When the test specimen has cooled to about 5° above its expected congealing point, adjust the bath to a temperature 7° to 8° below the expected congealing point. Stir the specimen continuously during the remainder of the test by moving the loop up and down between the top and bottom of the specimen, at a regular rate of 20 complete cycles per minute.

Congelation frequently may be induced by rubbing the inner walls of the test tube with the thermometer, or by introducing a small fragment of the previously congealed substance. Pronounced supercooling may cause deviation from the normal pattern of temperature changes. If the latter occurs, repeat the test, introducing small particles of the material under test in solid form at 1° intervals as the temperature approaches the expected congealing point.

Record the reading of the test tube thermometer every 30 seconds. Continue stirring only so long as the temperature is gradually falling, stopping when the temperature becomes constant or starts to rise slightly. Continue recording the temperature in the test tube every 30 seconds for at least 3 minutes after the temperature again begins to fall after remaining constant.

The average of not less than four consecutive readings that lie within a range of 0.2° constitutes the congealing temperature. These readings lie about a point of inflection or a maximum, in the temperature-time curve, that occurs after the temperature becomes constant or starts to rise and before it again begins to fall. The average to the nearest 0.1° is the congealing temperature.

Add the following:

▲⟨659⟩ PACKAGING AND STORAGE REQUIREMENTS

Every monograph in the *USP* and *NF* shall have packaging and storage requirements. For the packaging portion of the statement, the choice of containers is given in this chapter. For drug product packaging requirements, definitions are provided to guide selection and adaptation. For active pharmaceutical ingredients (APIs), the choice would be tight, well-closed, or, where needed, a light-resistant container. For excipients, given their typical presentation as large-volume commodity items (containers ranging from drums to tank cars), a well-closed container is an appropriate default.

Where no specific directions or limitations are provided in the article's labeling, articles shall be protected from moisture, freezing, and excessive heat, and where necessary, from light during shipping and distribution. Drug substances are exempt from this standard.

PACKAGING

Packaging must not interact physically or chemically with official articles in any way that causes their safety, identity, strength, quality, or purity to fail to conform to requirements. This chapter provides definitions of both packaging and storage.

GENERAL DEFINITIONS

Packaging System (also referred to as a container–closure system)**:** The sum of packaging components that together contains and protects the article. This includes primary packaging components and secondary packaging components, if the latter is intended to provide additional protection.

Container: A receptacle that holds an intermediate compound, active pharmaceutical ingredient, excipient, or dosage form and is in direct contact with the articles.

Packaging Component: Any single part of the package or container–closure system including the container (e.g., ampules, prefilled syringes, vials, bottles); container liners (e.g., tube cartridge liners); closures (e.g., screw caps, stoppers); ferrules and overseals; closure liners; inner seals; administration ports; overwraps; administration accessories; and labels.

Primary Packaging Component: Packaging components that are in direct contact or may become in direct contact with the article.

Secondary Packaging Component: Packaging components that are not and will not be in direct contact with the article but may provide additional protection.

Tertiary Packaging: Packaging components that are not in direct contact with the article but facilitate the handling and transport in order to prevent damage from physical handling and storage conditions to which the article is subjected.

Materials of Construction: Refers to the materials (e.g., glass, plastic, elastomers, metal) used to manufacture a packaging component.

Multiple-Dose (also referred to as multi-dose)**:** A packaging system that permits withdrawal of successive portions of an article for parenteral administration without changing the safety, strength, quality, or purity of the remaining portion. See *Multi-Dose Containers* in *Injections* ⟨1⟩, *Determination of Volume of Injection in Containers*.

Multiple-Unit: A packaging system that permits withdrawal of successive portions of an article without changing the safety, strength, quality, or purity of the remaining portion.

Single-Unit: A packaging system that holds a quantity of an article intended for administration as a single dose or a single finished device intended for single use.

Single-Dose (see also *Injections* ⟨1⟩*, Containers for Injections*)**:** A single-unit package for an article intended for parenteral administration. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-Dose: A single-unit packaging system for an article intended for administration by other than the parenteral route as a single dose.

Unit-of-Use: A packaging system that contains a specific quantity of an article that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. *Unit-of-Use* packaging may not be repackaged for sale.

Pharmacy Bulk Package: A container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes.

After constitution, the closure shall be penetrated only one time with a suitable sterile transfer device or dispensing set that allows measured dispensing of the contents. The *Pharmacy Bulk Package* is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

Designation as a *Pharmacy Bulk Package* is limited to *Injections, for Injection, or Injectable Emulsion* as defined under *Injections* ⟨1⟩*, Nomenclature*.

Pharmacy Bulk Packages, although containing more than one single dose, are exempt from the multiple-dose container volume limit of 30 mL and the requirement that they contain a substance or suitable mixture of substances to

prevent the growth of microorganisms. Where a container is offered as a *Pharmacy Bulk Package*, the label shall (a) state prominently "Pharmacy Bulk Packages—Not for direct infusion," (b) contain or refer to information on proper techniques to help assure safe use of the product, and (c) bear a statement limiting the time frame in which the container may be used once it has been entered, provided it is held under the labeled storage conditions.

Small-Volume Injections: A single-dose injection that is intended for intravenous use and is packaged in containers labeled as containing 100 mL or less.

Large-Volume Injections: A single-dose injection that is intended for intravenous use and is packaged in containers labeled as containing more than 100 mL.

Child-Resistant: A packaging system designed or constructed to meet Consumer Product Safety Commission standards pertaining to opening by children (16 CFR § 1700.20).

Senior-Friendly: A packaging system designed or constructed to meet Consumer Product Safety Commission standards pertaining to opening by senior adults (16 CFR § 1700.20).

Tamper-Evident: A packaging system that may not be accessed without obvious destruction of the seal or some portion of the packaging system.

Tight: A packaging system that protects the articles from contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution. See *Containers—Performance Testing* ⟨671⟩.

Well-Closed: A packaging system that protects the articles from contamination by extraneous solids and liquids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution. See *Containers—Performance Testing* ⟨671⟩.

Light-Resistant: A packaging system that protects from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. A clear and colorless or a translucent container may be made light-resistant by means of an opaque covering or by use of secondary packaging, in which case the label of the container bears a statement that the opaque covering or secondary packaging is needed until the articles are to be used or administered. See *Containers—Performance Testing* ⟨671⟩, *Light Transmission Test.*

MEDICAL GAS PACKAGING

Gas Cylinder: A gas cylinder is a metallic packaging system constructed of steel or aluminum designed to hold medical gases under pressure. Medical gases include Carbon Dioxide USP, Helium USP, Medical Air USP, Nitric Oxide, Nitrous Oxide USP, Nitrogen NF, and Oxygen USP. As a safety measure, for carbon dioxide, cyclopropane, helium, medical air, nitrous oxide, and oxygen, the Pin-Index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

ASSOCIATED COMPONENTS

Many associated components are graduated for dose administration. It is the responsibility of the manufacturer to ensure the appropriate dosing component is provided or a general purpose component, such as those described in this section, is specified for delivering the appropriate dose with the intended accuracy. The graduations should be legible and indelible.

Graduated associated components described in this section are for general use. Graduated markings should be legible, indelible, and on an extraoral nonproduct contact surface. Under ideal conditions of use, the volume error incurred in measuring liquids for individual dose administration by means of such graduated components should be not greater than 10% of the indicated amount of the liquid preparation with which the graduated component will be used. Few liquid preparations have the same surface and flow characteristics. Therefore, the volume delivered varies materially from one preparation to another.

Polymers and ingredients added to polymers that are used in the fabrication of associated components must conform to the requirements in the applicable sections of the Code of Federal Regulations, Title 21, *Indirect Food Additives.*

Dosing Cups: A measuring device consisting of a small cup that is packaged with oral liquid articles or that may be sold and purchased separately.

Dosing Spoon: A measuring device consisting of a bowl and a handle that is packaged with oral liquid articles or that may be sold and purchased separately. The handle may be a graduated tube.

Medicine Dropper: A measuring device consisting of a transparent or translucent barrel or tube that is generally fitted with a collapsible bulb. It is packaged with oral liquid articles or may be sold and purchased separately.

Droppers typically vary in capacity; however, the delivery end should be a round opening having an external diameter of about 3 mm. The barrel may be graduated. [NOTE—Few medicinal liquids have the same surface and flow characteristics as water, and therefore the size of drops varies materially from one preparation to another.]

Oral Syringe: A measuring device consisting of a plunger and barrel made of suitable rigid transparent or translucent plastic material and a seal on the end. It is packaged with oral liquid articles or may be sold and purchased separately. The syringe should expel a measured amount of a liquid article directly into the patient's mouth. Finger grips located at the open end of the barrel should be the appropriate size, shape, and strength and should allow the syringe to be held securely during use. The barrel may be graduated.

Teaspoon: A measuring device consisting of a shallow bowl, oval or round, at the end of a handle. A teaspoon has been established as containing 4.93 ± 0.24 mL. For the practice of administering articles, the teaspoon may be regarded as representing 5 mL.

Articles intended for administration by teaspoon should be formulated on the basis of dosage in 5-mL units, such that any component used to administer liquid articles should deliver 5 mL wherever a teaspoon calibration is indicated. A household spoon is not an acceptable alternative to the graduated teaspoon described herein.

POISON PREVENTION PACKAGING ACT (PPPA)

This act requires special packaging of most human oral prescription drugs, oral controlled drugs, certain non-oral prescription drugs, certain dietary supplements, and many over-the-counter (OTC) drug preparations in order to protect the public from personal injury or illness from misuse of these preparations (16 CFR §1700.14).

The immediate packaging of substances regulated under the PPPA must comply with the special packaging standards (16 CFR §1700.15 and 16 CFR §1700.16) and applies to all packaging types including reclosable, nonclosable, and unit-dose types.

Special packaging is not required either for drugs dispensed within a hospital setting for inpatient administration or by manufacturers and packagers of bulk-packaged prescription drugs repackaged by the pharmacist. PPPA-regulated prescription drugs may be dispensed in nonchild-resistant packaging upon the request of the purchaser or when directed in a legitimate prescription (15 U.S.C. §1473).

Manufacturers or packagers of PPPA-regulated OTC preparations are allowed to package one size in nonchild-resistant

packaging as long as popular-size, special packages are also supplied. The nonchild-resistant packaging requires special labeling (16 CFR §1700.5).

STORAGE CONDITIONS

Specific directions are stated in some monographs with respect to storage conditions, e.g., the temperature or humidity at which an article must be stored and shipped. Such directions apply, except where the label on the article has different storage conditions that are based on stability studies. Where no specific storage conditions are provided in the individual monograph, but the label of an article states storage conditions based on stability studies, such labeled storage directions apply (see *Pharmaceutical Stability* ⟨1150⟩). Current storage conditions for articles are defined by the following terms.

Freezer: A place in which the temperature is maintained between –25° and –10° (–13° and 14 °F).

Refrigerator: A place in which the temperature is maintained between 2° and 8° (36° and 46 °F).

Cold: Any temperature not exceeding 8° (46 °F).

Cool: Any temperature between 8° and 15° (46° and 59 °F). [NOTE—An article for which storage in a cool place is directed may, alternatively, be stored and shipped as refrigerated, unless otherwise specified by the individual monograph.]

Room Temperature: The temperature prevailing in a work area.

Controlled Room Temperature: The temperature maintained at the usual and customary working environment of 20° to 25° (68° to 77 °F). The following conditions also apply.

The mean kinetic temperature shall not exceed 25°. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations.

Excursions between 15° and 30° (59° and 86 °F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed, provided the mean kinetic temperature does not exceed 25°.

Transient spikes up to 40° are permitted as long as they do not last for more than 24 hours. Spikes above 40° may be permitted only if the manufacturer so instructs.

Articles may be labeled for storage at "controlled room temperature" or at "up to 25°", or other wording based on the same mean kinetic temperature.

An article for which storage at *Controlled Room Temperature* is directed may, alternatively, be stored and shipped in a cool place or refrigerated, unless otherwise specified in the individual monograph or on the label.

Warm: Any temperature between 30° and 40° (86° and 104 °F).

Excessive Heat: Any temperature above 40° (104 °F).

Dry Place: The term "dry place" denotes a place that does not exceed 40% average relative humidity at 20° (68 °F) or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value does not exceed 40% relative humidity. Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered a dry place.

Protection from Freezing: Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Protection from Light: Where light subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from light.

▲*USP35*

⟨660⟩ CONTAINERS—GLASS

Glass containers for pharmaceutical use are intended to come into direct contact with pharmaceutical preparations. Glass used for pharmaceutical containers is either a borosilicate (neutral) glass or a soda-lime glass. Borosilicate glass contains a significant amount of boric oxide, aluminum oxide, and alkali and/or alkaline earth oxides. Borosilicate glass has a high hydrolytic resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Soda-lime glass is a silica glass containing alkali metal oxides. Soda-lime glass has a moderate hydrolytic resistance due to the chemical composition of the glass itself; it is classified as Type III glass. The inner surface of glass containers may be treated, for example, to improve hydrolytic resistance. The treatment of Type III soda-lime glass containers will raise their hydrolytic resistance from a moderate to a high level, changing the classification of the glass to Type II.

The outer surface of glass containers may be treated to reduce friction or for protection against abrasion or breakage. The treatment of the outer surface does not come into contact with the inner surface of the container. Glass may be colored to provide protection from light or may have a coating applied to the outer surface. Such containers will meet the requirements for *Light Transmission* under *Containers—Performance Testing* ⟨671⟩. A clear and colorless or a translucent container that is made light-resistant by means of an opaque enclosure (see *Light-Resistant Container* in *Preservation, Packaging, Storage, and Labeling* under the *General Notices*) is exempt from the requirements for *Light Transmission.*

The quality of glass containers is defined by measuring their resistance to chemical attack. In addition, Type I containers for aqueous parenteral preparations are tested for arsenic release, and colored glass containers are tested for light transmission.

CHEMICAL RESISTANCE

The following tests are designed to determine the resistance to water attack of new (not previously used) glass containers. The degree of attack is determined by the amount of alkali released from the glass under the influence of the attacking medium under the conditions specified. This quantity of alkali is extremely small in the case of the more resistant glasses, thus calling for particular attention to all details of the tests and the use of apparatus of high quality and precision. The tests should be conducted in an area relatively free from fumes and excessive dust.

Glass Types—Glass containers suitable for packaging Pharmacopeial preparations may be classified as in *Table 1* on the basis of the tests set forth in this section. Containers of Type I borosilicate glass are generally used for preparations that are intended for parenteral administration. Containers of Type I glass, or of Type II glass (i.e., soda-lime glass that is suitably dealkalized) are usually used for packaging acidic and neutral parenteral preparations. Type I glass containers, or Type II glass containers (where stability data demonstrate their suitability), are used for alkaline parenteral preparations. Type III soda-lime glass containers usually are not used for parenteral preparations, except where