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Pharmaceutical Preparations

General Notices

(Ph. Eur. monograph 2619)

Ph Eur

INTRODUCTION

This monograph is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms, which are to be applied in the manufacture/preparation of pharmaceuticals, but not a guide on how to manufacture as there is specific guidance available covering methods of manufacture and associated controls.

It does not cover investigational medicinal products, but competent authorities may refer to pharmacopoeial standards when authorising clinical trials using investigational medicinal products.

DEFINITION

Pharmaceutical preparations are medicinal products generally consisting of active substances that may be combined with excipients, formulated into a dosage form suitable for the intended use, where necessary after reconstitution, presented in a suitable and appropriately labelled container.

Pharmaceutical preparations may be licensed by the competent authority, or unlicensed and made to the specific needs of patients according to legislation. There are 2 categories of unlicensed pharmaceutical preparations:

— extemporaneous preparations, i.e. pharmaceutical preparations individually prepared for a specific patient or patient group, supplied after preparation;

— stock preparations, i.e. pharmaceutical preparations prepared in advance and stored until a request for a supply is received.

In addition to this monograph, pharmaceutical preparations also comply with the General Notices and with the relevant general chapters of the Pharmacopoeia. General chapters are normally given for information and become mandatory when referred to in a general or specific monograph, unless such reference is made in a way that indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information.

Where relevant, pharmaceutical preparations also comply with the dosage form monographs (e.g. *Capsules (0016)*, *Tablets (0478)*) and general monographs relating to pharmaceutical preparations (e.g. *Allergen products (1063)*, *Herbal teas (1435)*, *Homoeopathic preparations (1038)*, *Homoeopathic pillules, coated (2786)*, *Homoeopathic pillules, impregnated (2079)*, *Immunosera for human use, animal (0084)*, *Immunosera for veterinary use (0030)*, *Live biotherapeutic products for human use (3053)*, *Monoclonal antibodies for human use (2031)*, *Radiopharmaceutical preparations (0125)*, *Vaccines for human use (0153)*, *Vaccines for veterinary use (0062)*).

ETHICAL CONSIDERATIONS AND GUIDANCE IN THE PREPARATION OF UNLICENSED PHARMACEUTICAL PREPARATIONS

The underlying principle of legislation for pharmaceutical preparations is that, subject to specific exemptions, no pharmaceutical preparation may be placed on the market without an appropriate marketing authorisation. The exemptions from the formal licensing requirement allow the supply of unlicensed products to meet the special needs of individual

patients. However, when deciding to use an unlicensed preparation all health professionals involved (e.g. the prescribing practitioners and/or the preparing pharmacists) have, within their area of responsibilities, a duty of care to the patient receiving the pharmaceutical preparation.

In considering the preparation of an unlicensed pharmaceutical preparation, a suitable level of risk assessment is undertaken.

The risk assessment identifies:

— the criticality of different parameters (e.g. quality of active substances, excipients and containers; design of the preparation process; extent and significance of testing; stability of the preparation) to the quality of the preparation; and

— the risk that the preparation may present to a particular patient group.

Based on the risk assessment, the person responsible for the preparation must ensure, with a suitable level of assurance, that the pharmaceutical preparation is, throughout its shelf-life, of an appropriate quality and suitable and fit for its purpose. For stock preparations, storage conditions and shelf-life have to be justified on the basis of, for example, analytical data or professional judgement, which may be based on literature references.

PRODUCTION

Manufacture/preparation must take place within the framework of a suitable quality system and be compliant with the standards relevant to the type of product being made. Licensed products must comply with the requirements of their licence. For unlicensed products a risk assessment as outlined in the section ‘Ethical considerations and guidance in the preparation of unlicensed pharmaceutical preparations' is of special importance, as these products are not previously assessed by the competent authority.

Where pharmaceutical preparations are manufactured/prepared using materials of human or animal origin, the general requirements of general chapters *5.1.7. Viral safety* and *5.2.6. Evaluation of safety of veterinary vaccines and immunosera* and of the general monograph *Products with risk of transmitting agents of animal spongiform encephalopathies (1483)* apply, where appropriate.

Formulation

During pharmaceutical development or prior to manufacture/preparation, suitable ingredients, processes, tests and specifications are identified and justified in order to ensure the suitability of the product for the intended purpose. This includes consideration of the properties required in order to identify whether specific ingredient properties or process steps are critical to the required quality of the pharmaceutical preparation.

Active substances and excipients

Active substances and excipients used in the formulation of pharmaceutical preparations comply with the requirements of the relevant general monographs, e.g. *Substances for pharmaceutical use (2034)*, *Essential oils (2098)*, *Herbal drug extracts (0765)*, *Herbal drugs (1433)*, *Herbal drug preparations (1434)*, *Herbal drugs for homoeopathic preparations (2045)*, *Mother tinctures for homoeopathic preparations (2029)*, *Methods of preparation of homoeopathic stocks and potentisation (2371)*, *Products of fermentation (1468)*, *Products of recombinant DNA technology (0784)*, *Vegetable fatty oils (1579)*.

In addition, where specific monographs exist, the quality of the active substances and excipients used complies with the corresponding monographs.

Where no specific monographs exist, the required quality must be defined, taking into account the intended use and the involved risk.

When physicochemical characteristics of active substances and functionality-related characteristics (FRCs) of excipients (e.g. particle-size distribution, viscosity, polymorphism) are critical in relation to their role in the manufacturing process and quality attributes of the pharmaceutical preparation, they must be identified and controlled.

Detailed information on FRCs is given in general chapter *5.15. Functionality-related characteristics of excipients*.

Microbiological quality

The formulation of the pharmaceutical preparation and its container must ensure that the microbiological quality is suitable for the intended use.

During development, it shall be demonstrated that the antimicrobial activity of the preparation as such or, if necessary, with the addition of a suitable preservative or preservatives, or by the selection of an appropriate container, provides adequate protection from adverse effects that may arise from microbial contamination or proliferation during the storage and use of the preparation. A suitable test method together with criteria for evaluating the preservative properties of the formulation are provided in general chapter *5.1.3. Efficacy of antimicrobial preservation*.

If preparations do not have adequate antimicrobial efficacy and do not contain antimicrobial preservatives they are supplied in single-dose containers, or in multidose containers that prevent microbial contamination of the contents after opening.

In the manufacture/preparation of non-sterile pharmaceutical preparations, suitable measures are taken to ensure their microbial quality; recommendations on this aspect are provided in general chapters *5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use* and *5.1.8. Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation*.

Sterile preparations are manufactured/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*.

N-Nitrosamines

As many *N*-nitrosamines are classified as probable human carcinogens, manufacturers of medicinal products, except products for veterinary use only and unlicensed pharmaceutical preparations, are expected to evaluate the potential risk of *N*-nitrosamine formation and contamination occurring throughout their manufacturing process and throughout their shelf-life, according to the requirements of the relevant competent authorities. If the risk is confirmed, manufacturers should mitigate as much as possible the presence of *N*-nitrosamines – for example by modifying the manufacturing process – and a control strategy must be implemented to detect and control these impurities. General chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

Containers

A suitable container is selected. Consideration is given to the intended use of the preparation, the properties of the container, the required shelf-life, and product/container incompatibilities. Where applicable, containers for pharmaceutical preparations comply with the requirements for containers (*3.2* and subsections) and materials used for the manufacture of containers (*3.1* and subsections).

Stability

Stability requirements of pharmaceutical preparations are dependent on their intended use and on the desired storage time.

Where applicable, the probability and criticality of possible degradation products of the active substance(s) and/or reaction products of the active substance(s) with an excipient and/or the immediate container must be assessed. Depending on the result of this assessment, limits of degradation and/or reaction products are set and monitored in the pharmaceutical preparation. Licensed products require a stability exercise.

Methods used for the purpose of stability testing for all relevant characteristics of the preparation are validated as stability indicating, i.e. the methods allow the quantification of the relevant degradation products and physical characteristic changes.

TESTS

Relevant tests to apply in order to ensure the appropriate quality of a particular dosage form are described in the specific dosage form monographs.

Where it is not practical, for unlicensed pharmaceutical preparations, to carry out the tests (e.g. batch size, time restraints), other suitable methods are implemented to ensure that the appropriate quality is achieved in accordance with the risk assessment carried out and any local guidance or legal requirements.

Stock preparations are normally tested to a greater extent than extemporaneous preparations.

The following tests are applicable to many preparations and are therefore listed here.

Appearance

The appearance (e.g. size, shape and colour) of the pharmaceutical preparation is controlled.

Identity and purity tests

Where applicable, the following tests are carried out on the pharmaceutical preparation:

— identification of the active substance(s);

— identification of specific excipient(s), such as preservatives;

— purity tests (e.g. investigation of degradation products, residual solvents (2.4.24) or other related impurities, sterility (2.6.1));

— safety tests (e.g. safety tests for biological products).

Related substances

Medicinal products containing one or more chemically defined active substances comply with the test(s) for related substances in the relevant individual monograph.

In exceptional circumstances and if justified by the applicant to the satisfaction of the competent authority, the latter may approve a wider limit than that described in the monograph. In these rare cases, the competent authority shall bring this to the attention of the Ph. Eur. Commission for review of the monograph and, where appropriate, its revision.

Elemental impurities

General chapter 5.20. *Elemental impurities* applies to pharmaceutical preparations except products for veterinary use, unlicensed preparations and other products that are excluded from the scope of this chapter.

For pharmaceutical preparations outside the scope of general chapter 5.20, manufacturers of these products remain responsible for controlling the levels of elemental impurities using the principles of risk management.

If appropriate, testing is performed using suitable analytical procedures according to general chapter 2.4.20. *Determination of elemental impurities*.

Uniformity (2.9.40 or 2.9.5/2.9.6)

Pharmaceutical preparations presented in single-dose units comply with the test(s) as prescribed in the relevant specific dosage form monograph. If justified and authorised, general chapter 2.9.40 can be applicable only at the time of release.

Special uniformity requirements apply in the following cases:

— for herbal drugs and herbal drug preparations, compliance with general chapter 2.9.40 is not required;

— for homoeopathic preparations, the provisions of general chapters 2.9.6 and 2.9.40 are normally not appropriate, however in certain circumstances compliance with these chapters may be required by the competent authority;

— for single- and multivitamin and trace-element preparations, compliance with general chapters 2.9.6 and 2.9.40 (*content uniformity only*) is not required;

— in justified and authorised circumstances, for other preparations, compliance with general chapters 2.9.6 and 2.9.40 may not be required by the competent authority.

Reference standards

Reference standards may be needed at various stages for quality control of pharmaceutical preparations. They are established and monitored taking due account of general chapter 5.12. *Reference standards*.

ASSAY

Unless otherwise justified and authorised, contents of active substances and specific excipients such as preservatives are determined in pharmaceutical preparations. Limits must be defined and justified.

Suitable and validated methods are used. If assay methods prescribed in the respective active substance monographs are used, it must be demonstrated that they are not affected by the presence of the excipients and/or by the formulation.

Reference standards

See Tests.

LABELLING AND STORAGE

The relevant labelling requirements given in the general dosage form monographs apply. In addition, relevant European Union or other applicable regulations apply.

GLOSSARY

Formulation

The designing of an appropriate formula (including materials, processes, etc.) that will ensure that the patient receives the suitable pharmaceutical preparation in an appropriate form that has the required quality and that will be stable and effective for the required length of time.

Licensed pharmaceutical preparation

A medicinal product that has been granted a marketing authorisation by a competent authority.

Manufacture

All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

Preparation (of an unlicensed pharmaceutical preparation)

The ‘manufacture' of unlicensed pharmaceutical preparations by or at the request of pharmacies or other healthcare establishments (the term ‘preparation' is used instead of ‘manufacture' in order clearly to distinguish it from the industrial manufacture of licensed pharmaceutical preparations).

Reconstitution

Manipulation to enable the use or application of a medicinal product with a marketing authorisation in accordance with the instructions given in the summary of product characteristics or the patient information leaflet.

Risk assessment

The identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Unlicensed pharmaceutical preparation

A medicinal product that is exempt from the need of having a marketing authorisation issued by a competent authority but is made for specific patients' needs according to legislation.

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