Technical Guide for the elaboration of monographs

ON SYNTHETIC PEPTIDES AND RECOMBINANT DNA PROTEINS

European Pharmacopoeia

EDQM

Edition 2018

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Technical guide for the elaboration of monographs on synthetic peptides and recombinant DNA proteins

European Pharmacopoeia

2nd revision, Edition 2018

European Directorate for the Quality of Medicines & HealthCare

English version
2018

European Directorate for the Quality of Medicines & HealthCare (EDQM)
Council of Europe
7, allée Kastner
CS 30026
F-67081 STRASBOURG
FRANCE

Director of the publication: Dr S. Keitel

Page layout: EDQM
www.edqm.eu

Cover photos:
(1) © Sergey Nivens – Fotolia
(2) © EDQM

Contents

Technical guide for the elaboration of monographs on synthetic peptides and recombinant DNA proteins

1. Purpose of the guide

This document is intended to provide guidance to authors, contributors and users of the European Pharmacopoeia (Ph. Eur.) on the elaboration of active substance monographs for synthetic peptides and products of recombinant DNA (rDNA) technology, referred to as rDNA proteins throughout the document. This applies in particular to:

1. Group of Experts 6 (Biological substances), Monoclonal Antibodies (MAB) and P4 Bio Working Parties;
2. authorities responsible for granting marketing authorisation for synthetic peptides and recombinant DNA proteins;
3. Official Medicines Control Laboratories (OMCLs);
4. manufacturers of synthetic peptides and rDNA proteins;
5. public and private analytical laboratories working for one of the above;
6. the Ph. Eur. Secretariat and other departments of the European Directorate for the Quality of Medicines & HealthCare (EDQM).

It is to be read in conjunction with the *Technical Guide for the Elaboration of Monographs* and the *European Pharmacopoeia Style Guide*.

2. Status and scope of the guide

The monographs and general chapters of the Ph. Eur. set out the official standards for medicinal products. This guide provides information on the elaboration and use of these standards but has no official status. In the event of doubt or dispute, the text of the Ph. Eur. alone is authoritative.

Monographs on finished products derived from synthetic peptides and rDNA proteins are out of scope of this document.

The present guide does not cover the field of blood products or vaccines. Where relevant, the principles applied in this guide to recombinant DNA proteins (see section 5) may also apply to proteins of human or animal origin.

3. General information

3.1. Pharmacopoeial requirements

Monographs and general chapters of the Ph. Eur. must be interpreted with reference to the General Notices. All users of the Ph. Eur. must be familiar with this text.

Statements in monographs are mandatory requirements unless otherwise stated:

> 'Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements. General chapters become mandatory when referred to in a 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.'
> (Ph. Eur. 9th Edition)

As regards compliance with the Ph. Eur., the General Notices state that:

> '(1) An article [that is the subject of a monograph] is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process.
>
> (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 Pharmacopoeia.'
> (Ph. Eur. 9th Edition)

3.2. Alternative methods

As regards the use of alternative methods, the General Notices state that:

> 'The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative.'
> (Ph. Eur. 9th Edition).

USE OF ANIMALS FOR SCIENTIFIC PURPOSES

The Introduction to the 9th Edition of the European Pharmacopoeia states as follows:

> 'In accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (CETS No. 123),[1] elaborated under the auspices of the Council of Europe, the [European Pharmacopoeia] Commission is committed to the reduction of animal usage wherever possible in pharmacopoeial testing, and encourages those associated with its work to seek alternative procedures. An animal test is included in a monograph only if it has

1 European convention for the protection of vertebrate animals used for experimental and other scientific purposes. European Treaty series No. 123. Council of Europe (1986).

clearly been demonstrated that it is necessary to achieve satisfactory control for pharmaceutical purposes'.

Additionally, as stated in the General Notices, in demonstrating compliance with the Ph. Eur., 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 minimised as much as possible.

In consideration of the above, general recommendations on 3Rs' approaches are usually not repeated in individual monographs.

4. Analytical methods: general principles

4.1. Validation of analytical procedures

Analytical methods included in monographs must have been validated according to the principles set out in Chapter III of the *Technical guide for the elaboration of monographs* and to those in ICH guideline Q2 (R1) *Validation of Analytical Procedures: Text and Methodology* (previously Q2A (R1) *Validation of analytical procedures: definitions and terminology* and Q2B (R1) *Validation of analytical procedures: methodology*), taking into account specific issues concerning the unique tests used for analysing biotechnological/biological products.

4.2. Reference standards

Biological assays are calibrated using World Health Organization (WHO) International Standards, Ph. Eur. standards or in-house standards calibrated in terms of the primary WHO standard. If neither a WHO International Standard nor a Ph. Eur. standard has been established, the manufacturer must have established an appropriately characterised in-house biological reference material.

Physico-chemical analytical methods are qualified and calibrated using Ph. Eur. chemical reference substances (CRSs) for the active substance and, where appropriate, for specified impurities.

Further information on the establishment of reference standards is outlined in the general chapter *Reference standards (5.12)*.

5. Monographs on recombinant DNA proteins

5.1. General monograph

The general monograph on *Products of Recombinant DNA technology (0784)* provides general requirements for the manufacture and control of finished products derived from rDNA technology, and includes requirements for the active substance in these products. Active substances produced by rDNA technology are expected to meet the requirements given in the corresponding section of the general monograph.

5.2. Individual monographs

5.2.1. Title

The title of the monograph usually reflects the International Nonproprietary Name (INN) established by the WHO.

For monographs covering substances in solid form, the name of the substance constitutes the monograph title.

For monographs covering substances in liquid form, the mention 'concentrated solution' is specified in the title. The term 'solution' alone is to be avoided in the title as it may be understood as a formulated material (finished product). The information about the physical state covered by a monograph may be supplemented in its *Definition* section.

5.2.2. Definition

The *Definition* section states:

- molecular formula (monomer or unique protomers in case of homo- and hetero-multimeric proteins, respectively) and corresponding CAS number, where applicable;
- approximate molecular mass; for glycoproteins, the figure stated in the beginning of each monograph corresponds to the glycosylated protein; for complex glycoproteins (e.g. multiple N- and O-glycosylation sites), the figure corresponds to non-glycosylated protein and indication 'without glycosylation' is provided in brackets, while (apparent) molecular mass of glycosylated protein is further indicated in the descriptive part of the section;
- physical form;
- amino-acid sequence of the protein chain(s), modified residues and glycosylation sites (predominant/potential), either indicated in the graphic formula or in the form of a list (clearly stated if the list is not exhaustive), where appropriate;
- disulfide bridges, either indicated in the graphic formula or in the form of a list (clearly stated if the list is not exhaustive);
- identity and biological activity of the substance and its naturally occurring analogue;
- protein content expressed in mass per volume (milligrams per millilitre) or mass per mass (percentage range);
- specific biological activity expressed in activity units per mass of protein.

5.2.3. Production

As defined in the General Notices, statements under the heading *Production* draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. 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 in-process testing; or to testing that is to be carried out by the manufacturer on the final article, either on selected batches or on each batch prior to release. These statements 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 examination of data received from the manufacturer, by inspection of manufacture or by testing appropriate samples.

The *Production* section may include:

- appropriate details on the production method;

- (specific) biological activity and considerations on potency determination if not covered by assay in the monograph;
- test procedures for process-related impurities derived from the upstream process (e.g. host-cell proteins and DNA) and from the downstream process (e.g. protein A)
- requirements for clearance of process-related impurities derived from the modification procedure for conjugated or chemically modified protein, e.g. by-products of pegylation reaction, reagents;
- quality requirements for reagents (e.g. pegylation reagent) used in the manufacturing process;
- process-related considerations, such as requirements for demonstration of production consistency (process-dependent quality attributes, e.g. glycan occupancy);
- test procedures that measure process-dependent heterogeneity, e.g. glycan analysis and charged variants determination;
- procedures for validation of the production process as described in the monograph *Products of recombinant DNA technology (0784)*.

Where relevant in individual monographs, the following sentence precedes the tests listed in the *Production* section:

> 'Prior to release, the following tests are carried out on each batch of [name of the substance], unless exemption has been granted by the competent authority'.

5.2.4. **Characters**

As defined in the General Notices, statements under the heading *Characters* are not to be interpreted in a strict sense and are not regarded as analytical requirements.

The appearance of the substance in a liquid or solid form should be described. The solubility of substances in solid form, if applicable, should be provided.

5.2.5. **Identification**

GENERAL CONSIDERATIONS

With the purpose to provide a confirmation of the identity of a substance, the identification section of a monograph comprises tests that should be specific for the substance and should be based on unique aspects of its molecular structure and/or other specific properties. More than 1 test (physico-chemical, biological and/or immunochemical) is considered mandatory for the establishment of identity; methods used in the determination of potency or purity may be employed or modified as appropriate to serve as identification criteria.

Whilst the precise range of tests that comprise the identification criteria depends on the nature of the product and cannot be specified in advance, it can be considered that the Identification section of a monograph generally comprises techniques that verify the size of the molecule, its primary sequence, its isoelectric profile, its chromatographic properties and that the molecule has adopted the correct functional configuration. Typically this battery of tests comprises:

- bioassay;
- peptide mapping;
- reversed-phase liquid chromatography (LC);
- size-exclusion LC;
- ion exchange LC;
- isoelectric focusing/capillary isoelectric focusing;
- electrophoresis/capillary electrophoresis.

- Generally, acceptance criteria for physico-chemical test procedures used for identification are based on a comparative analysis of results, using a dedicated chemical reference standard.

BIOASSAY

Generally, for rDNA proteins, compliance with the requirements stated under *Assay/potency* is an important identification criterion. It may be replaced entirely by physico-chemical tests only in cases where:

- sufficient physico-chemical information about the protein including higher-order structure, can be thoroughly established by such physico-chemical methods; relevant correlation to biological activity is established;
- biological activity of related proteins present in the product is known;
- there exists a well-documented manufacturing history.

PEPTIDE MAPPING

Peptide mapping is considered to provide direct evidence of the sequence, and at present is usually considered essential. For identification purposes in a monograph, confirmation of identity by comparing the generated protein fingerprint with that obtained with a dedicated reference standard (i.e. CRS) is described, whereby corresponding profiles of chromatograms (comparison with regard to number of peaks, relative retention, peak areas and peak area ratios) are to be obtained. The system suitability requirements for the marker peaks ('signature peptides') usually refer to a qualitative similarity (i.e. overall elution pattern, number of peaks, relative retentions, no additional peaks) of the chromatogram obtained with the reference standard to that supplied with the CRS.

It is recognised that peptide mapping may often be used in conjunction with mass spectrometry.

LIQUID CHROMATOGRAPHY

Cross-reference to one or more LC procedures (typically reversed-phase and size-exclusion LC) is often used as an identification criterion. In instances where the nature of the protein renders it not amenable to fractionation by these methods (e.g. for very large proteins, or for heterogeneous glycoproteins), electrophoretic or ion-exchange chromatographic techniques should be considered as replacements.

OTHER TESTS

Additional methods that may be employed as identification tests include:

- electrophoretic methods based on size or charge;
- antibody-binding methods, either alone or in conjunction with electrophoretic methods (Western blotting);
- spectroscopic methods, including mass spectrometry;
- N-terminal sequence analysis;
- glycan analysis techniques, for glycosylated proteins.

5.2.6. **Tests**

PURITY TESTS

Analytical methods for proteins are usually developed on the basis of size, charge and hydrophobicity (e.g. size-exclusion LC, ion-exchange LC, reversed-phase LC, SDS-PAGE, isoelectric focusing and capillary electrophoresis). In elaboration of monographs it is usually possible to remove one by demonstrating redundancy (e.g. ion-exchange LC can be covered by reversed-phase LC or capillary electrophoresis). Additional tests such as monosaccharide analysis (e.g. sialic acid) or, where

appropriate, other analysis techniques are included if known to be necessary for specific product-related impurities/substances, or if the combination of reversed-phase LC and size-exclusion LC does not cover all relevant product-related impurities and substances. When SDS-PAGE is prescribed, the conditions to be used should be those described in general chapter on *Electrophoresis (2.2.31)*, unless it is demonstrated that these conditions are not appropriate for the substance to be tested.

Size-exclusion LC for the determination of dimers and higher-molecular-mass impurities remains an important purity test as aggregated molecules may exhibit immunogenicity. Where possible, this test should be elaborated using non-denaturing conditions (neutral, aqueous buffers), to avoid dissociation and consequent non-detection of non-covalent aggregates.

Where specific impurities are known to have clinical consequences, specific procedures for their detection and quantification as well as acceptance criteria are included in the monograph.

Generally, acceptance criteria for product-related substances and impurities are expressed as numerical limits or ranges; they may also include a requirement of matching electropherograms/chromatograms using a dedicated chemical reference standard as comparator.

TESTS FOR BACTERIAL ENDOTOXINS

When a substance for pharmaceutical use is intended for parenteral use, it has to comply with the test for *Bacterial endotoxins (2.6.14)*. Guidance on how to establish limits is given in chapter *Guidelines for using the test for bacterial endotoxins (5.1.10)*. As compliance with the test is requested via the general monograph *Substances for pharmaceutical use (2034)*, this requirement may not be repeated in the individual monographs.

5.2.7. **Assay**

The *Assay* section of the monograph usually comprises two procedures: i) determination of protein content and ii) a bioassay referring to the WHO International Standard or a Ph. Eur. standard calibrated in International Units. In case reference to the WHO International Standard is made in the monograph, the following wording is typically used:

> 'The International Unit is the activity contained in a stated amount of the International Standard. The equivalence in International Units of the International Standard is stated by the World Health Organization.'

Protein content may be determined by UV spectroscopy (typically at 280 nm) using the protein specific absorbance or a dedicated reference standard with assigned protein content. When appropriate, other methods such as a comparative LC procedure against a defined reference standard may also be used.

Bioassay limits are calculated as specified in general chapter *Statistical analysis of results of biological assays and tests (5.3)* and are typically expressed as an acceptable range for the estimated potency (e.g. 80-125 per cent of the stated potency[2]), and an acceptable range for the confidence limits of the estimated potency (e.g. 64-156 per cent of the stated potency).

In exceptional circumstances, other strategies may be employed:

- where the battery of physico-chemical tests does not adequately characterise structural aspects of the molecule known to affect the biological activity *in vivo*, for example glycosylation, the

2 In this example the range of 80-125 per cent of the stated potency was derived from log-transformation method of data analysis; the range is based on multiplication by 1.25 from lower limit (80 per cent) to the target (100 per cent) and from the target to the upper limit (125 per cent).

monograph may include an *in vivo* bioassay; where an *in vivo* assay is used to assess the extent of glycosylation, this should only be replaced with an *in vitro* assay where it has been shown that the physico-chemical analysis adequately addresses the glycosylation pattern; detailed description of the steps necessary to perform the assay, including system suitability criteria, may be included; for complex assays, a suitable procedure may be given as example.

- where the battery of physico-chemical tests has been shown to adequately cover the quality of the protein, according to the criteria outlined under *Bioassay* on page 10 of this guide, a physico-chemical assay alone may be employed; where a physico-chemical assay procedure is used, the limits are typically asymmetric, the upper limit being 100 per cent + the permitted assay reproducibility (typically up to 5.0 per cent for reversed-phase LC), and the lower limit being 100 per cent – (the permitted assay reproducibility + the maximum permitted level of impurity).

5.2.8. **Storage**

Although the statements given under this heading in a Ph. Eur. monograph do not constitute pharmacopoeial requirements, the appropriate information to safeguard the quality of a pharmacopoeial material during storage is to be given here where appropriate.

5.2.9. **Labelling**

The status of the Labelling section is defined in the General Notices:

> 'In general, labelling is subject to supranational and national regulation and to international agreements. The statements under the heading *Labelling* therefore are not comprehensive and, moreover, for the purposes of the Pharmacopoeia 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 Pharmacopoeia, 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.'

The parameters included in this section are determined on a case-by-case basis.

5.3. Flexibility

In monographs for complex glycoproteins, the requirements related to process-dependent heterogeneity (e.g. glycosylation, charge profile) are set to allow for flexibility.

Example: Glycan analysis

Generally, this multi-step procedure requires the use of a suitable method developed according to general chapter *Glycan analysis of glycoproteins (2.2.59)*, section 2-3: three main steps are to be performed, namely:

- release of glycans using one of the agents described in Table 2.2.59.-1;
- labelling of released glycans, if needed, with one of the fluorescent labelling agents described in Table 2.2.59.-2;
- analysis of the (labelled) glycans by liquid chromatography (2.2.29),

whereas a suitable procedure, including conditions for sample preparation, enzymatic digestion, labelling (if applicable) and chromatographic separation, is given as an example.

Such procedures usually require the use of two types of reference standards: 1) a dedicated CRS to demonstrate method performance (system suitability); 2) a suitable in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate

consistency of production for assessment of acceptance criteria (usually by visual comparison of chromatograms/electropherograms).

The term 'suitable' is a conventional term, which is defined in the General Notices as follows:

> 'In certain monographs or other texts, the terms "suitable" and "appropriate" are used to describe a reagent, micro-organism, test method etc.; if criteria for suitability are not described in the monograph, suitability is demonstrated to the satisfaction of the competent authority.'

The requirement to use a 'suitable method' ('suitable procedure') is usually accompanied by general indications on the test procedure, such as main steps to be carried out, type of method/assay, of readout, of cells, (grade) of reagents, etc. In certain cases (e.g. complex test procedures/bioassays), exact protocols with specific instructions, including sample preparation and purification, quantities/concentrations/composition of reagents/buffers, chromatographic conditions, plate design for cell assay, readout etc. and notably system suitability criteria may be described as examples. In such cases, the following sentence typically precedes the respective detailed procedure: 'The following procedure is given as an example.'

The term 'example' means that the respective test method may be used as such or replaced by a suitable, validated procedure (without having to demonstrate its equivalence to the 'example' method), subject to approval by the competent authority.

6. Synthetic peptides

Synthetic peptides may be considered to differ from products of recombinant DNA technology in two structural aspects:

- they are usually small, typically below 5 000 Da;
- they may have chemical structures that do not occur naturally in proteins or peptides.

As a consequence, they can generally be sufficiently characterised by a battery of physico-chemical tests which is reflected in the structure of monograph for synthetic peptides.

6.1. Title

The title of the monograph reflects the International Nonproprietary Name (INN) of the substance established by WHO.

As a general rule, the salt of the peptide is not specified in the title of the monograph. If required, appropriate clarifications are given in the *Definition* section.

6.2. Definition

The Definition section states:

- molecular formula and the corresponding CAS number;
- molecular mass;
- physical form;
- structural formula;
- identity and biological activity of the substance and, where appropriate, its naturally occurring analogue;
- assay specifications;
- route of production;
- salt form;

- any chemical modifications, such as esterification or amidation.

6.3. Characters

The appearance of the solid synthetic peptide should be described. The solubility, if applicable, should be provided.

6.4. Identification

Two methods are generally considered sufficient for the identification purpose.

Typically, the *Identification* section of the monograph comprises:

- amino-acid analysis or NMR spectrometry;
- reversed-phase LC.

While both amino-acid analysis and nuclear magnetic resonance (NMR) spectrometry may be described in the monograph in addition to the other identification test, flexibility is given to the users to perform only one of those tests.

Identification by NMR spectrometry applies to peptides comprising up to approximately 15 amino acids.

Where appropriate, for instance where the peptide comprises unnatural amino acids, or when prescribed in individual monographs, the use of NMR spectrometry may also be required in addition to conventional methods based on analysis of the amino-acid composition or sequence.

In many cases it may be appropriate to include more than one LC. The inclusion of multiple chromatographic identification tests is particularly important if a spectroscopic method is not included.

Where NMR spectrometry is prescribed for identification, a separate reference standard for NMR identification is established from a bulk of the substance; no assigned content is necessary.

6.5. Tests

6.5.1. Related peptides

Typically, monographs for synthetic peptides contain a reversed-phase LC test for related peptides. Such tests are validated for specified impurities known to be potential contaminants and are transparent with respect to these impurities.

The provisions for synthetic peptides in the general monograph *Substances for pharmaceutical use (2034)* apply to all synthetic peptides unless otherwise stated.

Monographs should include acceptance criteria for:

- each specified impurity;
- unspecified impurities, normally set at the identification threshold;
- total impurities.

Reference standards for specified impurities, mixtures of impurities or, where appropriate, the reference peptide spiked with the specified impurities are provided. Where necessary, specified impurities may have to be separately quantified using independent methods. Where a monograph depends on a single purity test, the capacity of the method to measure all relevant impurities should be demonstrated.

6.5.2. Optical rotation and absorbance

These useful tests should be retained where appropriate. Chiral chromatography may offer some potential to replace optical rotation.

6.5.3. Counter ion

Determination of counter ion is a general requirement for peptides. In case of peptides with acetate as the counter ion the method used for the determination of acetic acid is that described in general chapter *2.5.34. Acetic acid in synthetic peptides*, unless it has been demonstrated that this method is not appropriate for the peptide to be tested.

6.5.4. Loss on drying, water content

Loss on drying is used less frequently because it requires large quantities of material. It is often replaced by a water-content determination. The method for determining water content is that described in general chapter *2.5.12. Water: semi-micro determination* (Karl Fischer) or in general chapter *2.5.32. Water: micro determination* (coulometric titration).

6.5.5. Tests for bacterial endotoxins

When a substance for pharmaceutical use is intended for parenteral use, it has to comply with the test for *Bacterial endotoxins (2.6.14)*. As compliance with a test is required via the general monograph *Substances for pharmaceutical use (2034)*, this requirement may not be repeated in the individual monographs.

6.6. Assay

Assays for synthetic peptides are generally comparative chromatographic procedures, performed using a defined chemical reference substance as the standard. Results are normally expressed in terms of the counter ion-free, anhydrous substance. The permitted limits for such tests are typically asymmetric, the upper limit being 100 per cent + the permitted assay reproducibility (usually ± 2.0 per cent), and the lower limit being 100 per cent – (the permitted assay reproducibility + the maximum permitted level of impurity).

6.7. Storage

Although the statements given under this heading in a Ph. Eur. monograph do not constitute pharmacopoeial requirements, the appropriate information to safeguard the quality of a pharmacopoeial material during storage is to be given here where appropriate.

6.8. Labelling

The status of the labelling section is defined in the General Notices:

> 'In general, labelling is subject to supranational and national regulation and to international agreements. The statements under the heading *Labelling* therefore are not comprehensive and, moreover, for the purposes of the Pharmacopoeia 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 Pharmacopoeia, 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.'

The parameters included in this section are determined on a case-by-case basis.

ENG

www.edqm.eu

The Council of Europe is the continent's leading human rights organisation. It comprises 47 member states, 28 of which are members of the European Union. The European Directorate for the Quality of Medicines & HealthCare (EDQM) is a directorate of the Council of Europe. Its mission is to contribute to the basic human right of access to good quality medicines and healthcare and to promote and protect public health.

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE