DRAFT PROPOSAL FOR REVISION OF

GENERAL MONOGRAPHS: PARENTERAL PREPARATIONS

(July 2012)

Draft for comment

This document was provided by a quality control expert. Should you have any comments thereon, please send these to Dr Herbert Schmidt, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mail: schmidt@who.int with a copy to gaspardm@who.int by 7 September 2012.

In order to speed up the process for receiving draft monographs and for sending comments, please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

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**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/12.479**

*Draft proposal for revision of a published monograph in the Fourth Edition of The International Pharmacopoeia*

**PARENTERAL PREPARATIONS**

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DRAFT PROPOSAL FOR REVISION OF

GENERAL MONOGRAPHs: PARENTERAL PREPARATIONS

[Note from the Secretariat:
Revision proposals for this general monograph are part of the review of general monographs endorsed by the Expert Committee at its 42nd meeting. Account has been taken of the recently adopted revised texts for 3.2 Test for sterility, 3.4 Test for bacterial endotoxins, 5.6 Extractable volume and 5.7 Test for particulate contamination.

One of the major changes proposed is the required compliance of all parenteral preparations with tests for bacterial endotoxins (or, where justified, pyrogens). As a consequence, a review of the individual monographs for injections is necessary with addition of a test and limit for bacterial endotoxins to each monograph that currently does not include such a requirement.]

PARENTERAL PREPARATIONS

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 are sterile, pyrogen-free liquids (solutions, emulsions, or suspensions) or solid dosage forms containing one or more active ingredients, packaged in either single-dose or multidose containers. They are intended for administration by injection, infusion, or implantation into the body.

Preparations such as vaccines, human blood and products derived from human blood, peritoneal dialysis solutions, and radioactive pharmaceuticals require special formulation, methods of manufacture, or presentation appropriate to their particular use and may not comply with certain parts of this monograph.
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. It is freshly distilled by the process described under Water for injections, be free from carbon dioxide and complies with Test for bacterial endotoxins. Sterilization at this stage may be omitted, provided that the solution or preparation is immediately sterilized upon finalization. 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. Definition of a particular parenteral preparation as a solution, emulsion or suspension in Water for Injections in the individual monograph does not preclude the inclusion of such substances, where necessary, for this purpose.

There are four five main forms of parenteral preparations:

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Certain injections and intravenous infusions may be presented in the form of sterile concentrated solutions, which must be suitably diluted before use.

Parenteral preparations may contain excipients such as solvents, suspending agents, buffering agents, substances to make the preparation isotonic with blood, stabilizers, or antimicrobial preservatives. The addition of excipients should be kept to a minimum. When excipients are used, they should 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.

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, indicating those that are the most important.
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. From the clinical viewpoint all parenteral preparations must be pyrogen-free. For practical purposes, however, certain categories of parenteral preparations may be exempted from the test for bacterial endotoxins or the test for pyrogens as specified in the individual monograph.

During the development of a preparation, the formulation for which contains one or more antimicrobial preservatives, the effectiveness of the chosen preservative system 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 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 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 injections and infusions 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 Test for extractable volume.

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 container (absence of leakage, etc.). For dispersions controls should also include the particle size of the dispersed phase. For powders for injections controls should also include the uniformity of content and 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.

The presence of preservatives or other additives should be determined as these can influence the choice of assay method.

Containers
Parenteral preparations are usually supplied in glass ampoules, bottles or vials, plastic bottles or bags, and prefilled syringes, which are coloured in the case of light-sensitive substances.

Except where otherwise indicated in individual monographs, these 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. Plastic materials or elastomers of which the closure is composed are 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 the solutions and reconstituted solutions, using at least 20 containers for single-dose preparations and intravenous parenteral infusions (except dispersions). 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

All Intravenous parenteral preparations and powders for injections where the volume to be injected in a single dose is 15 ml or more comply with 3.4 Test for bacterial endotoxins, using the method indicated in the individual monograph; or, where justified, with 3.5 Test for pyrogens. In addition, where specified in the individual monographs for certain preparations where the active ingredients are of biological origin, injections and powders for injections must comply with the appropriate test, irrespective of the volume to be injected in a single dose. For injections, the amount to be tested should relate to the volume of the dose and should be specified in the individual monograph.
For powders and concentrates for injections and intravenous infusions, the amount of powder 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 infusion and solutions for injection comply with 5.7.1 Test 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, providing it has been demonstrated that the filter delivers a solution that complies with the test.

*Note from the Secretariat:* As a consequence of this proposed new requirement it will be necessary to review the individual monographs for injections to ascertain whether there are any, such as any intended for subcutaneous or intramuscular injection, for which it may be appropriate to set higher limits.

It will also be necessary to add an appropriate statement to the general monograph for Radiopharmaceutical Preparations exempting these preparations.]

**Labelling**

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

The label should include, as required by the national legislation, at least the following:

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 in uncoded form;
6. any special storage conditions or handling precautions that may be necessary;
7. directions for use, warnings, and precautions that may be necessary;
the name and address of the manufacturer or the person responsible for placing the product on the market.

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.

The use of single-dose injections without antimicrobial preservative is to be preferred and is essential when the preparation is intended for administration by routes where, for medical reasons, an antimicrobial preservative is not acceptable, e.g. intracisternally, intrathecally, epidurally or by any route giving access to the cerebrospinal fluid, or intra- or retroocularly.

Single-dose preparations

Single-dose preparations should contain a sufficient quantity of the injection readily to permit the withdrawal and administration of the volume specified on the label.

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. The particle size of the dispersed phase should be controlled by the manufacturer.

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 shaken with the prescribed volume of the appropriate sterile liquid, 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 (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

A requirement for compliance with the test for 5.1 Uniformity of content for single-dose preparations is specified in certain individual monographs where the active ingredient is less than 40 mg. In such cases, compliance with the test for 5.2 Uniformity of mass for single-dose preparations may not be 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.

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