General Chapters

General Tests and Assays

General Requirements for Tests and Assays

⟨1⟩ INJECTIONS

INTRODUCTION

Parenteral articles are preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they contain are administered, using gravity or force, directly into a blood vessel, organ, tissue, or lesion. Parenteral articles are prepared scrupulously by methods designed to ensure that they meet Pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of the growth of microorganisms. An Injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration.

NOMENCLATURE AND DEFINITIONS

Nomenclature*

The following nomenclature pertains to five general types of preparations, all of which are suitable for, and intended for, parenteral administration. They may contain buffers, preservatives, or other added substances.

1. *[DRUG] Injection*—Liquid preparations that are drug substances or solutions thereof.
2. *[DRUG] for Injection*—Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for *Injections.*
3. *[DRUG] Injectable Emulsion*—Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium.
4. *[DRUG] Injectable Suspension*—Liquid preparations of solids suspended in a suitable liquid medium.
5. *[DRUG] for Injectable Suspension*—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for *Injectable Suspensions.*

Definitions

PHARMACY BULK PACKAGE

A *Pharmacy bulk package* is 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.

The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set which 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 preparations from *Nomenclature* categories 1, 2, or 3 as defined above. *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 Package—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.

LARGE- AND SMALL-VOLUME INJECTIONS

Where used in this Pharmacopeia, the designation *Large-volume intravenous solution* applies to a single-dose injection that is intended for intravenous use and is packaged in containers labeled as containing more than 100 mL. The designation *Small-volume Injection* applies to an Injection that is packaged in containers labeled as containing 100 mL or less.

* This nomenclature has been adopted by the USP Drug Nomenclature Committee for implementation by supplemental revisions of *USP 23-NF 18.* For currently official monograph titles in the form *Sterile [DRUG]* that have not yet been revised, the following nomenclature continues in use in this Pharmacopeia: (1) medicaments or solutions or emulsions thereof suitable for injection, bearing titles of the form *[DRUG] Injection;* (2) dry solids or liquid concentrates containing no buffers, diluents, or other added substances, and which, upon the addition of suitable solvents, yield solutions conforming in all respects to the requirements for Injections, and which are distinguished by titles of the form *Sterile [DRUG];* (3) preparations the same as those described under (2) except that they contain one or more buffers, diluents, or other added substances, and which are distinguished by titles of the form *[DRUG] for Injection;* (4) solids which are suspended in a suitable fluid medium and which are not to be injected [illegible] distinguished [illegible]

BIOLOGICS

The Pharmacopeial definitions for sterile preparations for parenteral use generally do not apply in the case of the biologics because of their special nature and licensing requirements (see *Biologics* ⟨1041⟩).

INGREDIENTS

Vehicles and Added Substances

Aqueous Vehicles—The vehicles for aqueous Injections meet the requirements of the *Pyrogen Test* ⟨151⟩ or the *Bacterial Endotoxins Test* ⟨85⟩, whichever is specified. *Water for Injection* generally is used as the vehicle, unless otherwise specified in the individual monograph. Sodium chloride may be added in amounts sufficient to render the resulting solution isotonic; and *Sodium Chloride Injection,* or *Ringer's Injection,* may be used in whole or in part instead of *Water for Injection,* unless otherwise specified in the individual monograph. For conditions applying to other adjuvants, see *Added Substances* in this chapter.

Other Vehicles—Fixed oils used as vehicles for nonaqueous Injections are of vegetable origin, are odorless or nearly so, and have no odor suggesting rancidity. They meet the requirements of the test for *Solid paraffin* under *Mineral Oil,* the cooling bath being maintained at 10°, have a *Saponification Value* between 185 and 200 (see *Fats and Fixed Oils* ⟨401⟩), have an *Iodine Value* between 79 and 141 (see *Fats and Fixed Oils* ⟨401⟩), and meet the requirements of the following tests.

Unsaponifiable Matter—Reflux on a steam bath 10 mL of the oil with 15 mL of sodium hydroxide solution (1 in 6) and 30 mL of alcohol, with occasional shaking until the mixture becomes clear. Transfer the solution to a shallow dish, evaporate the alcohol on a steam bath, and mix the residue with 100 mL of water: a clear solution results.

Free Fatty Acids—The free fatty acids in 10 g of oil require for neutralization not more than 2.0 mL of 0.020 N sodium hydroxide (see *Fats and Fixed Oils* ⟨401⟩).

Synthetic mono- or diglycerides of fatty acids may be used as vehicles, provided they are liquid and remain clear when cooled to 10° and have an *Iodine Value* of not more than 140 (see *Fats and Fixed Oils* ⟨401⟩).

These and other nonaqueous vehicles may be used, provided they are safe, in the volume of Injection administered, and also provided they do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.

Added Substances—Suitable substances may be added to preparations intended for injection to increase stability or usefulness, unless proscribed in the individual monograph, provided they are harmless in the amounts administered and do not interfere with the therapeutic efficacy or with the responses to the specified assays and tests. No coloring agent may be added, solely for the purpose of coloring the finished preparation, to a solution intended for parenteral administration (see also *Added Substances* under *General Notices* and *Antimicrobial Effectiveness Testing* ⟨51⟩).

Observe special care in the choice and use of added substances in preparations for injection that are administered in a volume exceeding 5 mL. The following maximum limits prevail unless otherwise directed: for agents containing mercury and the cationic, surface-active compounds, 0.01%; for chlorobutanol, cresol, phenol, and similar types of substances, 0.5%; and for sulfur dioxide, or an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium, 0.2%.

A suitable substance or mixture of substances to prevent the growth of microorganisms must be added to preparations intended for injection that are packaged in multiple-dose containers, regardless of the method of sterilization employed, unless one of the following conditions prevails: (1) there are different directions in the individual monograph; (2) the substance contains a radionuclide with a physical half-life of less than 24 hours; and (3) the active ingredients are themselves antimicrobial. Such substances are used in concentrations that will prevent the growth of or kill

Assurance of Compendial Articles ⟨1211⟩). The air in the container may be evacuated or be displaced by a chemically inert gas. Where specified in a monograph, information regarding sensitivity of the article to oxygen is to be provided in the labeling.

Change to read:

LABELS AND LABELING

Labeling—[NOTE—See definitions of "label" and "labeling" under *Labeling* in the section *Preservation, Packaging, Storage, and Labeling* of the *General Notices and Requirements.*]

The label states the name of the preparation; in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume; in the case of a dry preparation, the amount of *active* ingredient; the route of administration; a statement of storage conditions and an expiration date; the name and place of business of the manufacturer, packer, or distributor; and an identifying lot number. The lot number is capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations.

Where the individual monograph permits varying concentrations of active ingredients in the large-volume parenteral, the concentration of each ingredient named in the official title is stated as if part of the official title, e.g., Dextrose Injection 5%, or Dextrose (5%) and Sodium Chloride (0.2%) Injection.

The labeling includes the following information if the complete formula is not specified in the individual monograph: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent is intended to be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone, if the formula is specified in the individual monograph], the amount to be used to attain a specific concentration of active ingredient and the final volume of solution so obtained, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration date limiting the period during which the constituted solution may be expected to have the required or labeled potency if it has been stored as directed.

Containers for Injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 L are labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections intended for veterinary use are labeled to that effect.

The container is so labeled that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

▲Aluminum in Large-Volume Injections (LVIs), Small-Volume Injections (SVIs), and Pharmacy Bulk Packages (PBPs) Used in Total Parenteral Nutrition (TPN) Therapy

(a) The aluminum content of LVIs used in TPN therapy must not exceed 25 µg per L.

(b) The package insert of LVIs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per L. This information must be contained in the "Precautions" section of the labeling of all LVIs used in TPN therapy.

(c) If the maximum amount of aluminum in SVIs and PBPs is 25 µg per L or less, instead of stating the exact amount of aluminum that each may contain, as in paragraph (d), the immediate container label for SVIs and PBPs used in the preparation or the administration of TPN injections (with exceptions as noted

container label must state the following: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L".

(d) The maximum level of aluminum at expiry must be stated on the immediate container label of all SVIs and PBPs used in the preparation or the administration of TPN injections and injectable emulsions. The aluminum content must be stated as follows: "Contains no more than __ µg/L of aluminum". This maximum amount of aluminum may be stated as the highest one of the following three levels:

1. The highest level for the batches produced during the last three years
2. The highest level for the latest five batches
3. The maximum level in terms of historical levels, but only until completion of production of the first five batches after the effective date of July 26, 2004

The package insert for all LVIs, SVIs, and PBPs used in the preparation or administration of TPN products must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling and must state the following: "WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products and of the lock-flush solutions used in their administration." ▲*USP29*

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see *Containers* ⟨661⟩).

For definitions of single-dose and multiple-dose containers, see *Containers* in the *General Notices and Requirements*. Containers meet the requirements under *Containers* ⟨661⟩.

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampul is prohibited, except for *Potassium Chloride for Injection Concentrate*.

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: "Warning: Paralyzing Agent" or "Paralyzing Agent" (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the *Assay* in a monograph provides a procedure for the *Assay preparation*, in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled "size" or that volume which is to be withdrawn. See *Injections* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Select one or more containers if the volume of the container is 10 mL or more, three or more if the volume is more than 3 mL and less than 10 mL, or five or more if the volume is 3 mL or less. Individually take up the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of the cylinder's rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in mL, being calculated as the weight, in g, of Injection taken divided by its density. The contents of up to five 1- or 2-mL containers may be pooled for the measurement, provided that a separate dry syringe assembly is used for each container. The content of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.

For Injections in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. Cool to 25° before measuring the volume.

For Injections in cartridges or prefilled syringes, assemble the container with any required accessories such as a needle or plunger. Following the same procedure as above, and without emptying the needle, transfer the entire contents of each container to a dry, tared beaker by slowly and constantly depressing the plunger. Weigh, and calculate the volume as described above. The volume of each container is not less than the labeled volume.

For large-volume intravenous solutions, select 1 container, and transfer the contents into a dry measuring cylinder of such size that the volume to be measured occupies at least 40% of its rated volume. The volume is not less than the labeled volume.

Printing on Ferrules and Cap Overseals

Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: "Warning", "Dilute Before Using", "Paralyzing Agent", "I.M. Use Only", "Chemotherapy", etc.

The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.

Packaging and Storage

The volume of injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

Injections packaged for use as irrigation solutions, for hemofiltration or dialysis, or for parenteral nutrition are exempt from the 1-L restriction of the foregoing requirements relating to packaging.

Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 L.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

Change to read:

▲FOREIGN AND PARTICULATE MATTER

All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in *Particulate Matter in Injections* ⟨788⟩ and other foreign matter. Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed "visible particulates") in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates. Qualification of the inspection process shall be performed with reference to particulates in the visible range of a place when inspecting for other critical defects, such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

Where the nature of the contents or the container-closure system permits only limited capability for the inspection of the total contents, the 100% inspection of a lot shall be supplemented with the inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container) contents of a sample of containers from the lot.

All large-volume Injections for single-dose infusion and small-volume Injections are subject to the light obscuration or microscopic procedures and limits for subvisible particulate matter set forth in *Particulate Matter In Injections* ⟨788⟩, unless otherwise specified in the individual monograph. An article packaged as both a large-volume and a small-volume Injection meets the requirements set forth for small-volume Injections where the container is labeled as containing 100 mL or less, if the individual monograph states a test for *Particulate Matter* ⟨788⟩; it meets the requirements set forth for large-volume Injections for single-dose infusion where the container is labeled as containing more than 100 mL. Injections administered exclusively by the intramuscular or subcutaneous route or packaged and labeled for use as irrigating solutions are exempt from requirements for *Particulate Matter* ⟨788⟩.▲USP29

STERILITY

Sterility Tests—Preparations for injection meet the requirements under *Sterility Tests* ⟨71⟩.

CONSTITUTED SOLUTIONS

Dry solids from which constituted solutions are prepared for injection bear titles of the form *[DRUG] for Injection*. Because these dosage forms are constituted at the time of use by the health care practitioner, tests and standards pertaining to the solution as constituted for administration are not included in the individual monographs on sterile dry solids or liquid concentrates. However, in the interest of assuring the quality of injection preparations as they are actually administered, the following nondestructive tests are provided for demonstrating the suitability of constituted solutions when they are prepared just prior to use.

Completeness and Clarity of Solution—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form.

A: The solid dissolves completely, leaving no visible residue as undissolved matter.

B: The constituted solution is not significantly less clear than an equal volume of the diluent or of Purified Water contained in a similar vessel and examined similarly.

Particulate Matter—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form: the solution is essentially free from particles of foreign matter that can be observed on visual inspection.

⟨11⟩ USP REFERENCE STANDARDS

USP Reference Standards are established and released under the authority of the USPC Board of Trustees upon recommendation of the USP Reference Standards Committee, which passes on the selection and suitability of each lot. The critical characteristics of each lot of specimen selected for the standard are usually determined independently in three or more laboratories. The USP Reference Standards Laboratory (see *Preface*) and the FDA laboratories participate in testing almost all new Standards and replacements for existing Standards. In addition, laboratories throughout the world, both academic and industrial, participate in the testing