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1.1 GENERAL STATEMENTS

1.1.1 General principles

The General Notices apply to all texts of the European Pharmacopoeia.

The texts of the European Pharmacopoeia are published in English and French. Translations in other languages may be prepared by the signatory States of the European Pharmacopoeia Convention. In case of doubt or dispute, the English and French versions published by the EDQM are alone authoritative.

The date on which texts of the European Pharmacopoeia are to be implemented is fixed by a resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care (Partial Agreement) of the Council of Europe, following a recommendation by the Ph. Eur. Commission. This date is usually 1 year after adoption and about 6 months after publication. Where a text needs to be implemented at a date earlier than the next publication date of a new edition or supplement of the European Pharmacopoeia, a resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care is issued, giving the full text to be implemented. The text is also published in Pharmeuropa Online for information and posted on the EDQM website as part of the resolution.

In the texts of the European Pharmacopoeia, the word '*Pharmacopoeia*' without qualification means the European Pharmacopoeia. The official abbreviation '*Ph. Eur.*' may also be used for this purpose.

1.1.1.1 Quality systems

The quality standards represented by monographs are valid only where the articles in question are produced within the framework of a suitable quality system. The quality system must assure that the articles consistently meet the requirements of the Ph. Eur.

1.1.1.2 Conventional terms

Medicinal product. (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings and/or animals; or (b) any substance or combination of substances that may be used in or administered to human beings and/or animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Active substance. Any substance intended to be used in the manufacture of a medicinal product and that, when so used, becomes an active ingredient of the medicinal product. Such substances are intended to have a pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

Excipient (auxiliary substance). Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilisers, antimicrobial preservatives, diluents and antioxidants are examples of excipients.

Herbal medicinal product. Any medicinal product exclusively containing as active ingredients one or more herbal drugs or one or more herbal drug preparations, or one or more such herbal drugs in combination with one or more such herbal drug preparations.

Competent authority. The national, supranational or international body or organisation vested with the authority for making decisions concerning the issue in question. It may, for example, be a national pharmacopoeia authority (NPA), a licensing authority or an official medicines control laboratory (OMCL).

'*Unless otherwise justified and authorised*'. This expression means that the requirements must be met, unless the competent authority authorises a modification (e.g. of an analytical procedure or limit) or an exemption, if justified by the manufacturer in a particular case.

'*Should*'. Statements containing the word '*should*' are informative or advisory.

'*Suitable*', '*appropriate*'. In certain texts, the terms '*suitable*' and '*appropriate*' are used to describe a reagent, test, micro-organism, etc.; in such cases, if criteria for suitability are not described in the text, suitability is demonstrated to the satisfaction of the competent authority.

1.1.1.3 References to regulatory documents

Monographs and general chapters may contain references to documents issued by regulatory authorities for medicines, for example directives and notes for guidance of the European Union. These references are provided to users of the Ph. Eur. for information. Inclusion of such a reference does not modify the status of the documents referred to, unless explicitly stated in the text.

1.1.2 Compliance with the Ph. Eur.

1.1.2.1 Scope

The use of the title or the Latin subtitle of a monograph implies that the article complies with the requirements of that monograph. Such references to monographs in the texts of the Ph. Eur. are shown using the monograph title and reference number in *italics*.

The scope of a monograph is stated in its definition.

Shelf life and re-test period. A medicinal product must comply with the relevant monograph throughout its shelf life; the shelf life and the time point from which that period is to be calculated are proposed by the manufacturer in light of experimental results of stability studies and are approved by the competent authority. A distinct shelf life and/or specifications for opened or broached containers may be decided by the competent authority. Monographs on medicinal products provide shelf-life specifications that may differ from release specifications indicated in marketing authorisations.

The subject of any other monograph must comply throughout its re-test period, except for some substances (e.g. substances known to be labile, biotechnological/biological substances and certain antibiotics) where a shelf life is established rather than a re-test period.

Human and/or veterinary use. The active substances, excipients, medicinal products and other articles described in monographs are intended for human and veterinary use unless explicitly restricted to one of these uses in the title or the definition.

Grades. Certain articles that are the subject of a monograph may exist in different grades that are suitable for different purposes. Unless otherwise indicated in the monograph, the requirements apply to all grades of the article.

In some monographs, particularly those on excipients, a list of functionality-related characteristics that are relevant to the use of the substance may be appended to the monograph, for information. Analytical procedures for determination of one or more of these characteristics may be given, also for information.

1.1.2.2 Demonstration of compliance with the Ph. Eur.

Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements.

(1) An article is of Ph. Eur. quality if it complies with all of the requirements stated in the monograph. This does not imply that a manufacturer must perform all of the tests described in a monograph when assessing compliance with the Ph. Eur. before release. The manufacturer may obtain assurance that an article is of Ph. Eur. quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process.

In certain monographs, the sentence '*The following procedure is given as an example*' means that the analytical procedure described has been validated and may be implemented as is or may be replaced by a suitable, validated procedure (without having to demonstrate its equivalence to the '*example*' procedure), subject to approval by the competent authority.

(2) An enhanced approach to quality control could utilise process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone. Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Ph. Eur.

(3) Reduction of animal testing: the Ph. Eur. is committed to phasing out the use of animals for test purposes, in accordance with the 3Rs (Replacement, Reduction, Refinement) set out in the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. In demonstrating compliance with the Ph. Eur. as indicated above (1), manufacturers may consider establishing additional systems to monitor consistency of production. With the agreement of the competent authority, the choice of tests performed to assess compliance with the Ph. Eur. when animal tests are prescribed is established in such a way that animal usage is kept to a minimum.

1.1.2.3 Demonstration of suitability of monographs

The manufacturer must evaluate the suitability of the monograph for the quality control of their substance or medicinal product, since the choice of analytical procedures may be influenced by the manufacturing process and/or the composition of the medicinal product. In cases where the specification described in a monograph is considered to be insufficient to ensure the quality of the product or substance by a competent authority, the latter may request more-appropriate specifications from the manufacturer in line with national or regional regulations. In such cases, the competent authority informs the Ph. Eur. Commission through either the national pharmacopoeia authority or the Secretariat of the Ph. Eur. Commission (EDQM). The manufacturer is requested to provide the national pharmacopoeia authority or the EDQM with the details of the alleged insufficiency and the additional specifications applied, so that the Ph. Eur. Commission can decide on the need to revise the monograph in question.

1.1.2.4 Validation and implementation of Ph. Eur. analytical procedures

The analytical procedures given in an individual monograph have been validated in accordance with accepted scientific practice and recommendations on analytical validation. Unless otherwise stated in the individual monograph or in the corresponding general chapter, validation of these procedures by the user is not required.

The analytical procedures provided in general chapters may be used for active substances, excipients, medicinal products and other articles that are not covered by an individual monograph. In such cases, validation of the procedures is the responsibility of the user.

When implementing a Ph. Eur. analytical procedure, the user must assess whether and to what extent its suitability under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.

1.1.2.5 Alternative analytical procedures

The tests and assays described are the official analytical procedures upon which the standards of the Ph. Eur. are based. With the agreement of the competent authority, alternative analytical procedures may be used for control

purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used. In the event of doubt or dispute, the analytical procedures of the Ph. Eur. are alone authoritative.

1.1.2.6 Pharmacopoeial harmonisation

The Ph. Eur. is engaged in a process of pharmacopoeial harmonisation with the Japanese Pharmacopoeia and the United States Pharmacopeia, within an informal structure referred to as the Pharmacopoeial Discussion Group (PDG). More information is available in general chapter *5.8. Pharmacopoeial harmonisation*.

1.2 OTHER PROVISIONS APPLYING TO MONOGRAPHS AND GENERAL CHAPTERS

1.2.1 Quantities

In tests with numerical limits and assays, the quantity stated to be taken for examination corresponds to the quantity used during development of the analytical procedure. The amount actually used may deviate by not more than 10 per cent from the stated quantity. In all cases, the amount used is accurately measured and the result of the test is calculated from this exact quantity.

In tests where the limit is not numerical, which usually depend instead upon comparison with the behaviour of a reference substance in the same conditions, the stated quantity is taken for examination.

Reagents are used in the prescribed amounts.

The number of significant figures of a quantity value implies specific requirements for the quantities (masses and volumes) to be measured, as detailed below.

For masses, requirements for balances for analytical purposes are provided in general chapter *2.1.7* and are applicable to all texts. In addition, during weighing, the indication of a balance must match the target mass value given in the text when mathematically rounded to the same number of significant figures. For example, if the target mass value in the text is 50.0 mg, the '*minimum weight*' (m_{min}) of the balance used must be smaller and the weighing is done within ± 5 subunits after the last figure of the stated mass value (for example, 50.0 mg is to be interpreted as 49.95 mg to 50.04 mg or 49.950 mg to 50.049 mg, depending on the readability of the balance).

For volumes, if the figure after the decimal point is a zero or ends in a zero (for example, 10.0 mL or 0.50 mL), the target volume is measured using a volumetric pipette, a volumetric flask or a burette, as appropriate; otherwise, a graduated measuring cylinder or a graduated pipette may be used. Volumes stated in microlitres are measured using a micropipette or microsyringe.

It is recognised, however, that in certain cases the number of significant figures with which quantities are stated does not correspond to the number of significant figures stated in a specified numerical limit. The stated quantities are then measured with a sufficiently improved accuracy.

1.2.2 Glassware

Volumetric glassware complies with Class A requirements of the appropriate International Standard issued by the International Organisation for Standardisation (ISO).

Unless otherwise prescribed, visual comparative tests are carried out using identical colourless, transparent, neutral glass tubes with a flat base; the volumes of liquid prescribed are for use with tubes having an internal diameter of 16 mm, but tubes with a larger internal diameter may be used provided the volume of liquid used is adjusted (see general chapter *2.1.5. Tubes for comparative tests*). Equal volumes of the liquids to be compared are examined down the vertical axis of the tubes against a white background, or if necessary against a black background. The examination is carried out in diffuse light.

1.2.3 Temperature

Unless otherwise prescribed, analytical procedures are carried out at a temperature between 15 °C and 25 °C.

Where a text describes a temperature without giving a figure, the general terms used have the following meaning:

- in a deep-freeze: below – 15 °C;
- in a refrigerator: 2 °C to 8 °C;
- cold or cool: 8 °C to 15 °C;
- room temperature: 15 °C to 25 °C.

1.2.4 Water-bath

The term '*water-bath*' means a bath of boiling water unless water at another temperature is indicated. Other methods of heating may be substituted provided the temperature is near to but not higher than 100 °C or the indicated temperature.

1.2.5 Drying and ignition to constant mass

The terms '*dried to constant mass*' and '*ignited to constant mass*' mean that 2 consecutive weighings do not differ by more than 0.5 mg, the second weighing carried out after an additional period of drying or ignition appropriate to the nature and quantity of the residue.

Where drying is prescribed using one of the expressions '*in a desiccator*' or '*in vacuo*', it is carried out using the conditions described in general chapter *2.2.32. Loss on drying*.

1.2.6 Solutions

'*Freshly prepared solution*' means that the solution is prepared each time the test/assay is to be carried out and is used within 24 h.

'*Immediately before use*' indicates that the stability of the corresponding solution(s) has been found to be critical during the elaboration of the text. The time between preparation and use must be minimised.

1.2.7 Reagents and solvents

The proper conduct of the analytical procedures described in the Ph. Eur. and the reliability of the results depend, in part, upon the quality of the reagents used. The reagents are described in the Ph. Eur. in *4. Reagents* and subsections. It is assumed that reagents of analytical grade are used; for some reagents, tests to determine suitability are included in the description.

Any solvent required in a test or assay in which an indicator is to be used is previously neutralised to the indicator, unless a blank determination is prescribed.

Where the name of the solvent is not stated, the term '*solution*' implies a solution in water.

Where the use of water is specified or implied in the analytical procedures described in the Ph. Eur. or for the preparation of reagents, water complying with the requirements of the monograph *Purified water (0008)* is used, except that for many purposes the requirements for bacterial endotoxins (Purified water in bulk) and microbial contamination (Purified water in containers) are not relevant. The term '*distilled water*' indicates purified water prepared by distillation.

Dilutions of ethanol are indicated by the term '*ethanol*' or '*alcohol*' followed by a statement of the percentage by volume of ethanol (C_2H_6O) required.

1.2.8 Expression of content

In defining content, the expression '*per cent*' is used according to circumstances with one of two meanings:

- '*per cent m/m*' (percentage, mass in mass) expresses the number of grams of substance in 100 g of final product;
- '*per cent V/V*' (percentage, volume in volume) expresses the number of millilitres of substance in 100 mL of final product.

The expressions '*parts per million*' (ppm) and '*parts per billion*' (ppb) refer to mass in mass, unless otherwise specified.

1.2.9 Caution statements

Articles described in monographs and reagents specified for use in the Ph. Eur. may be injurious to health unless adequate precautions are taken. The principles of good quality control laboratory practice and the provisions of any appropriate regulations are to be observed at all times. Attention is drawn to particular hazards in certain monographs or general chapters by means of a caution statement; absence of such a statement is not to be taken to mean that no hazard exists.

1.3 GENERAL CHAPTERS

General chapters (see sections 2, 3 and 5 of the Ph. Eur.) become mandatory when referred to in a monograph, unless the wording clearly indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information.

When a general chapter is not referred to in any monograph or general chapter, it is given for information; this is usually indicated in the preamble to the general chapter.

General chapters also become mandatory when referred to in another general chapter that is itself referred to in a monograph, unless otherwise stated.

Requirements included in general chapters are not repeated in the individual monographs, unless specific to the article in question (e.g. symmetry factor, signal-to-noise ratio of general chapter *2.2.46. Chromatographic separation techniques*).

1.3.1 Materials for containers and containers

Materials used for containers are described in *3.1. Materials used for the manufacture of containers* and subsections. Each subsection covers a defined plastic material with a positive list of accepted additives. The specifications for each of these materials depend on the formulation and are therefore applicable only for materials whose formulation is covered by the preamble to the specification. The use of materials with different formulations, and the corresponding tests and limits applied to them, are subject to approval by the competent authority.

The specifications for containers in *3.2. Containers* and subsections have been developed for general application to containers of the stated category, but in view of the wide variety of containers available and possible new developments, the publication of a specification does not exclude the use, in justified circumstances, of containers that comply with other specifications, subject to approval by the competent authority.

Containers for human blood and blood components, transfusion sets and syringes that are not designed to serve as primary packaging for medicinal products are described in *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes* and subsections. Most of these texts are published for information only.

Reference may be made within the monographs of the Ph. Eur. to the definitions and specifications for containers. The general monographs on dosage forms may, in the Definition/Production section, require the use of certain types of container, as described in *3.2. Containers* and subsections; certain other monographs may, in the Storage section, indicate the type of container that is recommended for use.

1.4 GENERAL MONOGRAPHS AND GENERAL MONOGRAPHS ON DOSAGE FORMS

General monographs and individual monographs are complementary.

Whenever an individual monograph is used, it is essential to ascertain whether there are one or more general monographs applicable to the article in question.

Substances and medicinal products that are the subject of an individual monograph are also required to comply with relevant, applicable general monographs. Cross-references to applicable general monographs are not given in individual monographs. However, exceptions are possible; for example, individual monographs on medicinal products containing chemically defined active substances include a reference to the relevant general monograph on the dosage form.

General monographs give requirements that are applicable to all articles in the given class or, in some cases, to any article in the given class for which there is an individual monograph in the Ph. Eur. Where no restriction on scope of a general monograph is given in a preamble, it is applicable to all articles in the class defined, irrespective of whether there is an individual monograph for the article in the Ph. Eur.

If the provisions of a general monograph do not apply to a particular article, this is expressly stated in the individual monograph.

General monographs on dosage forms apply to all medicinal products of the type defined. The requirements are not necessarily comprehensive for a specific medicinal product and requirements additional to those prescribed in the general monograph may be imposed by the competent authority.

1.5 INDIVIDUAL MONOGRAPHS

1.5.1 GENERAL PRINCIPLES

1.5.1.1 Titles

Monograph titles are in English or French in the respective versions and there is a Latin subtitle.

Where available, the international nonproprietary name (INN) is used, unless there are justifiable reasons for not doing so. If needed, it is supplemented by the name of the anion or cation and by the degree of hydration. Additional qualifiers may limit the applicability of the monograph to certain classes or forms (e.g. veterinary use, dosage form, route of administration).

1.5.1.2 Relative atomic and molecular masses, formulae

The relative atomic mass (A_r) or the relative molecular mass (M_r) is shown, where appropriate, at the beginning of each monograph.

The relative atomic and molecular masses and the molecular and graphic formulae do not constitute analytical standards for the substances described.

1.5.1.3 CAS registry number

Chemical Abstract Service (CAS) registry numbers are included for information in monographs, where applicable, to provide convenient access to useful information for users. CAS Registry Number® is a registered trademark of the American Chemical Society.

1.5.1.4 Definition

This section provides the official definition of the article that is the subject of the monograph.

Limits of content. If prescribed, limits of content are those determined using the analytical procedure described under Assay.

1.5.1.5 Production

Statements in the Production section draw attention to particular aspects of the manufacturing process but are not necessarily exhaustive. They constitute mandatory requirements for manufacturers, unless otherwise stated. They may relate, for example, to source materials, to the manufacturing process itself and its validation and control, to process-related heterogeneity of the article, to in-process testing, or to tests that are to be carried out by the manufacturer on the final article, either on selected batches or on each batch prior to release. These requirements cannot necessarily be verified on a sample of the final article by an independent analyst. The competent authority may establish that the instructions have been followed, for example, by examining data received from the manufacturer, through inspection or by testing samples.

The absence of a Production section does not imply that attention to features such as those referred to above is not required.

Choice of vaccine strain, Choice of vaccine composition. The Production section of a vaccine monograph may define the characteristics of a vaccine strain or vaccine composition. Unless otherwise stated, analytical procedures given for verification of these characteristics are provided for information as examples of suitable procedures. Subject to approval by the competent authority, other procedures may be used without validation against the procedure shown in the monograph.

1.5.1.6 Potential adulteration

Due to the rise in fraudulent activities and cases of adulteration, information may be made available to users of the Ph. Eur. to help them detect adulterated articles (i.e. active substances, excipients, intermediate products, bulk products and medicinal products).

To this end, an analytical procedure for the detection of potential adulterants and relevant limits may be included in this section of monographs on substances for which an incident has occurred or which are at risk of deliberate contamination. In such cases, a reminder that a suitable quality system is applied at all stages of production and sourcing is also provided. The frequency of testing by manufacturers or by users (e.g. manufacturers of intermediate products, bulk products and medicinal products) depends on a risk assessment, taking into account the level of knowledge of the whole supply chain and national requirements.

The requirements listed in this section apply to the whole supply chain, from manufacturers to users. The absence of this section does not imply that attention to features such as those referred to above is not required.

1.5.1.7 Characters

The statements in the Characters section do not constitute Ph. Eur. requirements and are given for information only.

Hygroscopicity, crystallinity, solubility. See general chapter *5.11. Characters section in monographs*.

Polymorphism. Where a substance shows polymorphism, this is usually stated. Except in rare cases, no particular crystalline form is required in monographs. However, depending on the function of a given substance in a medicinal product, it may be necessary for a manufacturer to ensure that a particular crystalline form is used. The information given in the Characters section is intended to alert users to the need to evaluate this aspect during the development of a medicinal product. See also general chapter *5.9. Polymorphism*.

1.5.1.8 Identification

Scope. The tests given in the Identification section are not designed to give a full confirmation of the chemical structure or composition of the article; they are intended to give confirmation, with an acceptable degree of assurance, that the article conforms to the description on the label.

An identification test may refer to a test in the Tests section of the monograph.

If the monograph lists, for example, identification tests A, B and C, all three tests must be carried out and must satisfy the requirements.

Certain monographs give two or more sets of identification tests that are equivalent and may be used independently. They are preceded by a sentence of the type '*Carry out either tests A, B or tests C, D*'. For example, one test determines enantiomeric purity by chromatography, while the other is a test for specific optical rotation; the intended purpose of the two is the same, i.e. verification that the correct enantiomer is present.

In some monographs the Identification section is subdivided as follows.

- *First identification*. The test(s) that constitute the first identification may be used in all circumstances.
- *Second identification*. The test(s) that constitute the second identification may be used in pharmacies only, provided it can be demonstrated that the article is fully traceable to a batch certified to comply with all the other requirements of the monograph. The implementation of the tests under the second identification is subject to national regulation.

1.5.1.9 Tests and assays

Scope. The requirements are not designed to take all possible impurities into account. It is not to be presumed, for example, that an impurity that is not detectable by means of the prescribed tests is tolerated if common sense and good pharmaceutical practice require that it be absent. See also under 1.5.1.12. Impurities.

Calculation. Where the result is to be calculated with reference to the dried or anhydrous substance or on another specified basis, the determination of loss on drying, water content or another property is carried out by the procedure prescribed in the monograph. The words '*dried substance*' or '*anhydrous substance*' etc. appear in parentheses after the result.

Where a quantitative determination of a residual solvent is carried out and a test for loss on drying is not carried out, the residual solvent content is taken into account when calculating the assay content of the substance, the specific optical rotation and the specific absorbance. No further indication is given in the individual monograph.

Limits. The prescribed limits are based on data obtained in routine analytical practice and are intended to demonstrate that the article being examined complies with the requirements of the monograph. They take account of normal analytical errors, of acceptable variations in manufacture/preparation and of deterioration to an extent considered acceptable. No further tolerances are to be applied to the prescribed limits.

In determining compliance with a numerical limit, the calculated result of an analytical procedure is first rounded to the number of significant figures stated, unless otherwise prescribed. The limits, regardless of whether the values are expressed as percentages or as absolute values, are considered significant to the last digit shown (for example, 0.15 indicates 2 significant figures and 140 indicates 3 significant figures). When rounding, only the digit immediately to the right of the last place in the limit is to be considered. If this digit is smaller than 5, it is eliminated and the preceding digit is not changed. If this digit is equal to or greater than 5, it is eliminated and the preceding digit is increased by 1.

Indication of permitted limits for impurities. The limits for related substances are expressed either in terms of comparison of peak areas (comparative method) or as numerical values (quantitative method). For tests using the comparative method, the approximate tolerated content of the named impurity, or of the sum of impurities, may be indicated in brackets for information only. Acceptance or rejection is determined on the basis of compliance or non-compliance with the stated limits.

If the use of a reference standard for the named impurity is not prescribed, the impurity content may be expressed as a nominal concentration of the substance used to prepare the reference solution specified in the monograph, unless otherwise described.

Chiral substances. Monographs describing a particular enantiomer include a test to confirm enantiomeric purity, either using specific optical rotation or a chromatographic procedure.

A test for racemic character using optical rotation is included only if there is information on the specific optical rotation of the enantiomers that indicates that such a test would be discriminating in terms of enantiomeric purity.

Equivalents. Where an equivalent is given, only the figures shown are to be used in applying the requirements of the monograph. For example, for titrations: 1 mL of *1 M hydrochloric acid* is equivalent to 50.05 mg of $CaCO_3$.

Culture media. The culture media described in monographs and general chapters have been found to be satisfactory for the intended purpose. However, the components of media, particularly those of biological origin, are of variable quality, and for optimal performance it may be necessary to modulate the concentration of some ingredients, notably:

- peptones and meat or yeast extracts, with respect to their nutritive properties;
- buffering substances;
- bile salts, bile extract, deoxycholate and colouring matter, depending on their selective properties;
- antibiotics, depending on their activity.

1.5.1.10 Storage

The information and recommendations given in the Storage section do not constitute a pharmacopoeial requirement.

The articles described in the Ph. Eur. are stored in such a way as to prevent contamination and, as far as possible, deterioration. Where special storage conditions are recommended, including the type of container (see 1.3.1. Materials for containers and containers) and limits of temperature, they are stated in the monograph.

The following expressions are used in monographs under Storage with the meaning shown below.

'*In an airtight container*' means that the article is stored in an airtight container (*3.2. Containers*). Care is to be taken when the container is opened in a damp atmosphere. A low moisture content may be maintained, if necessary, by the use of a desiccant in the container provided that direct contact with the article is avoided.

'*Protected from light*' means that the article is stored either in a container made of a material that absorbs actinic light sufficiently to protect the contents from changes induced by such light, or in a container enclosed in an outer cover that provides similar protection, or that the article is stored in a place from which all such light is excluded.

1.5.1.11 Labelling

In general, labelling of medicinal products is subject to supranational and national regulation and to international agreements.

The statements in the Labelling section are not therefore comprehensive. In addition, for the purposes of the Ph. Eur., only those statements that are necessary to demonstrate compliance or non-compliance with the monograph are mandatory. Any other labelling statements are included as recommendations.

When the term '*label*' is used in the Ph. Eur., the labelling statements may appear on the container, the package, a leaflet accompanying the package, or a certificate of analysis accompanying the article, as decided by the competent authority.

1.5.1.12 Impurities

Monographs may include a list of all known and potential impurities that have been shown to be detected by the tests. See also general chapter *5.10. Control of impurities in substances for pharmaceutical use*. The impurities are designated by a letter or letters of the alphabet. Where a letter appears to be missing, the impurity designated by this letter has been deleted from the list during monograph development prior to publication or during monograph revision.

1.5.1.13 Functionality-related characteristics of excipients

This section is included in some monographs on excipients. Its contents do not constitute mandatory requirements, but the characteristics may be relevant for a particular use of an excipient and are given for guidance. The decision to control a functionality-related characteristic of an excipient remains with the manufacturer of the medicinal product and is taken with knowledge of the formulation of the medicinal product in which it is to be used; the analytical procedures, limits and tolerances are determined on a contractual basis by the user and the supplier of the excipient (see also Grades under 1.1.2.1. Scope).

1.5.2 MONOGRAPHS ON HERBAL DRUGS

This section complements section 1.5.1. General principles.

Definition. In monographs on herbal drugs, the definition indicates whether the subject of the monograph is, for example, the whole drug or the fragmented drug. Where a monograph applies to the drug in several states, for example both to the whole drug and to the fragmented drug, the definition clearly indicates this.

Identification. Monographs on herbal drugs may contain schematic drawings of the most diagnostic microscopic botanical structures. These drawings complement the description given in the relevant identification test.

Tests and Assay. The sulfated ash, total ash, water-soluble matter, alcohol-soluble matter, water content, and content of constituents with known therapeutic activity or markers are calculated with reference to the drug that has not been specially dried, unless otherwise prescribed in the monograph.

1.5.3 MONOGRAPHS ON MEDICINAL PRODUCTS CONTAINING CHEMICALLY DEFINED ACTIVE SUBSTANCES

This section complements section 1.5.1. General principles.

Monographs on medicinal products are intended for human use only, unless otherwise indicated in the monograph.

Medicinal products comply with the general monograph *Pharmaceutical preparations (2619)*, the relevant dosage form monograph, any relevant individual monograph, and any other relevant text.

1.5.3.1 Titles

The title of monographs on medicinal products containing an active substance present as a salt (e.g. raltegravir potassium) usually contains the modified international nonproprietary name (INNM) of the active substance (e.g. *Raltegravir potassium tablets (2938)*).

1.5.3.2 Related substances

Medicinal product monographs limit degradation products arising during the manufacture and the shelf life of the medicinal product, including any impurities of synthesis that are also degradation products.

In certain circumstances, it is necessary to identify impurities of synthesis in the medicinal product, for example when they are detected in the test for related substances at a level greater than the reporting threshold in the medicinal product. Consequently, the monograph describes how to identify any such known impurities of synthesis, so that they are disregarded and are not taken into account.

Monographs on medicinal products are not designed to control impurities of synthesis that are not degradation products. However, tests provided in the monograph could be used to control impurities of synthesis known to be detected by the monograph, if further validated for that purpose by the user.

It is acknowledged that additional controls may be required to monitor degradation products other than those controlled by the monograph (e.g. degradation products related to different excipients or containers used, or from a different manufacturing process).

1.5.3.3 Dissolution/Disintegration

The following terms are used hereafter:

- *monograph dissolution test*: analytical procedure and acceptance criteria described in the individual monograph;
- *product-specific dissolution test*: analytical procedure and acceptance criteria proposed by the applicant in a marketing authorisation application (MAA) for a medicinal product;

– *in-house dissolution test*: analytical procedure developed and acceptance criteria defined by the applicant.

In line with the relevant guidelines applied nationally or regionally (such as the ICH Q6A guideline) and with the relevant Ph. Eur. dosage form monograph, a suitable product-specific dissolution test has to be proposed by the applicant for routine quality control to confirm batch-to-batch consistency. This test must be described in the MAA for submission to the competent authority, unless there is data justifying the replacement of the dissolution test by a disintegration test (see below). The demonstration of the suitability of the dissolution test has to be made by the applicant to the satisfaction of the competent authority.

Where appropriate, a dissolution test is described in an individual monograph on a medicinal product. In such cases, the applicant may either select the monograph dissolution test or develop an in-house dissolution test as the product-specific dissolution test. In all cases, the applicant has to demonstrate the suitability of the selected test to the satisfaction of the competent authority.

If an in-house dissolution test is proposed, justification for not selecting the monograph dissolution test and demonstration of compliance with the monograph dissolution test is normally not requested as part of the MAA.

However, when tested, the medicinal product has to comply with the monograph dissolution test, unless otherwise justified by the applicant.

Where a given medicinal product does not comply with the monograph dissolution test and this product is approvable by a competent authority, then the competent authority shall bring this to the attention of the Ph. Eur. Commission so that it can review the monograph and revise it where appropriate.

As outlined in the ICH Q6A guideline, for rapidly dissolving medicinal products containing active substances that are highly soluble throughout the physiological range, a disintegration test may be substituted for a dissolution test. Such a substitution has to be justified by the applicant to the satisfaction of the competent authority.

1.5.3.4 Impurities

Impurities already listed in the monograph on the active substance, designated by a capital letter (A, B, C, D, etc.), keep their name. Impurities specific to the medicinal product are designated by '*FP-*' followed by a letter of the alphabet (FP-A, FP-B, etc.).

1.5.3.5 Storage

As for other monographs, the statements included under Storage in a medicinal product monograph constitute recommendations only; other conditions may be applied depending on the medicinal product, subject to approval by the competent authority.

1.6 REFERENCE STANDARDS

Certain monographs require the use of reference standards, which can be chemical reference substances (CRSs), herbal reference standards (HRSs), biological reference preparations (BRPs) or reference spectra. See also general chapter *5.12. Reference standards*. Unless otherwise stated, the reference standards referred to in texts are alone authoritative in case of arbitration.

1.7 ABBREVIATIONS AND SYMBOLS

A	Absorbance
$A_{1\ \mathrm{cm}}^{1\ \mathrm{per\ cent}}$	Specific absorbance
A_r	Relative atomic mass
$[\alpha]_D^{20}$	Specific optical rotation
bp	Boiling point
BRP	Biological reference preparation
CRS	Chemical reference substance
d_{20}^{20}	Relative density
λ	Wavelength
HRS	Herbal reference standard
IU	International Unit
M	Molarity
M_r	Relative molecular mass
mp	Melting point
n_D^{20}	Refractive index
Ph. Eur. U.	European Pharmacopoeia Unit
ppb	Parts per billion (micrograms per kilogram)
ppm	Parts per million (milligrams per kilogram)
R	Substance or solution defined under *4. Reagents*
RV	Substance used as a primary standard in volumetric analysis (see general chapter *4.2.1. Primary standards for volumetric solutions*)

Abbreviations used in the monographs on immunoglobulins, immunosera/antisera and vaccines

CFU	Colony-forming units
LD_{50}	The statistically determined quantity of a substance that, when administered by the specified route, may be expected to cause the death of 50 per cent of the test animals within a given period
MLD	Minimum lethal dose
L+/10 dose	The smallest quantity of a toxin that, in the conditions of the test, when mixed with 0.1 IU of antitoxin and administered by the specified route, causes the death of the test animals within a given period
L+ dose	The smallest quantity of a toxin that, in the conditions of the test, when mixed with 1 IU of antitoxin and administered by the specified route, causes the death of the test animals within a given period
lr/100 dose	The smallest quantity of a toxin that, in the conditions of the test, when mixed with 0.01 IU of antitoxin and injected intracutaneously causes a characteristic reaction at the site of injection within a given period
Lp/10 dose	The smallest quantity of toxin that, in the conditions of the test, when mixed with 0.1 IU of antitoxin and administered by the specified route, causes paralysis in the test animals within a given period
Lo/10 dose	The largest quantity of a toxin that, in the conditions of the test, when mixed with 0.1 IU of antitoxin and administered by the specified route, does not cause symptoms of toxicity in the test animals within a given period
Lf dose	The quantity of toxin or toxoid that flocculates in the shortest time with 1 IU of antitoxin
$CCID_{50}$	The statistically determined quantity of virus that may be expected to infect 50 per cent of the cell cultures to which it is added
ED_{50}	The statistically determined dose of a vaccine that, in the conditions of the test, may be expected to induce specific antibodies for the relevant vaccine antigens in 50 per cent of the animals into which it is inoculated

EID_{50}	The statistically determined quantity of virus that may be expected to infect 50 per cent of the fertilised eggs into which it is inoculated
ID_{50}	The statistically determined quantity of a virus that may be expected to infect 50 per cent of the animals into which it is inoculated
PD_{50}	The statistically determined dose of a vaccine that, in the conditions of the test, may be expected to protect 50 per cent of the animals into which it is inoculated against a challenge dose of the micro-organisms or toxins against which it is active
PFU	Pock-forming units or plaque-forming units
SPF	Specified-pathogen-free

Collections of micro-organisms

ATCC	American Type Culture Collection
CIP	Collection des bactéries de l'Institut Pasteur
IMI	International Mycological Institute
IP	Institut Pasteur, Collection Nationale de Cultures de Microorganismes (CNCM)
NBRC	NITE Biological Resource Center
NCIMB	National Collection of Industrial Food and Marine Bacteria Ltd
NCPF	National Collection of Pathogenic Fungi
NCTC	National Collection of Type Cultures
NCYC	National Collection of Yeast Cultures
SSI	Statens Serum Institut

1.8 UNITS OF THE INTERNATIONAL SYSTEM (SI) USED IN THE PH. EUR. AND EQUIVALENCE WITH OTHER UNITS

INTERNATIONAL SYSTEM OF UNITS (SI)

The International System of Units comprises 2 main classes of units, namely base units and derived units(1). The base units are the metre, the kilogram, the second, the ampere, the kelvin, the mole and the candela.

The derived units are formed as products of powers of the base units according to the algebraic relationships linking the corresponding quantities. Some of these derived units have special names and symbols. The derived units used in the Ph. Eur. are shown in Table 1.8.-1.

Some important and widely used units outside the International System are shown in Table 1.8.-2.

The prefixes shown in Table 1.8.-3 are used to form the names and symbols of the decimal multiples and submultiples of SI units.

Table 1.8.-1. – *Derived units used in the Ph. Eur. and equivalence with other units*

Quantity		Unit				Conversion of other units into SI units
Name	Symbol	Name	Symbol	Expression in SI base units	Expression in other SI units	
Wave number	ν	one per metre	1/m	m^{-1}		
Wavelength	λ	micrometre nanometre	µm nm	10^{-6} m 10^{-9} m		
Area	A, S	square metre	m^2	m^2		
Volume	V	cubic metre	m^3	m^3		1 mL = 1 cm^3 = 10^{-6} m^3
Frequency	ν	hertz	Hz	s^{-1}		
Density	ρ	kilogram per cubic metre	kg/m^3	$kg \cdot m^{-3}$		1 g/mL = 1 g/cm^3 = 10^3 $kg \cdot m^{-3}$
Velocity, speed	v	metre per second	m/s	$m \cdot s^{-1}$		
Force	F	newton	N	$m \cdot kg \cdot s^{-2}$		1 dyne = 1 $g \cdot cm \cdot s^{-2}$ = 10^{-5} N 1 kp = 9.806 65 N
Pressure, stress	p	pascal	Pa	$m^{-1} \cdot kg \cdot s^{-2}$	$N \cdot m^{-2}$	1 dyne/cm^2 = 10^{-1} Pa = 10^{-1} $N \cdot m^{-2}$ 1 atm = 101 325 Pa = 101.325 kPa 1 bar = 10^5 Pa = 0.1 MPa 1 mm Hg = 133.322 387 Pa 1 Torr = 133.322 368 Pa 1 psi = 6.894 757 kPa
Dynamic viscosity	η	pascal second	Pa·s	$m^{-1} \cdot kg \cdot s^{-1}$	$N \cdot s \cdot m^{-2}$	1 P = 10^{-1} Pa·s = 10^{-1} $N \cdot s \cdot m^{-2}$ 1 cP = 1 mPa·s
Kinematic viscosity	ν	square metre per second	m^2/s	$m^2 \cdot s^{-1}$	$Pa \cdot s \cdot m^3 \cdot kg^{-1}$ $N \cdot m \cdot s \cdot kg^{-1}$	1 St = 1 $cm^2 \cdot s^{-1}$ = 10^{-4} $m^2 \cdot s^{-1}$
Energy	W	joule	J	$m^2 \cdot kg \cdot s^{-2}$	N·m	1 erg = 1 $cm^2 \cdot g \cdot s^{-2}$ = 1 dyne·cm = 10^{-7} J 1 cal = 4.1868 J
Power, radiant flux	P	watt	W	$m^2 \cdot kg \cdot s^{-3}$	$N \cdot m \cdot s^{-1}$ $J \cdot s^{-1}$	1 erg/s = 1 dyne·cm·s^{-1} = 10^{-7} W = 10^{-7} $N \cdot m \cdot s^{-1}$ = 10^{-7} $J \cdot s^{-1}$
Absorbed dose (of radiant energy)	D	gray	Gy	$m^2 \cdot s^{-2}$	$J \cdot kg^{-1}$	1 rad = 10^{-2} Gy
Electric potential difference, voltage	U	volt	V	$m^2 \cdot kg \cdot s^{-3} \cdot A^{-1}$	$W \cdot A^{-1}$	

(1) The definitions of the units used in the International System are given in the booklet '*Le Système International d'Unités (SI)*', published by the *Bureau International des Poids et Mesures*, Pavillon de Breteuil, F-92310 Sèvres (www.bipm.org).

Quantity		Unit				Conversion of other units into SI units
Name	**Symbol**	**Name**	**Symbol**	**Expression in SI base units**	**Expression in other SI units**	
Electric resistance	*R*	ohm	Ω	$m^2 \cdot kg \cdot s^{-3} \cdot A^{-2}$	$V \cdot A^{-1}$	
Electric charge	*Q*	coulomb	C	A·s		
Activity referred to a radionuclide	*A*	becquerel	Bq	s^{-1}		1 Ci = $37 \cdot 10^9$ Bq = $37 \cdot 10^9$ s^{-1}
Concentration (of amount of substance), molar concentration	*c*	mole per cubic metre	mol/m^3	$mol \cdot m^{-3}$		1 mol/L = 1 M = 1 mol/dm^3 = 10^3 $mol \cdot m^{-3}$
Mass concentration	*ρ*	kilogram per cubic metre	kg/m^3	$kg \cdot m^{-3}$		1 g/L = 1 g/dm^3 = 1 $kg \cdot m^{-3}$
Catalytic activity	*Z*	katal	kat	$mol \cdot s^{-1}$		

NOTES

1. In the Pharmacopoeia, the Celsius temperature is used (symbol *t*). This is defined by the following equation:

$$t = T - T_0$$

where T_0 = 273.15 K by definition. The Celsius or centigrade temperature is expressed in degrees Celsius (symbol °C). The unit '*degree Celsius*' is equal to the unit '*kelvin*'.

2. The radian is the plane angle between two radii of a circle that cut off on the circumference an arc equal in length to the radius.

3. In the Ph. Eur., conditions of centrifugation are defined by reference to the acceleration of gravity (*g*):

$$g = 9.806\,65\ m \cdot s^{-2}$$

4. Certain quantities without dimensions are used in the Ph. Eur.: relative density (*2.2.5*), absorbance (*2.2.25*), specific absorbance (*2.2.25*) and refractive index (*2.2.6*).

5. The microkatal is defined as the enzymatic activity that, under defined conditions, produces the transformation (e.g. hydrolysis) of 1 micromole of the substrate per second.

Table 1.8.-2. – *Non-SI units accepted for use with the SI units*

Quantity	Unit		Value in SI units
	Name	**Symbol**	
Time	minute	min	1 min = 60 s
	hour	h	1 h = 60 min = 3600 s
	day	d	1 d = 24 h = 86 400 s
Plane angle	degree	°	1° = (π/180) rad
Volume	litre	L	1 L = 1 dm^3 = 10^{-3} m^3
Mass	tonne	t	1 t = 10^3 kg
	dalton	Da	1 Da = 1.660539040(20) × 10^{-27} kg
Rotational frequency	revolution per minute	r/min	1 r/min = (1/60) s^{-1}
Energy	electronvolt	eV	1 eV = 1.602176634 × 10^{-19} J

Table 1.8.-3. – *Decimal multiples and sub-multiples of SI units*

Factor	Prefix	Symbol	Factor	Prefix	Symbol
10^{18}	exa	E	10^{-1}	deci	d
10^{15}	peta	P	10^{-2}	centi	c
10^{12}	tera	T	10^{-3}	milli	m
10^9	giga	G	10^{-6}	micro	μ
10^6	mega	M	10^{-9}	nano	n
10^3	kilo	k	10^{-12}	pico	p
10^2	hecto	h	10^{-15}	femto	f
10^1	deca	da	10^{-18}	atto	a