control the release rate of the API.

The API content of tapes is expressed as amount per surface area with respect to the tape surface exposed to the skin. The use of an occlusive dressing with the tape

enhances the rate and extent of delivery of the API to deeper layers of the skin and may result in greater systemic absorption of the API.

#### LABELING, STORAGE, AND USE

Label to indicate “External Use Only”. Tapes are stored in tight containers protected from light and moisture. To employ the tape, one cuts a patch slightly larger than the area that will be treated. The backing paper is removed from the adhesive side, and the tape is applied to the skin. To ensure optimal adhesion, the tape should not be applied to folds in the skin. To minimize systemic absorption and to ensure good adhesion, tapes should be applied to dry skin.

#### GLOSSARY

This glossary provides definitions for terms in use in medicine and serves as a source of official names for official articles. Examples of general nomenclature forms for the more frequently encountered categories of dosage forms appear in *Nomenclature* (1121). In an attempt to be comprehensive, this glossary was compiled without the limits imposed by current preferred nomenclature conventions. To clearly identify/distinguish preferred from not preferred terms, entries indicate when a term is not preferred and direct the user to the current preferred term. When a term is described as an attribute of a dosage form, it should not be used in the official name for the dosage form.

**AEROSOL:** A dosage form consisting of a liquid or solid preparation packaged under pressure and intended for administration as a fine mist. The descriptive term aerosol also refers to the fine mist of small droplets or solid particles that are emitted from the product.

**AROMATIC WATER (NOT PREFERRED; see *Solution*):** A clear, saturated, aqueous solution of volatile oils or other aromatic or volatile substances.

**AURAL (Auricular) (NOT PREFERRED; see *Otic*):** For administration into, or by way of, the ear.

**BEAD (NOT PREFERRED; see *Pellets*):** A solid dosage form in the shape of a small sphere. In most products a unit dose consists of multiple beads.

**BLOCKS:** A large veterinary product intended to be licked by animals and containing the API(s) and nutrients such as salts, vitamins, and minerals.

**BOLUS (NOT PREFERRED; see *Tablet*):** A large tablet intended for administration to large animals.

**CAPLET (NOT PREFERRED; see *Tablet*):** Tablet dosage form in the shape of a capsule.

**CAPSULE:** A solid dosage form in which the API, with or without other ingredients, is filled into either a hard or soft shell. Most capsule shells are composed mainly of gelatin.

**CHEWABLE:** Attribute of a solid dosage form that is intended to be chewed before swallowing.

**COATED:** Attribute of a solid dosage form that is covered by deposition of an outer solid that is different in composition from the core material.

**COLLODION (NOT PREFERRED; see *Solution*):** A preparation that is a solution dosage form composed of pyroxilin dissolved in a solvent mixture of alcohol and ether and applied externally.

**COLLOIDAL DISPERSION:** A system in which particles of colloidal dimension (i.e., typically between 1 nm and 1  $\mu$ m) are distributed uniformly throughout a liquid.

**CONCENTRATE:** A liquid or solid preparation of higher concentration and smaller volume than the final dosage form; usually intended to be diluted prior to administration. The term continues to be used for veterinary preparations but is being phased out of *USP–NF* titles for human applications.

CONVENTIONAL-RELEASE (NOT PREFERRED; see *Immediate-Release*): Descriptive term for a dosage form in which no deliberate effort has been made to modify the release rate of the API. In the case of capsules and tablets, the inclusion or exclusion of a disintegrating agent is not interpreted as a modification.

CREAM: An emulsion dosage form often containing more than 20% water and volatiles or containing less than 50% hydrocarbons, waxes, or polyols as the vehicle for the API. Creams are generally intended for external application to the skin or mucous membranes.

DELAYED-RELEASE: A type of modified-release dosage form. A descriptive term for a dosage form deliberately modified to delay release of the API for some period of time after initial administration. Release of the API is prevented in the gastric environment but promoted in the intestinal environment; this term is synonymous with *Enteric-Coated* or *Gastro-Resistant*.

DENTAL: Descriptive term for a preparation that is applied to the teeth and/or gums for localized action.

DERMAL: Route of administration to the skin surface.

DOSAGE FORM: A formulation of the API(s) and excipients in quantities and physical form designed to allow the accurate and efficient administration of the API to the human or animal patient.

DRY POWDER INHALER: A dosage form consisting of a mixture of the API(s) and carrier; all components exist in a finely divided solid state that is mobilized into a fine mist upon the oral inhalation by the patient.

EFFERVESCENT: Attribute of an oral dosage form, frequently tablets or granules, containing ingredients that, when in contact with water, rapidly release carbon dioxide. The dosage form is dissolved or dispersed in water to initiate the effervescence prior to ingestion.

ELIXIR (NOT PREFERRED; see *Solution*): A preparation that typically is a clear, flavored, sweetened hydroalcoholic solution intended for oral use. The term is no longer used in *USP–NF* but is commonly encountered in compounding pharmacy practice.

EMOLLIENT: Attribute of a cream or ointment indicating an increase in the moisture content of the skin following application of bland, fatty, or oleaginous substances.

EMULSION: A dosage form consisting of a two-phase system composed of at least two immiscible liquids, one of which is dispersed as droplets (internal or dispersed phase) within the other liquid (external or continuous phase), generally stabilized with one or more emulsifying agents. Emulsion is not used as a dosage form term if a more specific term is applicable (e.g., *Cream*, *Lotion*, or *Ointment*).

ENTERIC-COATED (NOT PREFERRED; see *Delayed-Release*): Descriptive term for a solid dosage form in which a polymer coating has been applied to prevent the release of the API in the gastric environment.

EXCIPIENT: An ingredient of a dosage form other than an API.

EXTENDED-RELEASE: Descriptive term for a dosage form that is deliberately modified to protract the release rate of the API compared to that observed for an immediate-release dosage form. The term is synonymous with prolonged- or sustained-release. Many extended-release dosage forms have a pattern of release that begins with a “burst effect” that mimics an immediate release followed by a slower release of the remaining API in the dosage form.

FEED ADDITIVE: A preparation used in veterinary medicine that is mixed with an animal’s food or water to deliver the API. Three types exist: type A medicated article, type B medicated feed, and type C medicated

feed. Only type C medicated feed preparations contain the API(s) in concentrations appropriate for administration directly to animals.

**FILM:** A term used to describe a thin, flexible sheet of material, usually composed of a polymer in an amorphous state. Films are applied to solid dosages for taste masking, product identification, and aesthetic purposes. Films also are employed as a means of oral administration of material in a rapidly dissolving form.

**FOAM:** An emulsion dosage form containing dispersed gas bubbles. When dispensed it has a fluffy, semisolid consistency.

**GAS:** One of the states of matter having no definite shape or volume and occupying the entire container when confined.

**GASTRO-RESISTANT (NOT PREFERRED; see *Delayed-Release*):** Descriptive term for a solid dosage form in which a polymer coating has been applied to prevent the release in the gastric environment.

**GEL:** A dosage form that is a semisolid dispersion of small inorganic particles or a solution of large organic molecules containing a gelling agent to provide stiffness. A gel may contain suspended particles.

**GRANULES (NOT PREFERRED):** A dosage form composed of dry aggregates of powder particles that may contain one or more APIs, with or without other ingredients. They may be swallowed as such, dispersed in food, or dissolved in water. Granules are frequently compacted into tablets or filled into capsules, with or without additional ingredients.

**GUM:** A dosage form in which the base consists of a pliable material that, when chewed, releases the API into the oral cavity.

**HARD-SHELL CAPSULE (NOT PREFERRED; see *Capsules*):** A type of capsule in which one or more APIs, with or without other ingredients, are filled into a two-piece

shell. Most hard-shell capsules are composed mainly of gelatin and are fabricated prior to the filling operation.

**IMMEDIATE-RELEASE:** Descriptive term for a dosage form in which no deliberate effort has been made to modify the API release rate. In the case of capsules and tablets, the inclusion or exclusion of a disintegrating agent is not interpreted as a modification.

**IMPLANT:** A dosage form that is a solid or semisolid material containing the API, that is inserted into the body. The insertion process is invasive, and the material is intended to reside at the site for a period consistent with the design release kinetics or profile of the API(s).

**INHALATION (BY INHALATION):** A route of administration for aerosols characterized by dispersion of the API into the airways during inspiration.

**BY INJECTION:** A route of administration of a liquid or semisolid deposited into a body cavity, fluid, or tissue by use of a needle.

**INSERT:** A solid dosage form that is inserted into a body cavity other than the rectum. A suppository is an insert intended for application to the rectum (see *Suppository*).

**INTRAOCULAR:** A route of administration (by injection) for a sterile liquid within the eye.

**IRRIGATION:** A sterile solution or liquid intended to bathe or flush open wounds or body cavities.

**JELLY (NOT PREFERRED; see *Gel*):** A semisolid dispersion of small inorganic particles or a solution of large organic molecules containing a gelling agent to promote stiffness.

**LIQUID:** A dosage form consisting of a pure chemical in its liquid state. This dosage form term should not be applied to solutions. The term is not used in article names. When liquid is used as a descriptive term, it indicates a material that is pourable and conforms to its container at room temperature.

**LOTION:** An emulsion liquid dosage form applied to the outer surface of the body. Historically, this term has also been applied to suspensions and solutions.

**LOZENGE:** A solid dosage form intended to disintegrate or dissolve slowly in the mouth.

**MODIFIED-RELEASE:** A descriptive term for a dosage form with an API release pattern that has been deliberately changed from that observed for the immediate-release dosage form of the same API.

**MOLDED TABLET (NOT PREFERRED; see *Tablet*):** A tablet that has been formed by dampening the ingredients and pressing into a mold, then removing and drying the resulting solid mass.

**MOUTHWASH (NOT PREFERRED; see *Solution*):** Term applied to a solution preparation used to rinse the oral cavity.

**NASAL:** Route of administration (mucosal) characterized by deposition in the nasal cavity for local or systemic effect.

**OCULAR (NOT PREFERRED; see *Intraocular*):** Route of administration (by injection) indicating deposition of the API within the eye.

**OINTMENT:** A semisolid dosage form, usually containing less than 20% water and volatiles and more than 50% hydrocarbons, waxes, or polyols as the vehicle. This dosage form generally is for external application to the skin or mucous membranes.

**OPHTHALMIC:** A route of administration (mucosal) characterized by application of sterile preparation to the external parts of the eye.

**ORAL:** A route of administration (gastro-intestinal) characterized by deposition of a preparation into the mouth for absorption or action in the digestive tract.

**ORALLY DISINTEGRATING:** A descriptive term for a solid oral dosage form that disintegrates rapidly in the mouth.

**ORO-PHARYNGEAL:** A route of administration characterized by deposition of a preparation into the buccal cavity and/or pharyngeal region to exert a local or systemic effect.

**OTIC:** A route of administration (mucosal) characterized by deposition of a preparation into, or by way of, the ear. Sometimes referred to as *Aural* (*Aural* NOT PREFERRED).

**PASTE:** A semisolid dosage form containing a high percentage of finely dispersed solids with a stiff consistency. This dosage form is intended for application to the skin, oral cavity, or mucous membranes.

**PELLET:** A small solid dosage form of uniform, often spherical, shape. Spherical pellets are sometimes referred to as *Beads* (*Beads* NOT PREFERRED).

**PILL (NOT PREFERRED but frequently incorrectly used to describe a *Tablet*):** A solid spherical pharmaceutical dosage form, usually prepared by a wet massing technique.

**PLASTER:** A semisolid dosage form supplied on a support material for external application. Plasters are applied for prolonged periods to provide protection, support, or occlusion (for macerating action).

**POWDER:** A dosage form composed of a solid or mixture of solids reduced to a finely divided state and intended for internal or external use.

**PROLONGED-RELEASE:** NOT PREFERRED; see *Extended-Release*.

**RECTAL:** A route of administration (mucosal) characterized by deposition into the rectum to provide local or systemic effect.

**RINSE:** A liquid preparation used to cleanse by flushing.

**SEMISOLID:** Attribute of a material characterized by a reduced ability to flow or conform to its container at room temperature. A semisolid does not flow at low shear stress and generally exhibits plastic flow behavior.

**SHAMPOO:** A solution or suspension dosage form used to clean the hair and scalp. May contain an API intended for topical application to the scalp.

**SOAP:** The alkali salt(s) of a fatty acid or mixture of fatty acids used to cleanse the skin. Soaps used as dosage forms may contain an API intended for topical application to the skin. Soaps have also been used as liniments and enemas.

**SOFT GEL CAPSULE (NOT PREFERRED; see *Capsule*):** A specific capsule type characterized by increased levels of plasticizers producing a more pliable and thicker-walled material than hard gelatin capsules. Soft gel capsules are further distinguished because they are single-piece sealed dosages. Frequently used for delivering liquid compositions.

**SOLUTION:** A clear, homogeneous liquid dosage form that contains one or more chemical substances dissolved in a solvent or mixture of mutually miscible solvents.

**SPIRIT (NOT PREFERRED; see *Solution*):** A liquid dosage form composed of an alcoholic or hydroalcoholic solution of volatile substances.

**SPRAY:** Attribute that describes the generation of droplets of a liquid or solution to facilitate application to the intended area.

**STENT, DRUG-ELUTING:** A specialized form of implant used for extended local delivery of the API to the immediate location of stent placement.

**STRIP (NOT PREFERRED; see *Tape*):** A dosage form or device in the shape of a long, narrow, thin solid material.

**SUBLINGUAL:** A route of administration (mucosal) characterized by placement underneath the tongue and for release of the API for absorption in that region.

**SUPPOSITORY:** A solid dosage form in which one or more APIs are dispersed in a suitable base and molded or otherwise formed into a suitable shape for insertion into the rectum to provide local or systemic effect.

**SUSPENSION:** A liquid dosage form that consists of solid particles dispersed throughout a liquid phase.

**SYRUP (NOT PREFERRED; see *Solution*):** A solution containing high concentrations of sucrose or other sugars. This term is commonly used in compounding pharmacy.

**TABLET:** A solid dosage form prepared from powders or granules by compaction.

**TAPE, MEDICATED:** A dosage form or device composed of a woven fabric or synthetic material onto which an API is placed, usually with an adhesive on one or both sides to facilitate topical application.

**TINCTURE (NOT PREFERRED; see *Solution*):** An alcoholic or hydroalcoholic solution prepared from vegetable materials or from chemical substances.

**TOPICAL:** A route of administration characterized by application to the outer surface of the body.

**TROCHE (NOT PREFERRED; see *Lozenge*):** A solid dosage form intended to disintegrate or dissolve slowly in the mouth and usually prepared by compaction in a manner similar to that used for tablets.

URETHRAL: A route of administration (mucosal) characterized by deposition into the urethra.

VAGINAL: A route of administration (mucosal) characterized by deposition into the vagina.

VEHICLE: A term commonly encountered in compounding pharmacy that refers to a component for internal or external use that is used as a carrier or diluent in which liquids, semisolids, or solids are dissolved or suspended. Examples include water, syrups, elixirs, oleaginous liquids, solid and semisolid carriers, and proprietary products (see *Excipient*).

VETERINARY: Descriptive term for dosage forms intended for nonhuman use. ■<sub>2S</sub> (USP33)

**Change to read:**

## INTRODUCTION

Water is widely used as a raw material, ingredient, and solvent in the processing, formulation, and manufacture of pharmaceutical products, active pharmaceutical ingredients (APIs) and intermediates, compendial articles, and analytical reagents. This general information chapter provides additional information about water, its quality attributes that are not included within a water monograph, processing techniques that can be used to improve water quality, and a description of minimum water quality standards that should be considered when selecting a water source.

This information chapter is not intended to replace existing regulations or guides that already exist to cover USA and International (ICH or WHO) GMP issues, engineering guides, or other regulatory (FDA, EPA, or WHO) guidances for water. The contents will help users to better understand pharmaceutical water issues and some of the microbiological and chemical concerns unique to water. This chapter is not an all-inclusive writing on pharmaceutical waters. It contains points that are basic information to be considered, when appropriate, for the processing, holding, and use of water. It is the user's responsibility to assure that pharmaceutical water and its production meet applicable governmental regulations, guidances, and the compendial specifications for the types of water used in compendial articles.

Control of the chemical purity of these waters is important and is the main purpose of the monographs in this compendium. Unlike other official articles, the bulk water monographs (*Purified Water* and *Water for Injection*) also limit how the article can be produced because of the belief that the nature and robustness of the purification process is directly related to the resulting purity. The chemical attributes listed in these monographs should be considered as a set of minimum specifications. More stringent specifications may be needed for some applications to ensure suitability for particular uses. Basic guidance on the appropriate applications of these waters is found in the monographs and is further explained in this chapter.

Control of the microbiological quality of water is important for many of its uses. ~~At~~

■**Most** ■<sub>2S</sub> (USP33)

## BRIEFING

⟨1231⟩ **Water for Pharmaceutical Purposes**, USP 32 page 741. Although the majority of water used for production is *Purified Water* and *Water for Injection* that is produced on site (referred to as "bulk water"), the Pharmaceutical Waters Expert Committee recognizes the need for and the use of commercially available "packaged" *Purified Water* and *Water for Injection* in some production environments. In addition, there are sterile waters such as *Sterile Purified Water* and *Sterile Water for Injection* (and *Inhalation* and *Irrigation*). As the tests and limits for these various types of waters have been updated in recent years, some of the terminology regarding "bulk", "sterile", and "packaged" needs to be updated and/or clarified. The proposed remedy is to distinguish between "bulk" water, "sterile" water, and "packaged bulk" water in the relevant monographs and general chapters. The term "packaged waters" has been used as a substitute for "sterile waters" and as a term to describe commercially available packages of *Purified Water* and *Water for Injection*. The Pharmaceutical Waters Expert Committee proposes that the term "packaged waters" be used for the packaged form of bulk *Purified Water* and *Water for Injection* that has been produced elsewhere. Requirements for packaged waters are contained in the *Purified Water* and *Water for Injection* monographs. Sterile waters, although they are also packaged articles, have their own unique monographs and uses. The Expert Committee is discouraging the use of the term "packaged water" to mean "sterile water".

There are companion changes in *Water Conductivity* ⟨645⟩ and the monographs for *Sterile Purified Water*, *Sterile Water for Injection*, *Sterile Water for Inhalation*, and *Sterile Water for Irrigation*. All changes align the use of these terms.

(PW: A. Hernandez-Cardoso.)     RTS—C76228