maceutical preparations, which are given elsewhere in this Pharmacopeia.

Change to read:

⟨1151⟩ PHARMACEUTICAL DOSAGE FORMS

▲GENERAL CONSIDERATIONS

This chapter provides general descriptions of and definitions for drug products, or dosage forms, commonly used to administer the 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 API and often 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.[1] 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 (see *Figure 1*).[2] 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.

Dose Uniformity (see also *Uniformity of Dosage Units* ⟨905⟩)—Consistency in dosing for a patient or consumer requires that the variation in the API 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 API 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 API in the blend is presumed to be uniform and well-controlled, as in solutions. In such cases the content of API 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. Successful development and manufacture of dosage forms requires careful evaluation of API 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 API in the dosage 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. For the example of tablets, capsules, and oral suspensions, 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 API, 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. With proper justification, in vitro release (e.g., disintegration and dissolution) testing may sometimes be 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. 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, gastrointestinal, parenteral (by injection), inhalation, and topical/dermal, and each has subcategories as needed. Many tests used 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 Tests* ⟨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 certain 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 droplet 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.

Excess Volume in Injections—Each container of an Injection is filled with a volume in slight excess of the labeled "size" or the volume that is to be withdrawn. The excess

[1] 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 packaging 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."

[2] 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.

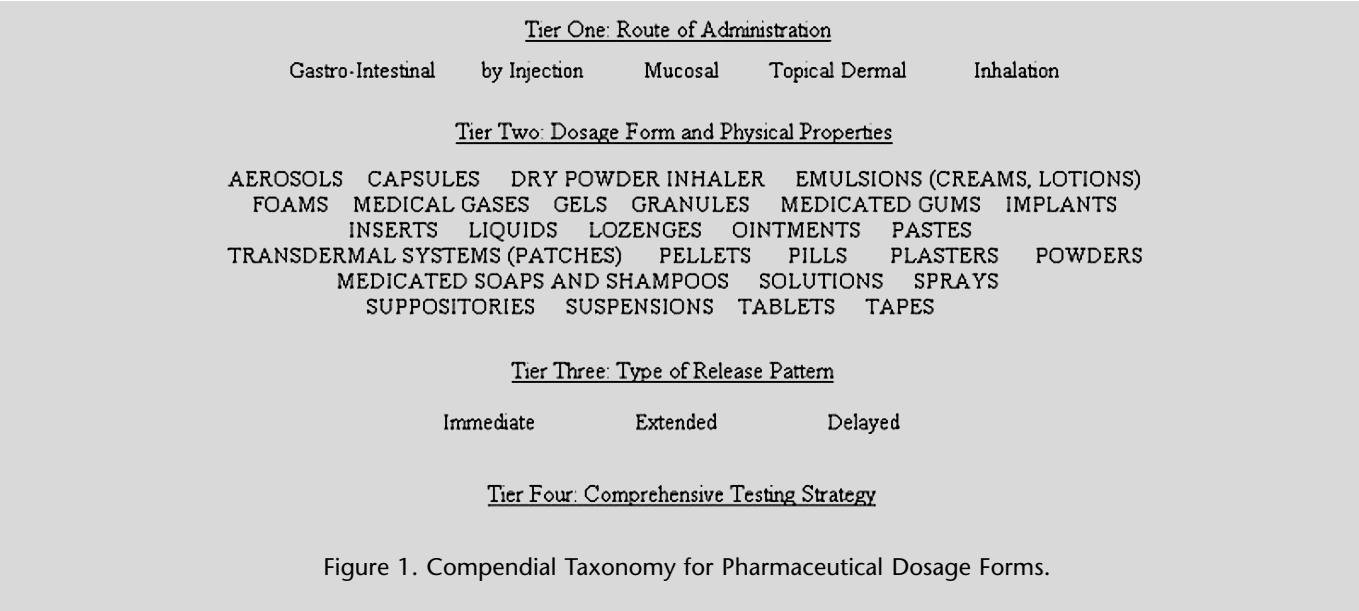

Figure 1. Compendial Taxonomy for Pharmaceutical Dosage Forms.

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%

Labeling Statements—Some dosage forms or articles have mandatory labeling statements that are given in the Code of Federal Regulations (e.g., 21 CFR 201.320 and 21 CFR 369.21). The text of 21 CFR should be consulted to determine the current recommendations.

PRODUCT QUALITY TESTS, GENERAL

ICH Guidance Q6A (available at 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 API(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 API(s) 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 API(s). 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 some cases, testing for heavy metal impurities is appropriate. *Heavy Metals* ⟨231⟩ provides the current procedures and criteria.

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* in the section *General Considerations* 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 Content—If antioxidants are present in the drug product, tests of their content should be performed to maintain the product's quality at all stages throughout its proposed usage and shelf life.

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

Dissolution—A test to measure release of the API(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⟩).

Breaking Force 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⟩).

Leachables—When evidence exists that leachables 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 leachables.

Other Tests—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, delivered dose uniformity, viscosity, 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 actuation of an appropriate valve system. Upon actuation of the valve system, the API is released as a plume of fine particles or droplets. Only one dose is released from the preparation upon actuation of a metered valve. In the case of topical products and depending on the nature of the API and the conditions being treated, actuation of the valve may result in a metered release of a controlled amount of the formulation or the continuous release of the formulation as long as the valve is depressed.

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 actuated (see *Glossary*). Other products that produce dispersions of fine droplets or particles will be covered in subsequent sections (e.g., *Inhalation Powders* and *Sprays*).

TYPICAL COMPONENTS

Typical components of aerosols are the formulation containing one or more API(s) 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 actuator directs the metered volume to a small orifice that is open to the atmosphere. Upon actuation, 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 API(s) dissolved in liquefied propellant. Co-solvents such as alcohol may be added to enhance the solubility of the API(s). Three-phase inhalation and nasal aerosol systems consist of suspended API(s) in propellant(s), co-solvents, and potentially other suitable excipients. The suspension or emulsion of the finely divided API 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 used as propellants.

Metal containers can withstand the vapor pressure produced by the propellant. 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 container, actuator, and metering valve, as well as the formulation, are designed to target the site of administration.

Inhalation aerosols, commonly known as metered-dose inhalers (MDIs), 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 is intended to release measured mass and appropriate quality of the active substance with each actuation.

Nasal aerosols, commonly known as nasal MDIs, produce fine particles or droplets for delivery through the nasal vestibule and deposition in the nasal cavity. Each actuation of the valve releases measured mass and appropriate quality of the active substance.

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

Topical aerosols produce fine particles or droplets for application to the skin.

Topical aerosol drug products may be designed, as needed, to deliver a metered amount of formulation upon actuation of the designed valve or continuous release of formulation during depressed status of the valve.

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

Refer to 21 CFR 201.320 and 21 CFR 369.21.

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. When no deliberate effort has been made to modify the API release rate, capsules are referred to as immediate-release.

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. There are two categories of modified-release capsule formulations recognized by the Pharmacopeia:

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.

Extended-Release Capsules—Extended-release capsules are formulated in such a manner as to make the contained API available over an extended period of time following ingestion. Expressions such as "prolonged-action", "repeat-action", "controlled-release", and "sustained-release" have also been used to describe such dosage forms. However, the term, extended-release, is used for Pharmacopeial purposes. Requirements for dissolution (see *Dissolution* ⟨711⟩) typically are specified in the individual monograph.

Methods for modifying API release from capsules include coating the filled capsule shells or the contents in the case of dry-filled capsules.

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[3] or various pigments, opaquing agents such as titanium dioxide, dispersing agents, plasticizers, and preservatives. Gelatin capsule shells normally contain between 12% and 16% water.

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 a designed locking joint between the cap and body. 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 polyethylene 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.

[3] 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.

Inhalation Powders

Inhalation Powders, commonly known as dry powder inhalers (DPIs), consist of a mixture of API(s) and typically the carrier; and all formulation components exist in a finely divided solid state packaged in a suitable container–closure system. The dose is released from the packaging by a mechanism and is mobilized into a fine dispersion upon oral inhalation by the patient.

TYPICAL COMPONENTS

The basic components of the DPI are the formulation consisting of the API(s) and typically the carrier, both in the dry state. The formulation may be packaged in pre-metered or device-metered units. Pre-metered DPIs contain a previously measured amount of formulation in individual units (e.g., capsules, blisters) that are inserted into the device before use. Pre-metered DPIs may also contain pre-metered dose units as ordered multidose assemblies in the delivery system. Pre-metered DPIs include a mechanism designed to pierce the capsule or open the unit-dose container and allow mobilization and aerosolization of the powder by the patient inhaling through the integral mouthpiece. Device-metered DPI(s) have an internal reservoir that contains a sufficient quantity of formulation for multiple doses that are metered by the device during actuation by the patient. To facilitate dosing compliance, device-metered DPIs incorporate a dosing administration information mechanism, such as a dose counter or a dose indicator system.

PACKAGING

For pre-metered DPIs packaged in blister units, the packs must be designed to allow individual unit 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. The components of the DPI container–closure system typically are made of plastic.

LABELING AND USE

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.

Veterinary Drugs and Drug Products Delivered in Animal Feeds

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

TYPE A MEDICATED ARTICLES

Type A medicated articles consist of a new animal drug(s) with or without a carrier (e.g., calcium carbonate, rice hull, corn, gluten) and with or without inactive ingredients. They 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 paper 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 special 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 used 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 using several methods: nasal cannulas, face masks, atmospheric tents, and endotracheal tubes for the pulmonary route; hyperbaric chambers for the pulmonary and dermal routes of administration; jetted tubes that are directed at dental tissue to promote drying in preparation for fillings and crowns; tubes for expanding the intestines to facilitate medical imaging during colonoscopy; tubes for expanding the pelvis via transuterine inflation in preparation for fallopian tubal ligation; and tubes for expanding angioplasty devices. 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

If required under the individual monograph, label to indicate the 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 are semisolids consisting either of suspensions of small inorganic particles or of organic molecules interpenetrated by a liquid. Jellies are a type of gel that typically have a higher water content. 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*). Gels may be thixotropic, forming semisolids on standing and becoming less viscous on agitation. They should be shaken before use to ensure homogeneity and should be so labeled.

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 can be used in veterinary medicine to treat mastitis.

PREPARATION

See *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩ for general procedures. Also see the information contained under *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 as granules or as suspensions, 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 reconstituted 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 dosage forms 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 binding solution, 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 two 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, and flavor; and for suspensions, to provide 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 course 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 two 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 thoroughly mixed or 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 often 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. API release from pellets for periods of six 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 API 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 micro-

spheres) generally range from 20 to 100 μm in diameter. They are composed of an API 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 API from the microparticles begins after physiological fluid enters the polymer matrix, dissolving some of the API 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 nonbiodegradable. 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. API 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 API release are two and three months for biodegradable implants and one year for nonbiodegradable implants. An advantage of biodegradable implants is that they do not require removal after release of all API content. Nonbiodegradable polymer implants can be removed before or after API 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 one year or more. Release kinetics are zero order. After the API is delivered, metal-based implants are removed.

API-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 nonbiodegradable 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 naturally occurring (nonsurgical) body cavity other than the mouth or 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 eight 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 used 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.

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. 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 medicaments, 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 homogenous 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*) 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 commonly used as a base for ophthalmic APIs. 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 API 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), an API 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 electric 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 sometimes 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 multilaminate 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, multiple pellets may be implanted in the ears of 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 710 μm to 2.36 mm. 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 extended 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 usually prepared by a wet massing and molding technique, while tablets are typically 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 *Inhalation Powders*). 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 µm or less (typically in the 50- to 100-µm 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 Fineness* ⟨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 individual 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".

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, two 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 preparation that contains one or more dissolved chemical substances in a suitable solvent or mixture of mutually miscible solvents. Because molecules of an API 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 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

Spray preparations may deliver either accurately metered or nonmetered amounts of formulation.

By definition and in accordance with the USP drug product monographs, a spray dosage form drug product delivers an accurately metered spray through the delivery system, i.e., device. A spray drug product is a preparation that contains an API(s) in either solution or suspension form, typically in presence of excipients for nasal sprays, and that is intended for administration using a predefined metered amount of formulation as a fine mist of aqueous droplets.

Alternatively, nonmetered spray drug products can be generated by package designs that do not accurately control the volume of formulation delivered. These preparations release the formulation as a fine mist of droplets upon physical manipulation 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.

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.

The mechanism for droplet generation and the intended use of the preparation distinguish various classes of sprays. A spray may be composed of a pump, container, actuator, valve, nozzle or mouthpiece in addition to the formulation containing the drug(s), solvent(s), and any excipient(s). The design of each component plays a role for the appropriate performance of the drug product and in determining the critical characteristics of the droplet size distribution. Droplet and particle size distributions, delivered dose uniformity, plume geometry, and droplet velocity are critical parameters that influence the efficiency of drug delivery. When the preparation is supplied as a multidose container, the addition of a suitable antimicrobial preservative may be necessary. Spray formulations intended for nasal or pulmonary administration have an aqueous base and are usually isotonic and may contain excipients to control pH and viscosity. Pulmonary spray preparations typically are solutions. Nasal spray preparations may be solutions, or suspensions intended for local or systemic effect. Nasal delivery may be used for APIs with high hepatic extraction ratios.

PACKAGING

Containers typically are made of a 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

Refer to CDER *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation*.

Many experts recommend the addition of a statement that patients should seek advice and instruction from a health care professional about the proper use of the device. Guidance 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 nonionized form of the API may help maximize bioavailability. Although nonionized 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 nonionic 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 stearates. 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 form 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 redispersed 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 redispersing 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 used to counter particle-settling tendencies, but these vehicles must not interfere with pouring or redispersal. 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.

Unless studies confirm that the formulation will not support microbial growth, suspensions should contain suitable antimicrobial agents to protect against bacterial, yeast, and mold contamination (see *Antimicrobial Effectiveness Testing* ⟨51⟩) or other appropriate measures should be taken to avoid microbial contamination.

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 μm 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 used 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 necessary, 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 temperature 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), extended 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.

Chewable Tablets—Formulated and manufactured to produce a pleasant-tasting residue in the mouth and to facilitate swallowing. Hard chewable tablets are typically prepared by compaction, usually utilizing mannitol, sorbitol, or sucrose as binders and fillers, and contain colors and flavors to enhance their appearance and taste. Soft chewable tablets are typically made by a molding or extrusion process, frequently with more than 10% water to help maintain a pliable, soft product. Hard chewable tablets in veterinary medicine often have flavor enhancers like brewer's yeast or meat/fish-based flavors.

Tablets for human use that include "Chewable" in the title must be chewed or crushed prior to swallowing to ensure reliable release of the API(s) or to facilitate swallowing. If tablets are designed so that they may be chewed (but chewing is not required for API release or ease of swallow-

ing), the title should not include a reference to "chewable". In that case, the product may still be described as "chewable" in the ancillary labeling statement.

Tablets for veterinary use that are intended to be chewed will include "Chewable" in the title. However, it is understood that for veterinary products it is not possible to ensure that tablets are chewed prior to ingestion. Chewable tablets may be broken into pieces and fed to animals that normally swallow treats whole.

Modified-Release Tablets—There are two categories of modified-release tablet formulations recognized by the Pharmacopeia:

Delayed-Release Tablets—Tablets sometimes are formulated with enteric coatings to protect acid-labile APIs from the gastric environment or to prevent adverse events such as irritation.

Extended-Release Tablets—Extended-release tablets are formulated in such a manner as to make the API available over an extended period of time following ingestion. Expressions such as "prolonged-release", "repeat-action", "controlled-release", and "sustained-release" have also been used to describe such dosage forms. However, the term "extended-release" is used for Pharmacopeial purposes. Requirements for dissolution (see *Dissolution* ⟨711⟩) typically are specified in the individual monographs.

Orally Disintegrating Tablets—Orally disintegrating tablets are intended to disintegrate rapidly within the mouth to provide a fine dispersion before the patient swallows the resulting suspension where the API is intended for gastrointestinal delivery and/or absorption. 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. Further details may be found in the CDER *Guidance for Industry: Orally Disintegrating Tablets*.

Sublingual Tablets—Sublingual tablets are 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 (diluents), 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 properties, 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 approach. 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 used 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, except when the definition specifically states that the term is not to be used in article names. 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 is intended to distinguish the term from those used for actual dosage form titles. While attribute terms are typically not used as the official name for the dosage form, when they are used they identify a specialized presentation of the dosage form. For example, the attribute, chewable, may be used with the dosage form term, tablets, to identify a specific type of tablet that must be chewed prior to swallowing.

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 or crushed 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.

Collodial Dispersion: An attribute of a preparation or formulation in which particles of colloidal dimension (i.e., typically between 1 nm and 1 μm) 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. This term is not used in article names.

Cream: An emulsion dosage form often containing more than 20% water and volatiles and/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. For example, 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 for localized action.

Dermal: A topical route of administration where the article is intended to reach or be applied to the dermis.

Dosage Form: A formulation that typically contains 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. This term is not used in article names.

Dry Powder Inhaler: A device used to administer an inhalation powder in a finely divided state suitable for oral inhalation by the patient. This term is not used in article names.

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 should not be used for new articles 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. This term should not be used in article names.

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. This term is not used in article names. The term, excipient, is synonymous with inactive ingredient.

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.

Film: A term used to describe a thin, flexible sheet of material, usually composed of a polymer. Films are used in various routes of administration including as a means of oral administration of material in a rapidly dissolving form. The term, film, also may be used as an attribute when applied to solid oral dosage forms for taste masking, product identification, and aesthetic purposes.

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: 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. This term is not used in article names.

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 naturally occurring (nonsurgical) body cavity other than the mouth or rectum. It should be noted that a suppository is intended for application into the rectum and is not classified as an insert (see *Suppository*).

Intraocular: A route of administration to deliver a sterile preparation 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. This term is not used in article names.

Molded Tablet: A tablet that has been formed by dampening the ingredients and pressing into a mold, then removing and drying the resulting solid mass. This term is not used in article names.

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 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 characterized by application of a sterile preparation to the external parts of the eye.

Orally Disintegrating: A descriptive term for a solid oral dosage form that disintegrates rapidly in the mouth prior to swallowing. The API is intended for gastrointestinal delivery and/or absorption. See also CDER *Guidance for Industry, Orally Disintegrating Tablets*.

Oro-Pharyngeal: A route of administration characterized by deposition of a preparation into the oral 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 (e.g., 20%–50%) of finely dispersed solids with a stiff consistency. This dosage form is intended for application to the skin, oral cavity, or mucous membranes.

Patch (not preferred): Frequently used to describe a *Transdermal System*).

Pellet: A small solid dosage form of uniform, often spherical, shape. Spherical pellets are sometimes referred to as *Beads*. Pellets intended as implants must be sterile.

Periodontal: Descriptive term for a preparation that is applied around a tooth for localized action.

Pill (not preferred but frequently incorrectly used to describe a *Tablet*): A solid spherical pharmaceutical dosage form, usually prepared by a wet massing technique. This term is not used in article names.

Plaster: A dosage form containing a semisolid composition supplied on a support material for external application. Plasters are applied for prolonged periods of time 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.

Powder, Inhalation: A powder containing an API for oral inhalation. The powder is used with a device that aerosolizes and delivers an accurately metered amount.

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.

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. This term is not used in article names.

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.

Transdermal System: Dosage forms designed to deliver the API(s) through the skin into the systemic circulation. Transdermal systems are typically composed of an outer covering (barrier), a drug reservoir (that may incorporate a rate-controlling membrane), a contact adhesive to affix the transdermal system to the administration site, and a protective layer that is removed immediately prior to application of the transdermal system.

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*). This term is not used in article names.

Veterinary: Descriptive term for dosage forms intended for nonhuman use.▲*USP35*

⟨1160⟩ PHARMACEUTICAL CALCULATIONS IN PRESCRIPTION COMPOUNDING

INTRODUCTION

The purpose of this chapter is to provide general information to guide and assist pharmacists in performing the necessary calculations when preparing or compounding any pharmaceutical article (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩, *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, and *Good Compounding Practices* ⟨1075⟩) or when simply dispensing prescriptions (see *Stability Considerations in Dispensing Practice* ⟨1191⟩).

Correct pharmaceutical calculations can be accomplished by using, for example, proper conversions from one measurement system to another and properly placed decimal points, by understanding the arithmetical concepts, and by paying close attention to the details of the calculations. Before proceeding with any calculation, pharmacists should do the following: (a) read the entire formula or prescription carefully; (b) determine which materials are needed; and then (c) select the appropriate methods of preparation and the appropriate calculation.

There are often several ways to solve a given problem. Logical methods that require as few steps as possible should be selected in order to ensure that calculations are done correctly. The best approach is the one that yields results that are accurate and free of error. The pharmacist must double-check each calculation before proceeding with the preparation of the article or prescription order. One way of double-checking is by estimation. This involves rounding off the quantities involved in the calculation, and comparing the estimated result with the calculated value.

Finally, the following steps should be taken: the dosage of each active ingredient in the prescription should be checked; all calculations should be doubly checked, preferably by another pharmacist; and where instruments are used in compounding, they should be carefully checked to ascertain that they will function properly. See *USP* general chapters *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩, *Deliverable Volume* ⟨698⟩, *Density of Solids* ⟨699⟩, *Osmolality and Osmolarity* ⟨785⟩, *pH* ⟨791⟩, *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩, *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, *Viscosity* ⟨911⟩, *Specific Gravity* ⟨841⟩, *Cleaning Glass Apparatus* ⟨1051⟩, *Medicine Dropper* ⟨1101⟩, *Prescription Balances and Volumetric Apparatus* ⟨1176⟩, *Teaspoon* ⟨1221⟩, *Weighing on an Analytical Balance* ⟨1251⟩, and *Good Compounding Practices* ⟨1075⟩ for information on specific instruments.

BASIC MATHEMATICAL CONCEPTS

SIGNIFICANT FIGURES

Expressed values are considered significant to the last digit shown (see *Significant Figures and Tolerances* in the *General Notices*). Significant figures are digits with practical meaning. The accuracy of the determination is implied by the number of figures used in its expression. In some calculations zeros may not be significant. For example, for a measured weight of 0.0298 g, the zeros are not significant; they are used merely to locate the decimal point. In the example, 2980 g, the zero may also be used to indicate the decimal point, in which case the zero is not significant. Alternately, however, the zero may indicate that the weight is