

1995

USP 23

NF 18

**THE UNITED STATES PHARMACOPEIA**

**THE NATIONAL FORMULARY**

*By authority of the United States Pharmacopeial  
Convention, Inc., meeting at Washington, D.C.,  
March 8-10, 1990. Prepared by the Committee of  
Revision and published by the Board of Trustees*

*Official from January 1, 1995*



NPS EX. 2062  
CFAD v. NPS  
IPR2015-00990

UNITED STATES PHARMACOPEIAL CONVENTION, INC.

# 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

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.

##### 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

**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* of between 185 and 200 (see *Fats and Fixed Oils* (401)), have an *Iodine value* of between 79 and 128 (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 Preservatives—Effectiveness* (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 those of the types of chlorobutanol, cresol, and phenol, 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 otherwise directed in the individual monograph, or unless the active ingredients are themselves antimicrobial. Such substances are used in concentrations that will prevent the growth of or kill microorganisms in the preparations for injection. Such substances also meet the requirements of *Antimicrobial Preservatives—Effectiveness* (51) and *Antimicrobial Agents—Content* (341). Sterilization processes are employed even though such substances are used (see also *Parenteral and Topical Preparations* in the section *Added Substances* under *General Notices* and *Sterilization and Sterility 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.

## 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*.]

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 of the manufacturer and 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.

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 liter 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.

## 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.

For definitions of single-dose and multiple-dose containers, see *Containers* under *General Notices*. Containers meet the requirements under *Containers* (661).

Containers are closed by fusion, or by application of suitable closures, in such manner as to prevent contamination or loss of contents. 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, at once recloses the container against contamination.

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*.

### 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 *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