Certification of Substances Department

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Certification of suitability to the Monographs of the European Pharmacopoeia

How to read a CEP

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1. Introduction

This document has been created with the intention of clarifying the information to be concluded from a Certificate of suitability to the Monographs of the European Pharmacopoeia (CEP) for Industry and the Competent Authorities.
Specifically, this document describes in detail the information conveyed on a CEP.

Marketing Authorisation (MA) applicants are advised to read existing guidance published by the Competent Authorities in their countries, or to contact them directly for advice, when using a CEP to replace the respective quality part of the CTD dossier related to that given source, or in any variation.

Competent authorities may contact the EDQM if they have questions concerning the content of the CEP which prevent them performing the evaluation of the MA application (MAA). If necessary, they may ask for the CEP assessment report.

CEPs are normally accepted in all countries which are members of the Ph. Eur. Convention. CEPs may be accepted in countries which are not members of the Ph. Eur. Convention at the discretion of the authorities in those countries.

The regulatory basis for the CEP procedure is:

- Resolution AP-CSP (07) 1 "Certification of suitability to the monographs of the European Pharmacopoeia" (available on the EDQM website), adopted by the Public Health Committee (Partial Agreement) of the Council of Europe.
- In the EU, EU Directives 2001/82/EC and 2001/83/EC, as amended, of the European Council and of the Parliament on the Community code relating to medicinal products for human and veterinary use.
- In the EU, NfG "Summary of Requirements for Active Substances in the Quality part of the dossier" (CHMP/QWP/297/97 Rev 1 corr & EMEA/CVMP/1069/02).

This document should be read in conjunction with other applicable Certification Policy Documents and Guidelines.

2. Aim and Scope of a CEP

A CEP covering chemical purity and microbiological quality certifies, based on the specific data supplied by the manufacturer, that the quality of a substance can be suitably controlled by the Ph. Eur. monograph, i.e. that the quality of a substance corresponds to the quality defined in the Ph. Eur. monograph.

Furthermore, as stated in EU Directives 2001/83/EC (Part I, section 3.2, paragraph 5) and 2001/82/EC (Part II, section C 1.1), where the substance "has been prepared by a method liable to leave impurities not controlled in the respective Ph. Eur. monograph, these impurities and their maximum tolerance limits must be declared and a suitable test

procedure must be described". The additional impurities (not included in the Ph. Eur.) and their acceptable limits will be listed on the CEP and the analytical method will be appended to it so these impurities can be suitably controlled. These additional tests and acceptance criteria supplement, as necessary, the monographs of the Ph. Eur. for the control of this particular source of the substance.

Biologicals are outside the scope of the CEP procedure (see also 4.3.6).

Another type of CEP, for TSE risk, certifies that the substance complies with monograph 1483 of the Ph. Eur. "Products with risk of transmitting agents of animal spongiform encephalopathies", current edition including supplements. A TSE CEP does not certify that the quality of the substance is suitably controlled by a specific Ph. Eur. monograph.

A CEP does not certify that a specific batch or batches of the substance covered by the CEP from a certain manufacturer complies with the Ph. Eur. monograph and additional tests stated on the respective CEP. CEPs are not equivalent to batch release certificates and shall be complemented by certificates of analysis demonstrating such batch-related compliance.

A CEP is not a GMP certificate: although when submitting a CEP application the manufacturer has to confirm that the substance covered by the CEP is produced according to GMP requirements, the CEP is granted following evaluation of data described in the submitted dossier. As a complementary activity to dossier evaluation, the CEP procedure includes scope for the performance of GMP inspections of sites involved in the manufacture of the respective substance. In line with the above-mentioned EU legislation, the selection of sites to be inspected is based on risk evaluation, which means that there is no routine inspection of all sites. As a consequence, a CEP may be granted with, prior to or without an inspection of the manufacturing site being performed. A CEP, therefore, is neither equivalent to a GMP certificate nor does it replace it. In addition, the CEP may cover different types of substance (e.g. active pharmaceutical ingredients or excipients) and the GMP/quality system which is applied by the company should be declared.

For CEPs covering only the TSE risk, an appropriate quality system, such as ISO 9000 certification, HACCP or GMP, must be implemented for monitoring the production process and for batch delineation (i.e. definition of batch, separation of batches, cleaning between batches).

3. Types of CEP

There are several types of CEP, depending on the evaluation performed:

- Certificate for chemical purity and microbiological quality ("Chemical CEP")
- Certificate for herbal drugs and herbal drug preparations ("Herbal CEP")
- TSE Certificate ("TSE CEP")

Combined CEPs can also be granted, as follows:

- Certificate for chemical purity/microbiological quality and sterility
- Double certificate (chemical + TSE)
- Double certificate (chemical + TSE) also covering sterility

The contents of each type of CEP are described below.
For details of grades/subtitles, refer to "Subtitle" under section 4.3.1.

4. Content of a CEP

4.1 CEP unique reference (valid for all types of CEP)

The alphanumerical reference of a CEP consists of the following three blocks:

- Unchanged root, linked to the number assigned to the original CEP application, composed of 12 characters: CEP procedure number + application year + chronological number, for example:

C	E	P		2	0	1	5	-	0	0	0

- Variable parts of the reference:

  Quinquennial indicator, which indicates the renewal status of the CEP: 3 characters, incremented five years after the original CEP is issued:

R	X	-

  Revision indicator, which indicates the revision status: 7 characters, incremented each time the CEP is revised:

-	R	e	v		X	X

These three blocks together constitute the full CEP number of 22 characters:

R	X	-	C	E	P		2	0	1	5	-	0	0	0	-	R	e	v		X	X

4.2 CEP declaration of access (valid for all types of CEP)

In order to control the use of CEPs, the CEP holder should authorise its customers to use a CEP in support of an MAA for a particular product(s). For that, the CEP holder has to make a copy of the original CEP and fill in the Declaration of access ("Box of access") at the end of the CEP, including the name of the pharmaceutical company, the name of the medicinal product(s) and reference of the MA (where available). By signing this box, the CEP holder also certifies that no changes to the operations as described in the CEP dossier have been made since the granting of the latest version of the CEP.

When a CEP has been revised/renewed, it is the responsibility of the CEP holder to provide a copy to its customers.

It is possible to verify the validity status of a CEP at any time by searching the Certification Database on the EDQM website www.edqm.eu, under section "Certification of Suitability".

Note: only the CEP holder possesses the original CEP and can issue a valid ("true") copy to its customers. The EDQM does not keep any original CEPs.

4.3 CEP statements

A number of statements are included on CEPs which provide transparency on the items that have/have not been considered during the assessment of the CEP application and provide useful additional information to CEP users (including Competent Authorities).

The statements vary depending on the type of evaluation performed, as follows:

4.3.1 Statements on a CHEMICAL CEP

NOTE: CEPs may contain information which does not fully reflect the active substance specification submitted in the CEP application and on the certificates of analysis (some information not being relevant to demonstrate suitability/compliance with the Ph. Eur. monograph). The criteria used to decide whether or not to include specific information, such as tests and limits, and to annex specific methods to the CEP are clarified below. It is thus important to keep in mind that the CEP frequently lists fewer tests and limits than are included in the specification of the substance which was accepted by EDQM.

- Subtitle (e.g. particle size, polymorphic form, sterile)

The CEP applicant can request that a subtitle is included on the CEP, provided that the conditions laid down in the Certification policy document PA/PH/CEP (04) 1 "Content of the Dossier for Chemical Purity and Microbiological Quality" (current version) are fulfilled.

Where a subtitle is requested by the CEP applicant, the acceptability of the requested subtitle is assessed within the CEP procedure, and only if the subtitle is accepted by the EDQM is it included on the CEP, together with the corresponding test(s) and limit(s) relative to that particular grade.

The absence of a subtitle on the CEP means either that the characteristics related to a particular grade have not been accepted by the EDQM, even where data have been provided in the CEP dossier, or the CEP applicant has not requested any subtitle.

If the method(s) used is/are not described in the Ph. Eur., the analytical method(s) used by the manufacturer is/are annexed to the CEP.

It is to be noted that grades such as "pyrogen-free" or "bacterial endotoxin-free" are only acceptable when this is stipulated under the "Labelling" section of the specific Ph. Eur. monograph.

In particular cases where the Ph. Eur. monograph covers different grades of a substance, it is possible to include these different grades in the subtitle of the CEP. However, different grades cannot be covered by a single CEP if these different grades require different limits and/or methods for the control of impurities. In such cases, separate certificates will be required and the respective relevant grades will be stated in the subtitles (e.g. povidone, macrogol).

A special subtitle case is "sterile" (see section 4.3.3 "Statements on a CEP for a sterile substance").

- Sites

The sites declared in the CEP application are stated on the CEP, according to their respective roles and depending on the subtitle requested for inclusion on the CEP:

The following sites are stated on a chemical CEP:

- CEP holder
- Substance manufacturing site(s)
- Intermediates manufacturing site(s)

The following sites are only included if a specific subtitle is requested (and accepted), and if not already listed on the CEP as the substance manufacturer:

- Site(s) performing the sterilisation steps
- Site(s) performing any physical treatment (e.g. micronisation, milling, sieving, lyophilisation)

CEPs granted before July 2013 might not cite all intermediate manufacturing sites. In this case, the CEP users need to request more detailed information from the CEP holder.

- Compliance statement

Statement by which the EDQM certifies that the quality of the substance produced at the site(s) listed on the CEP (or its annexes) is suitably controlled by the corresponding Ph. Eur. monograph (current edition including supplements), supplemented by the test(s) stated on the CEP and the analytical procedures included in the annex, where applicable. This means that the specification of the substance should include the tests from the Ph. Eur. monograph, together with the additional tests listed on the CEP.

- Impurities

The assessment carried out at the EDQM during the CEP procedure is performed taking into account the known use of an active substance. In particular, the maximal human[1] daily dose (MDD) and the route(s) of administration of the already approved medicinal products in which the active substance is included are used as a basis to establish acceptable limits for impurities not controlled by the monograph, as well as the options for controls in the case of residues of mutagenic and elemental impurities.

Limits for "additional related substances" (those not already mentioned in the Ph. Eur. monograph). Two cases are possible:

a) If additional related substances are present in the substance above the reporting threshold set by the Ph. Eur. general monograph "Substances for pharmaceutical use (2034), and they are detected by the test for related substances of the Ph. Eur. monograph, these in-house impurities are stated on the CEP with specified limits. Unspecified impurities (below the identification threshold) are not mentioned on the CEP and are automatically covered by the general limit for unspecified impurities.
In this case no method is annexed to the CEP.

b) If additional related substances are present in the substance above the reporting threshold set by the Ph. Eur. general monograph "Substances for pharmaceutical use (2034), and the Ph. Eur. monograph method is not suitable to control these impurities, they should be controlled by a validated in-house method and stated on the CEP (either with a specific limit or covered by the limit for unspecified impurities if found to be below the identification threshold).
The in-house method is annexed to the CEP and is considered an additional method.

In both cases (a and b), a limit for total impurities is also added if not stipulated in the specific Ph. Eur. monograph.

Non-quantitative methods:

If the method for related substances in the Ph. Eur. monograph is a non-quantitative method (e.g. TLC with a general limit), the test for related substances is replaced by a quantitative method which is annexed to the CEP where it is indicated as replacing the Ph. Eur. method.

[1] Unless the product is intended for veterinary use only, as stipulated in the corresponding Ph. Eur. monograph.

Alternative methods:
Manufacturers are free to use alternative methods to those described in the Ph. Eur. monographs provided these methods are at least equivalent to the Ph. Eur. methods; this has to be demonstrated in the CEP dossier and will be verified during the assessment of the CEP dossier. If the methods are cross-validated, and where the Ph. Eur. monograph is demonstrated as suitable to control the impurities present in the substance, the in-house methods are not annexed to the CEP. In the event of doubt or dispute, the texts of the Ph. Eur. are authoritative.

Limit for unspecified impurities:
When the Ph. Eur. monograph of the substance for which a CEP is granted does not include a general limit for unspecified impurities, according to the Ph. Eur. general monograph "Substances for pharmaceutical use" (2034), such a limit shall be introduced in the specification of the substance and is included on the CEP. The limit is defined according to the MDD of the substance and is in line with the thresholds set by Ph. Eur. general monograph 2034, unless the substance is out of the scope of this general monograph.

Genotoxic/mutagenic impurities:
Until 31 December 2015, the EMA "Guideline on the limits of genotoxic impurities" (EMEA/CHMP/QWP/251344/2006) and the EMA "Questions and answers on the Guideline on the limits of genotoxic impurities" (EMA/CHMP/SWP/431994/2007 Rev. 3) were applied.

With effect from 1 January 2016, ICH guideline M7, adopted by the CHMP and issued as EMA/CHMP/ICH/83812/2013, is applied.

The above-mentioned guidelines do not apply to substances intended for veterinary use only. Consequently, the requirements of these guidelines are not taken into consideration during the assessment of CEP applications for this type of substance.

Where necessary, and in line with the requirements of the above-mentioned documents, genotoxic/mutagenic impurities are stated on the CEP together with the accepted limit and the corresponding analytical method.

- Residual solvents:

Ph. Eur. general chapter 5.4 Residual Solvents is applicable to the CEP procedure.

The solvents that are stated on the CEP are those likely to be present in the substance, i.e. solvents used in the final manufacturing steps (regardless of their residual levels) and solvents that are used in earlier manufacturing steps which are not removed consistently by a validated process and whose levels in the substance are above 10% of the concentration (option 1) limit established by ICH Q3C (equal to the limits set by Ph. Eur. general chapter 5.4 Residual Solvents).

The limits for the residual solvents stated on the CEP are the manufacturer's proposed limits as accepted by the EDQM.

Some CEP holders may decide to test all solvents used in the synthesis, including those demonstrated to be absent. In these cases, the CEP cites fewer solvents than are included in the CEP applicant's specification for the substance.

Option 2 calculation for class 2 solvents:
For class 2 solvents, any limit higher than that of the ICH Q3C Option 1 limit should be justified according to Option 2 calculation. Option 2 allows use of the PDE (mg/day) according to the actual daily dose of the active substance.

When Option 2 has been applied by the manufacturer of the substance for which the CEP is granted, this is made transparent on the CEP for the users and should be considered in the frame of the MA assessment (further calculation of residual solvent levels may be required in the context of the final use of the active substance).

Concerning class 3 solvents, in exceptional cases, higher amounts than those allowed by the ICH Q3C Option 1 limit (5000 ppm or 0.5%) may also be acceptable provided they are justified in relation to manufacturing capability and GMP.

Control of class 3 solvents by Loss on drying test:
Where only class 3 solvents are likely to be present in an active substance, a Loss on drying test may be used. If a Loss on drying test is already included in the Ph. Eur. monograph with a limit of not more than 0.5%, this is reflected on the CEP with the names of the solvents used, and no method is annexed.

Where a mixture of class 2 and class 3 solvents is likely to be present in the active substance, and where a Loss on drying test with a limit of not more than 0.5% is included in the Ph. Eur. monograph, all class 3 solvents are normally stated on the CEP as being controlled by loss on drying, even if the manufacturer controls them with a specific method, while class 2 solvents are stated as being controlled by a specific method (usually gas chromatography).

Even if not described in the Ph. Eur. monograph, a test for loss on drying may be included in the specification of the active substance, performed as described in Ph. Eur. general chapter 2.2.32, with a limit of not more than 0.5%. In this case, this is stipulated on the CEP and no method description is annexed.

Where the limit for loss on drying of the Ph. Eur. monograph is higher than 0.5%, the policy is that a specific test for residual solvents should be included in the active substance specification. In this case, the names and limits for individual solvents are reported on the CEP and the in-house method is annexed.

Denaturants:
If denaturants used in solvents are likely to be carried over to the active substance, a limit in the specification of the active substance is expected, and such limits will be stated on the CEP.

- Use of water in the purification steps of the synthesis

The use of water in the purification step of the synthesis is stated on the CEP.

- Quality of water

By default, the minimum acceptable quality of the water used in the manufacture of an active substance for oral use is potable water (cf. CPMP/CVMP NfG on quality of water for pharmaceutical use, CPMP/QWP/158/01 Revision & EMEA/CVMP/115/01 Revision). The quality of water is stated on the CEP only when a particular grade/quality of an active substance is claimed (e.g. sterile).

- Residual metal catalysts and reagents/elemental impurities

Until August 2016, the EMEA/CHMP/SWP/4446/2000 "Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents" was applied (unless otherwise justified) for the evaluation of carryover of metal catalysts/reagents into the active substance.

Further calculation of residual metal levels might be necessary in the context of the final use of the drug substance.

With effect from September 2016, ICH Guideline Q3D "Guideline for elemental impurities", adopted by the CHMP and issued as EMA/CHMP/ICH/353369/2013, is applied to substances intended to be introduced in medicinal products within the scope of ICH Q3D.

For affected CEPs, the information reported on the CEP concerning elemental impurities will depend on the option chosen by the CEP applicant, as follows:

a) If a Risk Management Summary has been provided by the CEP applicant, the summary is appended to the CEP, with the necessary information on the level of contamination of the substance, in order to implement the ICH Q3D component approach to the finished medicinal product.

b) If no risk assessment has been performed by the CEP applicant, elemental impurities classified in ICH Q3D which are intentionally used in the process after the introduction of the starting materials are stated on the CEP, regardless of the levels found in the final substance. Alternatively, if no elemental impurities are intentionally added during the process, this is stated on the CEP.

NOTE: the EDQM does not make a final decision on compliance with ICH Q3D. This should be done within the context of the MAA for the medicinal product in which the substance covered by the CEP is used.

Where necessary, the limit(s) proposed by the CEP applicant (and accepted by the EDQM) will be stated on the CEP and the analytical method(s) will be annexed to it.

The above-mentioned guidelines do not apply to substances intended for veterinary use only. Consequently, the requirements of these guidelines are not taken into consideration during the assessment of CEP applications for this type of substance.

- Omitted tests

Where the Ph. Eur. monograph includes a specific test for a named compound (e.g. impurity, metal catalyst, reagent, solvent), but the compound is not used during synthesis by the substance manufacturer or cannot be present with the route of synthesis used, the Ph. Eur. test can be removed from the substance specification. This is clearly stated on the CEP.

- Microbial quality

Only where the Ph. Eur. monograph indicates specific requirements related to microbial quality for the manufacturing process (i.e. in the Production section of the Ph. Eur. monograph), is compliance to this aspect assessed as part of the CEP procedure.

- Container closure system

The packaging information is systematically assessed during the CEP procedure, even when no retest period is requested by the CEP applicant, and the full packaging material (immediate and outer) is described on the CEP.

However, CEPs issued before 1 September 2011 might not include this information. This should be considered by the CEP users who need to request this information from the CEP holder.

- Retest period

As stated in the EU Note for Guidance “Stability testing of existing active substances and related finished products” (CPMP/QWP/122/02 and EMEA/CVMP/846/99), for active substances described in an official pharmacopoeial monograph (Ph. Eur. or the Pharmacopoeia of a European Union Member State) which covers the degradation products, and for which suitable limits have been set but a retest period is not defined, results from stability studies are not necessarily required, provided that the active substance complies with the pharmacopoeial monograph immediately prior to use in the finished product. This is why not all CEPs carry a retest period.

If a retest period is requested as part of the CEP application, stability data are assessed by the EDQM and a retest period for the active substance is granted in line with the current EU requirements.

The granted retest period is stated on the CEP together with the packaging material and appropriate storage conditions if any restrictions apply. According to guideline CPMP/QWP/609/96 part B (Declaration of storage conditions) no declaration of specific storage condition means that the active substance is stable under climatic conditions for zone I/II (combination of long-term and accelerated conditions).

- Material of human or animal origin used in the manufacture of the substance

CEP applicants have to declare whether any material of animal or human origin is introduced in the production of the substance to be covered by the CEP (e.g. at the level of starting materials, reagents, additives, materials used in the media of fermentation processes). This declaration is not limited to TSE-risk materials.

The use of such material is made clear on the CEP in order to alert the Competent Authorities to the possible need to address any viral safety issues. Viral safety is not assessed at the EDQM, even if data are provided.

If the substance involved is likely to present a TSE risk, the relevant TSE assessment is systematically carried out (see section 4.3.5 “Statements on a TSE CEP”) and the relevant statement is included on the CEP (“double CEP”). In the absence of such a statement, users know that the substance does not pose any TSE risk.

- Production section

Statements on a Ph. Eur. monograph under the heading “Production” draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute instructions to manufacturers. 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.

When the evaluation has considered the Production requirements, no statement will be added to the CEP.

In cases where the specific Production requirements are out of the Certification scope (e.g. viral safety), a statement on the CEP makes clear that compliance with the Production section of the Ph. Eur. monograph has to be addressed at the level of the MAA.

4.3.2 Statements on a CEP for API-mix

A CEP application can only be accepted where there is a Ph. Eur. monograph which covers an API-mix (a mixture of a drug substance (API – active pharmaceutical ingredient) with excipients).

The information which is included on the CEP in such cases is dependent on the information included in the monograph, and the CEP reflects the Labelling section of the monograph. The CEP will supplement the monograph to provide transparency on the names and ranges of any excipients used and, where an additive is used (e.g. antioxidant), the control method is annexed to the CEP.

The document PA/PH/CEP (16) 70 and the EMA Question and Answer document (EMA/CHMP/CVMP/QWP/152772/2016) provide more information on this subject.

4.3.3 Statements on a CEP for a sterile substance

A particular case of a combined CEP is one where the substance is claimed to be sterile and therefore the evaluation for chemical purity is complemented with an evaluation of sterility aspects. Thus, a "sterility CEP" does not exist on its own, but is always combined with the chemical purity evaluation. CEP applications must fulfil the conditions laid down in the EDQM documents "Certificates of suitability for sterile active substances" (PA/PH/CEP/T0 (6) 13) and "Clarification on the acceptability of CEP applications for sterile grade material" (PA/PH/CEP (08) 60).

When granted, the CEP for chemical purity and sterility includes, in addition to the statements for a Chemical CEP (as applicable), the following statements related to sterility:

- The subtitle "Sterile"
- The quality of water in cases where water is used in the sterilisation steps
- Suitable limits if ethylene oxide[2] or ionising radiation are used during sterilisation
- Residual levels of solvents used during sterile filtration
- The statement: "The substance is sterile and shall comply with the relevant test for sterility of the Ph. Eur."
- The sterilisation method used
- The statement that the sterilisation process has been assessed and accepted
- The control of bacterial endotoxins if applicable

[2] In line with the EMA Note for Guidance on limitations to the use of ethylene oxide in the manufacture of medicinal products (EMEA/CVMP/271/01).

4.3.4 Statements on a Herbal CEP

- Subtitle for extracts
    - Drug Extract Ratio (DER): systematically included on CEPs for extracts granted after May 2012. It corresponds to the DER calculated on the genuine extract (extract without excipients).

- Sites
    - CEP holder
    - Substance manufacturing site(s)
    - Intermediate(s) manufacturing site(s)
    - Additional sites might be included if necessary

- Compliance statement

Statement by which the EDQM certifies that the quality of the substance produced at the site(s) listed on the CEP is suitably controlled by the corresponding Ph. Eur. monograph (current edition including supplements), supplemented by the test(s) mentioned on the CEP and the analytical procedures given in the annex, where applicable. This means that the specification of the substance includes the tests of the Ph. Eur. monograph together with the additional tests listed on the CEP.

- Residual solvents

Tests and limits for residual solvents are stated on the CEP and the corresponding in-house method(s) are annexed.

- Extraction solvent(s)

The solvent(s) used to prepare the extract are stated on the CEP (e.g. ethanol 60% v/v).

- Excipients

The excipient(s) included in the extract and their percentage content are stated on the CEP.
If the extract does not include any excipients, this is also made transparent on the CEP.

- Retest period

If a retest period is requested as part of the CEP application, stability data are assessed by the EDQM and a retest period for the active substance is granted in line with the current EU requirements. The granted retest period is stated on the CEP.

- Container closure system

The full packaging material (immediate and outer) is described on all Herbal CEPs.

- Material of human or animal origin used in the manufacture of the product

The use of such material in the manufacture of the product is made clear on the CEP.

4.3.5 Statements on a TSE CEP

- Subtitle

The manufacturing process is included as a subtitle on the CEP, where applicable (i.e. for gelatin).
In addition, for CEPs covering several qualities of the same product, the product codes (having been described in the application and accepted by the EDQM) are stated in the subtitle.

- Sites
    - CEP holder
    - Substance manufacturing site(s)

- Compliance statement

Statement by which the EDQM certifies that the substance produced at the site(s) listed on the CEP meets the criteria described in the current version of the monograph "Products with risk of transmitting agents of animal spongiform encephalopathies" (1483) of the Ph. Eur.

- Country(ies) of origin of source materials

The geographical origin of the animals used to source the organs or tissues used in the manufacture of the substance is stated on the CEP.

- Nature of animal tissues used in manufacture

The type of tissues used in the manufacturing process (e.g. bovine blood, bovine tendons) is stated on the CEP.

- Manufacturing process applied

Only when relevant for the safety of the product (e.g. gelatin).

A double CEP (Chemical + TSE) will include the statements from both types of CEP, where applicable.

4.3.6 CEPs for Biological substances

As laid down in Resolution AP-CSP (07) 1, the Certification procedure is not applicable to biological substances nor to substances extracted from animal tissues which fall under the category "Biological active substances of non-recombinant origin".

5. CEP Revision & Renewal

Revisions of CEP applications are handled by the EDQM. The document PA/PH/CEP (04) 2 (current version) "Guideline on requirements for revision/renewal of Certificates of

Suitability to the European Pharmacopoeia monographs", available on the EDQM website (www.edqm.eu), describes the requirements for the revision and renewal of CEPs.

This document has been elaborated taking into consideration the EU Regulation for Variations to Marketing Authorisation Applications (1234/2008/EC).

Revision of a CEP means that the changes made to an application are reviewed to ensure compliance with current requirements of the procedure. The holder of a CEP shall inform the EDQM of any change to information in the CEP application by sending an appropriate request for revision.

Renewal of a CEP means that an application is reviewed to ensure compliance with current requirements of the procedure. The renewal occurs 5 years after the date of issue of the original certificate, regardless of the number of revisions which may have occurred in the interim period.

Once a CEP has been revised or renewed, it is the responsibility of the CEP holder to immediately inform its customers and provide them with a copy of the revised/renewed CEP to allow them to implement the necessary modifications in the related MA application(s).

The review and approval of the changes made to a CEP application does not systematically lead to the issue of a revised CEP if, for example, the change has no impact on the quality of the active substance in relation to the Ph. Eur. monograph or on the content of the current CEP.

CEPs are always revised in the following cases:

- After any notification/minor revisions impacting the content of the CEP
- After any major revisions (even if the content of the CEP is not impacted)
- After renewal

Where minor changes made to a CEP application do not have any impact on the CEP content, the current CEP remains valid and the CEP holder is duly informed. However, even in these cases, the CEP holder is responsible for immediately informing its customers as stated above.

5.1 Updates of CEP applications following Ph. Eur. monograph revisions

Updates of CEP applications following Ph. Eur. monograph revisions are treated separately.

When a Ph. Eur. monograph is updated, the impact of the changes on the related CEP application has to be evaluated by the corresponding CEP holder.

In addition, the EDQM reviews the CEP applications concerned and initiates their update according to an established procedure. If necessary, CEP holders are requested to provide data to the EDQM, which are then subject to assessment. This is to ensure that all CEPs are always up-to-date and in line with the latest version of the Ph. Eur. monographs.

After the evaluation of the updated dossier the CEP is revised, where necessary.

6. CEP Suspension & Withdrawal

The EDQM document PA/PH/CEP (08) 17 (current version) "Suspension or withdrawal of a Certificate of suitability, closure of an application", available on the EDQM website, describes the EDQM policy for suspension, restoration or withdrawal of a CEP and for closure of a CEP application, in accordance with the provisions of Resolution AP-CSP (07) 1 of the Council of Europe.

Any statement of GMP non-compliance that is related to a manufacturing site covered by a CEP application initiates the decision-making process on the validity of the CEPs concerned by the EDQM, regardless of whether the EDQM has been involved in the inspection or not.

A decision is taken for all relevant CEPs and CEP applications. For example, when a GMP non-compliance has been observed for Site B (which manufactures substance A), all substances manufactured by Site B which are covered by a CEP (and not only substance A) are potentially affected by this GMP non-compliance and consequently all CEPs concerned are suspended or withdrawn, as applicable.
Suspension of a CEP means a temporary invalidation of a CEP (usually for a defined period of time).

Restoration of a suspended CEP means that the conditions for lifting the suspension have been met (e.g. a re-inspection in the case of suspension linked to a GMP non-compliance). The CEP restoration follows the same decision-making process as that for the suspension of the related CEP(s). In this case, a revised CEP is granted, which supersedes the suspended one.

Withdrawal of a CEP (cancellation) means a definitive invalidation of a CEP.

When confirmed, any change in the status of a CEP is made publicly available on the EDQM website.

Once a CEP has been suspended or withdrawn, it is the responsibility of the CEP holder to immediately inform its customers to allow them to take responsibility with regard to the substance concerned and any related MA or MAA.

Details on decisions to suspend or to withdraw a CEP are communicated by the EDQM in a confidential manner to the relevant authorities of the member states of the Ph. Eur. Convention, as well as to the countries/organisations with which special agreements have been made, to enable them to take appropriate actions regarding the MA or MAA concerned.

7. List of abbreviations

AP-CSP	Accord Partiel – Comité de Santé Publique (Partial Agreement - Public Health Committee)
API-mix	Mixture of an active pharmaceutical ingredient with one or more excipients
CEP	Certificate of suitability to the Monographs of the European Pharmacopoeia
CPMP	Committee for Medicinal Products for Human Use (EMA)
CTD	Common Technical Document
CVMP	Committee for Medicinal Products for Veterinary Use (EMA)
DER	Drug Extract Ratio
EDQM	European Directorate for the Quality Medicines & HealthCare
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
HACCP	Hazard Analysis Critical Control Point
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MDD	Maximal daily dose
NfG	Note for Guidance
OIE	World Organisation for Animal Health (Office International des Epizooties)
Ph. Eur.	European Pharmacopoeia
QWP	Quality Working Party
TSE	Transmissible Spongiform Encephalopathies