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⟨1⟩ INJECTIONS AND IMPLANTED DRUG PRODUCTS (PARENTERALS)—PRODUCT QUALITY TESTS

INTRODUCTION

Parenteral drug products include both injections and implanted drug products that are injected through the skin or other external boundary tissue, or implanted within the body to allow the direct administration of the active drug substance(s) into blood vessels, organs, tissues, or lesions. Injections may exist as either immediate- or extended-release dosage forms. Implanted parenteral drug products are long-acting dosage forms that provide continuous release of the active drug substance(s), often for periods of months to years. For systemic delivery, they may be placed subcutaneously; for local delivery, they may be placed in a specific region of the body. Routes of administration for parenteral drug products include intravenous, intraventricular, intra-arterial, intra-articular, subcutaneous, intramuscular, intrathecal, intracisternal, and intraocular.

Parenteral dosage forms include solutions, suspensions, emulsions, sterile powders for solutions and suspensions (including liposomes), implants (including microparticles), and products that consist of both a drug and a device such as drug-eluting stents. The definitions and descriptions of these dosage forms, and brief information about their composition and manufacturing processes, are found in *Pharmaceutical Dosage Forms* ⟨1151⟩. [Note—All references to chapters above 1000 are for informational purposes only, for use as a helpful resource. These chapters are not mandatory unless explicitly called out for application.]

This chapter is divided into three main sections: (1) universal product quality tests that are applicable to parenteral dosage forms; (2) specific product quality tests, which are tests that should be considered in addition to *Universal Tests*; and (3) product quality tests for specific dosage forms, which list applicable tests (universal and specific) for the specific dosage form.

This chapter applies, in whole or in part, when referenced in a drug product monograph (see *General Notices, 3.10 Applicability of Standards*).

The pharmacopeial definitions for sterile preparations for parenteral use may not apply to some biologics because of their special nature and licensing requirements (see *Biologics* ⟨1041⟩). However, some biological finished drug products containing “Injection” in the monograph title must meet the requirements of ⟨1⟩ or indicated chapter subparts, where it is specified in the monograph.

Change to read:

PRODUCT QUALITY TESTS COMMON TO PARENTERAL DOSAGE FORMS

Universal Tests

Universal tests are listed below and are applicable to parenteral dosage forms.

IDENTIFICATION

Identification tests are discussed in *General Notices, 5.40 Identification* should establish the identity of the drug or drugs present in the article and should discriminate between compounds of closely related structure that are likely to be present..

ASSAY

A specific and stability-indicating test should be used to determine the strength (content) of the drug product. In cases where the use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay.

IMPURITIES

Tests for *Impurities* are discussed in *General Notices, 5.60 Impurities and Foreign Substances*. All articles should be tested to ensure that they meet the requirements.

FOREIGN AND PARTICULATE MATTER

Articles intended for parenteral administration should be prepared in a manner designed to exclude particulate matter as defined in *Subvisible Particulate Matter in Therapeutic Protein Injections ⟨787⟩*, *Particulate Matter in Injections ⟨788⟩*, or ▲*Subvisible Particulate Matter in Intraocular Solutions ⟨789⟩*▲ (CN 1-May-2024) , as well as excluding other foreign matter as appropriate for the dosage form. Each final container of all parenteral preparations should 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 should be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates, as defined in *Visible Particulates in Injections ⟨790⟩*. Qualification of the inspection process should be performed with reference to particulates in the visible range and those particulates that might emanate from the manufacturing or filling process. Every container in which the contents show evidence of visible particulates must be rejected. The inspection for visible particulates may take place during examination for other defects such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

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

Large-volume injections for single-dose infusion, small-volume injections, and pharmacy bulk packages (PBPs) are subject to the light obscuration or microscopic procedures and limits for subvisible particulate matter set forth in ⟨788⟩, unless otherwise specified in the chapter or 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. 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.

STERILITY

The sterility of all drug products intended for parenteral administration should be confirmed by the use of methods described in *Sterility Tests ⟨71⟩* or by an approved alternative method.

BACTERIAL ENDOTOXINS

All articles intended for parenteral administration should be prepared in a manner designed to limit bacterial endotoxins as defined in *Bacterial Endotoxins Test ⟨85⟩* or *Pyrogen Test ⟨151⟩*.

CONTAINER CONTENT

Container contents should be determined when appropriate (see *Container Content for Injections ⟨697⟩*).

PACKAGING SYSTEMS

The packaging system should not interact physically or chemically with the preparation to alter its strength, quality, or purity beyond the official or established requirements. The packaging system should meet the requirements in *Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems ⟨381⟩*, *Packaging and Storage Requirements ⟨659⟩*, *Containers—Glass ⟨660⟩*, *Plastic Packaging Systems and their Materials of Construction ⟨661⟩*, *Plastic Materials of Construction ⟨661.1⟩*, and *Plastic Packaging Systems for Pharmaceutical Use ⟨661.2⟩*. Further information regarding packaging systems testing may be found in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems ⟨1663⟩* and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems ⟨1664⟩*.

CONTAINER—CLOSURE INTEGRITY

The packaging system should be 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 gain or loss of any chemical or physical parameter deemed necessary to protect the product (see *Package Integrity Evaluation—Sterile Products ⟨1207⟩*, *Package Integrity Testing in the Product Life Cycle—Test Method Selection and Validation ⟨1207.1⟩*, *Package Integrity Leak Test Technologies ⟨1207.2⟩*, and *Package Seal Quality Test Technologies ⟨1207.3⟩*).

LABELING

All articles intended for parenteral administration should meet the labeling requirements defined in *Labeling ⟨7⟩*.

Specific Tests

In addition to the *Universal Tests* listed above, the following specific tests may be necessary depending on the dosage form.

UNIFORMITY OF DOSAGE UNITS

This test is applicable for parenteral drug products and dosage forms packaged in single-unit containers. It includes both the mass of the dosage form and the content of the active substance in the dosage form (see *Uniformity of Dosage Units* ⟨905⟩).

VEHICLES AND ADDED SUBSTANCES

There are other vehicles, both aqueous and nonaqueous, beyond those that are discussed below. All vehicles should be suitable for their intended use and not impact drug product quality.

Aqueous vehicles: Aqueous vehicles must meet the requirements of ⟨151⟩ or ⟨85⟩, whichever is specified in the monograph. Water for injection is generally used as the vehicle. Sodium chloride or dextrose may be added 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.

Nonaqueous vehicles: Fixed oils are classified under *Nonaqueous vehicles*. Fixed oils used as vehicles are of vegetable origin and are odorless. They meet the requirements in the test for *Solid Paraffin* in the *Mineral Oil* monograph with the cooling bath maintained at 10°.

Nonaqueous vehicles should also meet the requirements of the following tests:

- *Fats and Fixed Oils* ⟨401⟩, *Saponification Value*: Between 185 and 200
- *Fats and Fixed Oils* ⟨401⟩, *Iodine Value*: Between 79 and 141
- *Fats and Fixed Oils* ⟨401⟩, *Unsaponifiable Matter*: NMT 1.5%
- *Fats and Fixed Oils* ⟨401⟩, *Acid Value*: NMT 0.2
- *Fats and Fixed Oils* ⟨401⟩, *Peroxide Value*: NMT 5.0
- *Water Determination* ⟨921⟩, *Method Ic*: NMT 0.1%
- *Limit of Copper, Iron, Lead, and Nickel*: [Note—The test for nickel is not required if the oil has not been subjected to hydrogenation, or a nickel catalyst has not been used in processing.] Proceed as directed in *Fats and Fixed Oils* ⟨401⟩, *Trace Metals* or *Elemental Impurities—Procedures* ⟨233⟩. Meet the requirements in *Elemental Impurities—Limits* ⟨232⟩.

Synthetic mono- or diglycerides of fatty acids may be used provided they are liquid and remain clear when cooled to 10° and have a *Iodine Value* of NMT 140.

Added substances: Suitable substances may be added to preparations in order to increase stability or usefulness unless they are proscribed in the monograph. No coloring agent may be added to a preparation solely for the purpose of coloring the finished preparation (see *General Notices, 5.20 Added Substances* and *Antimicrobial Effectiveness Testing* ⟨51⟩).

Observe special care in the choice and use of added substances in preparations with volumes that exceed 5 mL. The following limits prevail unless otherwise directed:

- Mercury and cationic surface-active agents: NMT 0.01%
- Chlorobutanol, cresol, phenol, and similar substances: NMT 0.5%
- Sulfur dioxide or an equivalent amount of sulfite, bisulfite, or metabisulfite of potassium or sodium: NMT 0.2%

ANTIMICROBIAL PRESERVATIVES

Antimicrobial agents must be added to preparations intended for injection that are packaged in multiple-dose containers 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 h; or (3) the active ingredients are themselves antimicrobial. Substances must meet the requirements of ⟨51⟩ and *Antimicrobial Agents—Content* ⟨341⟩.

WATER CONTENT

The water content of freeze-dried (lyophilized) products should be determined when appropriate (see ⟨921⟩).

ALUMINUM CONTENT

See *Labeling* ⟨7⟩, *Aluminum in Large-Volume Injections (LVIs), Small-Volume Injections (SVIs), and Pharmacy Bulk Packages (PBPs) Used in Parenteral Nutrition (PN) Therapy* for information related to specific labeling requirements associated with aluminum content.

COMPLETENESS AND CLARITY OF SOLUTIONS

The following tests are performed to demonstrate suitability of constituted solutions prepared before administration. Constitute the solution as directed in the labeling supplied by the manufacturer:

- The solid dissolves completely, leaving no undissolved matter.
- 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. Protein solutions may exhibit an inherent opalescence.

The constituted solution is free from particulate matter that can be observed on visual inspection (see ⟨790⟩).

PRODUCT QUALITY TESTS FOR SPECIFIC PARENTERAL DOSAGE FORMS

Product quality tests for the specific dosage forms are listed below. Specific chapter(s) referenced for the test can be found in the *Universal Tests* and *Specific Tests* sections.

Solutions

A solution is a clear, homogeneous liquid dosage form that contains one or more chemical substances (e.g., drug substances or excipients) dissolved in a solvent (aqueous or nonaqueous) or a mixture of mutually miscible solvents. Solutions intended for parenteral administration (e.g., by injection or for irrigation) must be sterile and biocompatible with the intended administration site. This includes consideration of factors such as tonicity, pH, pyrogenicity, extraneous particulate matter, and physicochemical compatibility, among others.

Unless otherwise justified, the following tests are required for solutions for injection:

- *Universal Tests*
- *Specific Tests*
    - *Antimicrobial Preservatives*

Sterile Powders for Solutions

Sterile powders for solutions (also referred to as sterile powders for injection) consist of drug substances and other components as dry-formulation ingredients to ensure the chemical and physical stability of the presentation within a final-use container. Companion sterile diluent or diluent compartments may be provided to facilitate constitution to the desired final volume.

The sterile article for injection may be presented in several forms: lyophilized powder intended for final solution, powdered solids intended for final solution, or dry solids that form viscous liquids upon constitution.

The description should include a section that deals with ease of dispersion and reconstitution. The dosage form is a homogeneous solid that is readily constituted to the final form with the specified diluent, and dispersion is completed with gentle agitation.

Unless otherwise justified, the following tests apply to sterile powders for injection:

- *Universal Tests*

The following applies to constituted solutions:

- Chapter ⟨905⟩: To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms that contain a single dose or a part of a dose of drug substance in each unit. For liquid dosage forms analysts should conduct the assay on an amount of well-mixed constituted material that is removed from an individual container under conditions of normal use, should express the results as delivered dose, and should calculate the acceptance value.

The following applies to dry cake:

- *Loss on Drying* ⟨731⟩: The procedure set forth in this chapter determines the amount of volatile matter of any kind that is driven off under the conditions specified.
- Chapter ⟨921⟩: Water or solvent content may have important effects on reconstitution and stability. For articles that require water or solvent content control, analysts should perform one of the methods described in ⟨921⟩ or a suitable replacement.
- *Appearance*: Analysts should assess the level of and the unit variation for the following parameters:
    - Color of Dry Cake: Varies within target parameters
    - Texture and Homogeneity of Dry Cake: Varies within target parameters
    - Presence of Foreign Material: All units with visible foreign material must be rejected

Suspensions

Parenteral suspensions are liquid dosage forms that contain solid particles in a state of uniform dispersion. Suspensions for parenteral administration must be sterile and compatible with the administration site. Consideration should be given to pH and pyrogenicity, and appropriate limits should be identified. Physical stability evaluations of parenteral suspension preparations should include evaluations to confirm that the particle size range of suspended matter does not change with time and to confirm that the solids in the preparation can be readily resuspended to yield a uniform preparation.

The following tests are required for suspensions for injection unless otherwise justified:

- *Universal Tests*
- *Specific Tests*
    - *Uniformity of Dosage Units*
    - *Antimicrobial Preservatives*

Liposomes

Liposomes are unique drug products with unique properties that can be either solutions or suspensions. Liposomes are aqueous dispersions of amphiphilic lipids and have low water solubility. They are organized as a bilayer sheet that encloses an internal aqueous compartment and are known as lipid bilayer vesicles. Liposomes can have a single lipid bilayer (unilamellar vesicle) or can have an onion-like multilayered structure (multilamellar vesicle). The amphiphilic lipids comprise a hydrated head group at the water interface of the bilayer attached to a hydrophobic group that forms the interior of the bilayer by association with the hydrophobic group of lipids from the opposite leaflet of the bilayer. The physical properties of the liposome and its bilayer can vary widely and depend on lipid composition, aqueous composition, and temperature relative to the acyl components' phase transition points. Because of the central aqueous compartment, a simple test for the presence of liposomes in a lipid dispersion is to determine the presence of an entrapped aqueous phase.

A liposome drug product consists of the drug substance, liposome components, and other inactive but critical ingredients such as an aqueous dispersion unless the contents are a lyophilized product.

Unless otherwise justified, the following tests are required for liposomes:

- *Universal Tests*
- *Specific Tests*
  - *Globule Size Distribution in Lipid Injectable Emulsions ⟨729⟩*

Sterile Powders for Suspensions

Sterile powders for suspensions consist of drug substances and other components as dry-formulation ingredients to ensure the chemical and physical stability of the presentation within a final-use container. Companion sterile diluent or diluent compartments may be provided to facilitate constitution to the desired final volume.

The sterile article for injection may be presented in several forms: lyophilized powder intended for final suspension, powdered solids intended for final suspension, and microparticles that retain their integrity and are delivered as a sterile suspension. The description should include a section that deals with ease of dispersion and reconstitution. The dosage form is a homogeneous solid that is readily constituted to the final form with the specified diluent, and dispersion is completed with gentle agitation.

Unless otherwise justified, the following tests apply to sterile powders for injection:

- *Universal Tests*

Microparticles: Some microparticles are provided as a sterile powder to be reconstituted as a suspension before injection. The majority of microparticle preparations are for reconstitution as a suspension for injection. For quality test requirements, please refer to *Implants*.

Emulsions

Emulsions for parenteral dosage forms are liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium. Oil-in-water or water-in-oil emulsions typically entrap the drug substance.

Emulsions typically are white, turbid, homogeneous liquid dosage forms that contain one or more chemical substances (e.g., drug substances and excipients) dissolved in a solvent (aqueous or nonaqueous) or mixture of mutually miscible solvents. Emulsions intended for intravenous administration must be sterile and must be compatible with the intended administration site.

Unless otherwise justified, the following tests are required for emulsions for injection:

- *Universal Tests*
- *Specific Tests*
  - Chapter ⟨729⟩

Implants

Implants for extended release consist of a matrix of drug substance and polymeric excipient that may or may not have an outer rate-controlling membrane. The polymeric excipient must be biocompatible but may or may not be bioresorbable. Some implants are made from medical-grade metal with an osmotic pump inside that effects the extended release of the drug substance. Implants must be sterile and usually are formed in the shape of a cylinder, although other shapes are used. Solvents used to dissolve the formulation can lead to sterilization, and thus the internal sterility test method should demonstrate that the sample preparation does not lead to sterilization of the test sample.

Cylindrically shaped implants for systemic delivery usually are provided in an inserter for subcutaneous or local administration such as local ocular delivery. Implants also can be surgically implanted for local delivery, e.g., ocular delivery.

Unless otherwise justified, the following tests are required for implants:

- *Universal Tests*
- *Specific Tests*
  - *Uniformity of Dosage Units*

In situ Gels

Sterile in situ gels are liquid preparations that are intended for injection into specific therapeutic targets. Typically they consist of polymers in organic solvents, and upon injection the solvents migrate away from the site, leaving a gelled mass. The preparations may be injected as-is, upon reconstitution, from in situ formation, or from chemically initiated catalysis that results in the final form.

Unless otherwise justified, the following tests are required for in situ gels:

- *Universal Tests*
- *Specific Tests*
  - *Antimicrobial Preservatives*

Microparticles

Injectable, resorbable microparticles for extended release generally range from 20 to 100 µm in diameter. They consist of drug substances embedded within a biocompatible, bioresorbable polymeric excipient, e.g., polyester excipients. Microparticles are provided as a sterile powder in a vial or syringe.

Just before intramuscular or subcutaneous administration, the microparticle powder should be suspended in an aqueous injection vehicle (diluent). The injection vehicle usually consists of water for injection, surfactant, and a viscosity enhancer, and the vehicle may contain a compound that adjusts osmolality, e.g., a sugar with or without a compound that controls pH, e.g., an acid. The injection vehicle must be sterile and must be tested according to requirements for solutions that are intended for parenteral administration.

Unless otherwise justified, the following tests are required for microparticles for injection:

- *Universal Tests*
- *Specific Tests*
  - *Uniformity of Dosage Units*
  - *Water Content*

Drug-Eluting Stents

Drug-eluting stents are tiny metal or polymer scaffolds used to keep arteries open following a medical intervention; the drug substance is incorporated into or onto the stent platform. Drug-eluting stents typically have two components of testing: (1) functional tests that generally are American Society for Testing and Materials (ASTM) International methods that fall outside the scope of this chapter and (2) analytical tests.

Unless otherwise justified, the following tests are required for drug-eluting stents:

- *Universal Tests*
- *Specific Tests*
  - *Uniformity of Dosage Units.* The content of the active substance in the dosage form is applicable for drug-eluting stents packaged in single-unit containers. The test can be performed by either content uniformity or weight variation (see ⟨905⟩). With appropriate justification, the number of stents needed for this test may be fewer than the recommended number of stents in ⟨905⟩.
  - ⟨88⟩*Biological ReactivityTests, In Vivo*

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<1> INJECTIONS	Ravikiran Kaja Senior Principal Scientist	GCDF2020 General Chapters - Dosage Forms 2020

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