Parenteral preparations

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The requirements of this monograph do not necessarily apply to human blood and products derived from human blood, to immunological preparations, to peritoneal dialysis solutions or radiopharmaceutical preparations.

Definition

Parenteral preparations are sterile preparations containing one or more active ingredients intended for administration by injection, infusion or implantation into the body. They are packaged in either single-dose or multidose containers.

Parenteral preparations may require the use of excipients such as solvents, substances to enhance solubility, suspending agents, buffering agents, substances to make the preparation isotonic with blood, stabilizers or antimicrobial preservatives. The addition of excipients is kept to a minimum. When excipients are used they do not adversely affect the stability, bioavailability, safety or efficacy of the active ingredient(s), or cause toxicity or undue local irritation. There must be no incompatibility between any of the components of the dosage form.

Water for injections is used as the vehicle for aqueous injections. Sterilization at this stage may be omitted, provided that the preparation is subject to terminal sterilization. For non-aqueous injections, fixed oils of vegetable origin are used as vehicles.

Unless otherwise specified in the individual monograph, sodium chloride or other suitable substance(s) may be added to an aqueous solution for injection in order to render the preparation isotonic. When an individual monograph defines a particular parenteral preparation simply as a solution, emulsion or suspension in *Water for injections*, this does not preclude the inclusion of such substances, where necessary, for this purpose.

The different categories of parenteral preparations include:

- injections;
- intravenous infusions;
- powders for injections or intravenous infusions;
- concentrates for injections or intravenous infusions;
- implants.

Manufacture

The manufacturing process should meet the requirements of good manufacturing practices (GMP). The following information is intended to provide broad guidelines concerning the main steps to be followed during production.

The quality and grade of starting materials, the design and maintenance of the equipment and the method of manufacture must be such as to ensure the stability of the active substance and of the final product and that the final product is sterile and free of pyrogens and particulate matter.

During development the effectiveness of any antimicrobial preservative present in the preparation shall be demonstrated to the satisfaction of the relevant regulatory authority.

For the sterilization of parenteral preparations follow *5.8 Methods of sterilization*. Heating in an autoclave (steam sterilization) is the method of choice for aqueous preparations and should therefore be used whenever possible.

When a parenteral preparation is liable to deterioration due to oxidation the operation of filling may be performed in an atmosphere of suitable sterile inert gas, such as nitrogen, whereby the air in the container is replaced by this gas.

In the manufacture of preparations containing dispersed particles measures are taken to ensure a suitable and controlled particle size with regard to the intended use.

In the manufacture of liquid preparations measures are taken to ensure that the volume of the preparation in the container is sufficient to permit withdrawal and administration of the nominal dose using a normal technique as demonstrated by *5.6 Extractable volume for parenteral preparations*.

Throughout manufacturing certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during manufacture of parenteral preparations should include monitoring of environmental conditions (especially with respect to particulate and microbial contamination), bacterial endotoxins, pH and clarity of solution, freedom from particulate matter and integrity of the container-closure system (absence of leakage, etc.). For powders for injections controls should also include uniformity of mass, moisture content and the ease of reconstitution of a solution or suspension. The validation of the manufacturing process and the in-process controls are documented.

Containers

Parenteral preparations are usually supplied in glass ampoules, bottles or vials, in plastic bottles or bags, or in prefilled syringes. In case of light-sensitive substances the container should protect the contents (for example, by the use of coloured glass).

Containers are made, as far as possible, from material that is sufficiently transparent to permit the visual inspection of the contents, except for implants and in other justified and authorized cases. They do not adversely affect the quality of the preparation, allow diffusion of any kind into or across the material of the container or yield foreign substances into the preparation.

Closures

Closures for parenteral preparation containers are equipped with a firm seal to prevent entry of microorganisms and other contaminants while permitting the withdrawal of a part or the whole of the contents without removal of the closure. They are not made of components that react with the contents or that allow foreign substances to diffuse into the preparation. The closure, composed of plastic materials or elastomers, is sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles. Closures for multidose containers are sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and protect the contents from airborne contamination. A tamper-evident container is fitted with a device that reveals clearly whether it has ever been opened.

Visual inspection

Inspect solutions and reconstituted solutions using at least 20 containers for single-dose preparations. They are clear and free from visible particulate matter. Evidence of physical and/or chemical instability may be phase separation in emulsions, discoloration or precipitation of solid matter.

Sterility

Parenteral preparations comply with *3.2 Test for sterility*.

Bacterial endotoxins/pyrogens

Parenteral preparations comply with *3.4 Test for bacterial endotoxins*, or, where justified, with *3.5 Test for pyrogens*.

For powders and concentrates for injections and intravenous infusions the amount of the preparation to be tested and the nature and volume of the liquid in which it is to be dissolved, suspended or diluted is specified in the individual monograph.

Particulate contamination

Solutions for intravenous infusions and solutions for injections comply with *5.7 Tests for particulate contamination. Subvisible particles.*

Preparations for which the label states that the product is to be used with a final filter are exempt from these requirements provided it has been demonstrated that the filter delivers a solution that complies with the test.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established under GMP.

The label should include:

(1) the name of the pharmaceutical product;

(2) the name(s) of the active ingredient(s); International Nonproprietary Names (INN) should be used wherever possible;

(3) the amount of the active ingredient(s) in a suitable dose volume and the volume in the container; for powder for injections: the amount of the active ingredient(s) in the container and a statement of the net contents (e.g. number of dosage units);

(4) the batch number assigned by the manufacturer;

(5) the expiry date and, when required, the date of manufacture;

(6) any special storage conditions or handling precautions that may be necessary;

(7) directions for use, warnings and precautions that may be necessary, for example, that the product has to be used together with a final filter;

(8) the name and address of the manufacturer or the person responsible for placing the product on the market;

(9) where applicable, information on any added antimicrobial preservative.

For parenteral preparations that are solutions or dispersions the concentration of the active ingredient(s) should be given in terms of mass or biological activity per volume. For concentrated solutions, labels should state the composition and the dilution to be carried out before use.

Requirements for specific types of parenteral preparations

Injections

Definition

Injections are sterile, pyrogen-free solutions or dispersions (emulsions or suspensions) of one or more active ingredients in a suitable vehicle.

Whenever possible an injection is prepared using an aqueous vehicle. If necessary suitable non-aqueous solvents are indicated in the individual monographs. Injections that are dispersions should remain sufficiently stable so that, after shaking, a homogeneous dose can be withdrawn.

Single-dose injections should not contain antimicrobial preservatives unless justified and authorized. Injections containing an antimicrobial preservative must not be administered intracisternally, intrathecally, epidurally or by any route giving access to the cerebrospinal fluid, or intra- or retro-ocularly.

Multidose preparations

Multidose preparations contain a suitable antimicrobial preservative in appropriate concentrations except in cases where the preparations themselves have adequate antimicrobial properties. The containers are equipped to ensure adequate protection of the contents after partial withdrawal. In order to minimize the risk of contamination resulting from multiple penetrations of the closure the contents of a multidose preparation should normally not exceed 30 mL.

Uniformity of content

Single-dose suspensions for injection comply with *5.1 Uniformity of content for single-dose preparations*.

Intravenous infusions

Definition

Intravenous infusions are sterile, pyrogen-free aqueous solutions or emulsions with water as continuous phase, usually prepared to be isotonic. They are intended for administration in large volumes (usually more than 100 mL) and do not contain any antimicrobial preservatives.

On visual inspection emulsions for intravenous injection should show no evidence of phase separation.

Powders for injections or intravenous infusions

Definition

Powders for injections or intravenous infusions are sterile, pyrogen-free solid substances (including freeze-dried materials), distributed in their final containers and which, when the prescribed volume of the appropriate sterile liquid is added, rapidly form either clear and practically particle-free solutions or uniform suspensions.

Powders for injections or intravenous infusions, after dissolution or suspension, comply with the requirements for injections or intravenous infusions, as appropriate.

Uniformity of mass

Powders for injections or intravenous infusions (single-dose use) comply with the test for *5.2 Uniformity of mass for single-dose preparations* unless otherwise specified in the individual monograph.

Uniformity of content

Where a requirement for compliance with the test for *5.1 Uniformity of content for single-dose preparations* is specified in an individual monograph for a powder for injections or intravenous infusions the test for *5.2 Uniformity of mass for single-dose preparations* is not required.

Concentrates for injections or intravenous infusions

Concentrates for injections or intravenous infusions are sterile, pyrogen-free solutions intended for injection or infusion after dilution. They are diluted to a prescribed volume with a prescribed liquid before administration.

Concentrates for injections or intravenous infusions, after dissolution or suspension, comply with the requirements for injections or intravenous infusions, as appropriate.

Implants

Definition

Implants are sterile solid preparations containing one or more active ingredients. They are of a size and shape suitable for parenteral implantation and provide release of the active ingredient(s) over an extended period of time. They are presented in individual sterile containers.

All requirements for these specialized dosage forms are given in the individual monographs.