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Parenteral Preparations

General Notices

(Ph. Eur. monograph 0520)

Unless otherwise justified and authorised, Parenteral Preparations comply with the appropriate requirements of the European Pharmacopoeia. These requirements are reproduced in the British Pharmacopoeia or, where they apply to veterinary preparations only, below.

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The requirements of this monograph do not necessarily apply to products derived from human blood, to immunological preparations or to radiopharmaceutical preparations. Special requirements may apply to preparations for veterinary use depending on the animal species for which the preparation is intended.

DEFINITION

Parenteral preparations are sterile preparations intended for administration into the human or animal body. They may be administered by injection, infusion or implantation.

They are liquid, semi-solid or solid preparations containing one or more active substances in a suitable vehicle. Liquid preparations for injection or infusion are solutions, colloidal dispersions, emulsions or suspensions.

Parenteral preparations may contain suitable excipients, for example to adjust the tonicity of the preparation relative to blood, to adjust or stabilise the pH, to increase the solubility of the active substances, to stabilise the preparation or to provide adequate antimicrobial properties. The excipients do not adversely affect the intended medicinal action or, at the concentrations used, cause toxicity or undue local irritation.

Wherever possible, containers for parenteral preparations are made from materials that are sufficiently transparent to permit the visual inspection of the contents, except for implants and in other justified and authorised cases.

Where applicable, containers for parenteral preparations comply with the requirements for *Materials used for the manufacture of containers* (*3.1* and subsections) and *Containers* (*3.2* and subsections). Parenteral preparations intended for chronic use or total parenteral nutrition should have appropriate limits for specific components or elements, taking long-term toxicity into account.

Parenteral preparations are supplied in glass containers (*3.2.1*) or in other containers such as plastic containers (*3.2.2*, *3.2.2.1* and *3.2.9*) and prefilled syringes. The tightness of the container is ensured by suitable means. Closures ensure a good seal, prevent micro-organisms and other contaminants from entering the container and closure system and usually permit the withdrawal of a part or all of the contents without the closure being removed. The plastic materials or elastomers (*3.2.9*) used to manufacture the closures are sufficiently firm and elastic to allow the passage of a needle without shedding of particles contaminating the preparation. Closures for multidose containers are sufficiently elastic to ensure that the puncture is resealed when the needle is withdrawn.

Several categories of parenteral preparations may be distinguished:

— injections;

— infusions;

— concentrates for injections or infusions;

— powders for injections or infusions;

— gels for injection;

— implants;

— intravitreal preparations.

PRODUCTION

During the development of parenteral preparations whose formulation contains a preservative, the need for and the efficacy of the chosen preservative shall be demonstrated to the satisfaction of the competent authority. A suitable test method together with criteria for judging the preservative properties of the formulation are provided in general chapter *5.1.3. Efficacy of antimicrobial preservation*.

Parenteral preparations are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of micro-organisms; recommendations on this aspect are provided in general chapter *5.1.1*. *Methods of preparation of sterile products*.

Water used in the manufacture of parenteral preparations complies with the requirements for water for injections in bulk given in the monograph *Water for injections (0169)*.

Liquid preparations for injection or infusion, examined under suitable conditions of visibility, are practically free from particles.

Recommendations on testing for visible particles are given in general chapter 5.17.2.

TESTS

Particulate contamination: sub-visible particles (*2.9.19*)

Liquid preparations for injection or infusion, if applicable after reconstitution, comply with the test. Unless otherwise justified and authorised, suspensions, emulsions and gels for injection comply with the test.

In the case of preparations for subcutaneous or intramuscular injection, higher limits may be appropriate. Radiopharmaceutical preparations are exempt from these requirements. Preparations for which the label states that the product is to be used with a final filter are exempt from these requirements, providing it has been demonstrated that the filtrate complies with the test.

For preparations for veterinary use, when supplied in containers with a nominal content of more than 100 mL and when the content is equivalent to a dose of more than 1.4 mL per kilogram of body mass, liquid preparations for injection or infusion, if applicable after reconstitution, comply with the test for particulate contamination: sub-visible particles.

Particulate contamination: visible particles (*2.9.20*)

Liquid preparations for injection or infusion, if applicable after reconstitution, examined under suitable conditions of visibility, are practically free from visible particles.

Recommendations on testing for visible particles are given in general chapter 5.17.2.

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

Sterility (*2.6.1*)

Parenteral preparations comply with the test.

Bacterial endotoxins - pyrogens

Parenteral preparations for human use, if applicable after reconstitution or dilution, comply with the test for bacterial endotoxins (*2.6.14*) or, where justified and authorised, with the test for pyrogens (*2.6.8*). Recommendations on the limits for bacterial endotoxins are given in general chapter *5.1.10*. The limit for intravitreal preparations is expressed per eye.

Where the label states that the preparation is free from bacterial endotoxins or that it is apyrogenic, the preparation complies with the test for bacterial endotoxins (*2.6.14*) or with the test for pyrogens (*2.6.8*), respectively.

Parenteral preparations for veterinary use comply with the test for bacterial endotoxins (*2.6.14*) or with the test for pyrogens (*2.6.8*) when the volume to be injected in a single dose is 15 mL or more and is equivalent to a dose of 0.2 mL or

more per kilogram of body mass.

STORAGE

In a sterile, airtight, tamper-evident container.

LABELLING

The label states:

— the name and concentration of any added preservative;

— where applicable, that the solution is to be used with a final filter;

— where applicable, that the preparation is free from bacterial endotoxins or that it is apyrogenic.

INJECTIONS

DEFINITION

Injections are sterile liquid parenteral preparations usually administered as a bolus injection. They are solutions, colloidal dispersions, emulsions or suspensions containing one or more active substances and any added excipients in water, in a suitable non-aqueous liquid, or in a mixture of these vehicles. The non-aqueous liquid may be non-sterile if justified and authorised.

Solutions for injection, examined under suitable conditions of visibility, are practically free from particles.

Emulsions for injection do not show any evidence of phase separation. Suspensions for injection may show a sediment that is readily dispersed on shaking to give a suspension that remains sufficiently stable to enable the correct dose to be delivered.

Aqueous injections supplied in multidose containers contain a suitable preservative at a suitable concentration except where the preparation itself has adequate antimicrobial properties. When an injection is supplied in a multidose container, the precautions to be taken for its administration and more particularly for its storage between successive withdrawals are stated on the label.

Aqueous injections that are prepared using aseptic precautions and that cannot be terminally sterilised may contain a suitable preservative at a suitable concentration.

No preservative is added when:

— the volume to be injected in a single dose exceeds 15 mL, unless otherwise justified;

— the injection is intended for administration by routes where, for medical reasons, a preservative is not acceptable, such as intracisternally, epidurally, intrathecally or by any route giving access to the cerebrospinal fluid, or intra- or retro-ocularly.

Such preparations are supplied in single-dose containers.

PRODUCTION

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

For injections supplied in single-dose containers, the volume of the injection in the container is sufficient to permit the withdrawal and administration of the nominal dose (*2.9.17*).

TESTS

Uniformity of dosage units (*2.9.40*)

Emulsions and suspensions for injection supplied in single-dose containers comply with the test or, where justified and authorised, with the test for uniformity of content shown below. Herbal drugs and herbal drug preparations present in the dosage form are not subject to the provisions of this paragraph.

Uniformity of content (*2.9.6*)

Unless otherwise prescribed or justified and authorised, emulsions and suspensions for injection supplied in single-dose containers and having a content of active substance less than 2 mg or less than 2 per cent of the total mass comply with the requirements under Test A. If the preparation contains more than one active substance, the requirement applies only to those substances that correspond to the above conditions.

INFUSIONS

DEFINITION

Infusions are sterile liquid parenteral preparations intended for administration in large volumes, usually slowly over a given period of time. They are aqueous solutions, colloidal dispersions or emulsions with an aqueous continuous phase. Their tonicity is usually adjusted relative to blood. They do not contain any added preservatives.

Solutions for infusion, examined under suitable conditions of visibility, are practically free from particles.

Emulsions for infusion do not show any evidence of phase separation.

PRODUCTION

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

The volume of the infusion in the container is sufficient to permit the withdrawal and administration of the nominal dose (*2.9.17*).

CONCENTRATES FOR INJECTIONS OR INFUSIONS

DEFINITION

Concentrates for injections or infusions are sterile solutions or dispersions intended for injection or infusion after dilution to the prescribed volume with a prescribed liquid. After dilution, they comply with the requirements for injections or for infusions.

LABELLING

The label states that the preparation must be diluted before injection or infusion.

POWDERS FOR INJECTIONS OR INFUSIONS

DEFINITION

Powders for injections or infusions are sterile parenteral preparations intended for injection or infusion after reconstitution with the prescribed volume of a prescribed sterile liquid. They may be prepared by lyophilisation.

They are supplied in their final containers and, when reconstituted, rapidly form either practically particle-free solutions or uniform dispersions. After dissolution or dispersion, they comply with the requirements for injections or for infusions.

Freeze-dried products for parenteral administration are considered to be powders for injections or infusions.

PRODUCTION

For freeze-dried products for parenteral administration, the uniformity of content and uniformity of mass are ensured by the in-process control of the amount of the solution prior to freeze-drying.

TESTS

Uniformity of dosage units (*2.9.40*)

Powders for injections or infusions comply with the test or, where justified and authorised, with the tests for uniformity of content and/or uniformity of mass shown below. Herbal drugs and herbal drug preparations present in the dosage form are not subject to the provisions of this paragraph.

Uniformity of content (*2.9.6*)

Unless otherwise prescribed or justified and authorised, powders for injections or infusions having a content of active substance less than 2 mg or less than 2 per cent of the total mass, or with a unit mass equal to or less than 40 mg comply with the requirements under Test A. If the preparation contains more than one active substance, the requirement applies only to those substances that correspond to the above conditions.

Uniformity of mass (*2.9.5*)

Powders for injections or infusions comply with the test. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

LABELLING

The label states the instructions for the preparation of injections and infusions.

GELS FOR INJECTION

DEFINITION

Gels for injection are sterile viscoelastic parenteral preparations formulated to ensure modified release of the active substance(s) at the site of injection.

TESTS

Release of active substance(s)

A suitable test is carried out to demonstrate the appropriate release of the active substance(s).

IMPLANTS

DEFINITION

Implants are sterile solid preparations of a size and shape suitable for parenteral implantation and release of the active substance(s) over an extended period of time. Each dose is supplied in a sterile container.

TESTS

Release of active substance(s)

A suitable test is carried out to demonstrate the appropriate release of the active substance(s).

Uniformity of dosage units (*2.9.40*)

Implants comply with the test or, where justified and authorised, with the tests for uniformity of content and/or uniformity of mass shown below.

Uniformity of content (*2.9.6*)

Unless otherwise prescribed or justified and authorised, implants having a content of active substance less than 2 mg or less than 2 per cent of the total mass, or with a unit mass equal to or less than 40 mg comply with the requirements under Test A. If the preparation contains more than one active substance, the requirement applies only to those substances that correspond to the above conditions.

Uniformity of mass (*2.9.5*)

Implants comply with the test. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

INTRAVITREAL PREPARATIONS

DEFINITION

Intravitreal preparations are sterile parenteral preparations intended for administration or implantation into the vitreous humour. They are solutions, colloidal dispersions, emulsions, suspensions or implants and comply with the requirements

for injections or implants, as appropriate. Unless otherwise justified and authorised, they are supplied in single-dose containers and do not contain any preservatives.

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