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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 describes in detail the information conveyed on a Certificate of suitability to the Monographs of the European Pharmacopoeia (CEP) and clarifies how this information should be interpreted by both industry and competent authorities. It should be read in conjunction with other applicable certification policy documents and guidelines (available on the EDQM website https://www.edqm.eu/).

2. Aim and scope of a CEP

There are several types of CEPs, depending on the assessment 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:

- Chemical CEP and "sterility";
- double certificate (chemical + TSE);
- double certificate and "sterility" (chemical + TSE + "sterility").

Based on the specific data supplied by the CEP holder, a Chemical or Herbal CEP certifies that the quality of a substance can be suitably controlled by the European Pharmacopoeia (Ph. Eur.) individual monograph for the substance in question and any supplementary tests deemed necessary in line with applicable (V)ICH and EMA guidelines.

A TSE CEP certifies that the substance complies with the Ph. Eur. general monograph entitled *Products with risk of transmitting agents of animal spongiform encephalopathies* (*1483*). A TSE CEP does not certify that the quality of the substance is suitably controlled by a specific Ph. Eur. monograph.

CEPs are not equivalent to certificates of analysis and thus do not demonstrate batch-related compliance.

A CEP is not a GMP certificate, although when submitting a CEP application, the manufacturer must confirm that the substance covered by the CEP is produced according to GMP requirements. As a complementary activity to dossier evaluation, the CEP procedure includes a GMP inspection programme for sites involved in the manufacture of the substance concerned on a risk-based approach.

3. General considerations

The CEP application for a substance is assessed on its own (not in connection with a medicinal product with a specific use) taking into consideration relevant ICH and EMA guidelines for human or, if applicable, veterinary use (when stated in the title of the corresponding Ph. Eur. monograph). When reading and using a CEP, it should be borne in mind that the CEP is granted in line with the requirements applicable at the time of the assessment and when the CEP is granted.

The assessment is carried out by the EDQM taking into account the known common use of an active substance. In particular, the common maximum human[1] daily dose (MDD) and the route(s) of administration of the medicinal products already approved in the EU 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.

Therefore, the EDQM does not make a final decision on compliance with the requirements related to the use of a substance in a medicinal product. Rather, this should be done within the context of the marketing authorisation application (MAA) for a particular medicinal product in which the substance covered by the CEP is used. For instance, further calculations may be needed for residual solvents, elemental impurities and/or mutagenic impurities in the context of the MAA.

Marketing authorisation (MA) applicants/holders are advised to read existing guidance published by the competent authorities of the regions (e.g. EU) and countries accepting CEPs 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.

In addition to a copy of the CEP, CEP holders should provide any necessary information in order to enable marketing authorisation holders (MAH) to evaluate the suitability of the substance for its intended use, as explained in the EDQM policy document “CEP holders’ responsibilities towards their customers” (PA/PH/CEP (21) 57).

Competent authorities may contact the EDQM directly if they have questions concerning information given in the CEP that prevents them from performing the evaluation of the MAA.

It is possible to verify the validity status of a CEP at any time in the public Certification Database on the EDQM website.

4. CEP formats

Major changes were introduced to the CEP document in September 2023, resulting in three different formats referenced in this document as “CEP 2.0”, “old CEP” and “hybrid CEP”. The main differences (not exhaustive) between these three formats are illustrated below:

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

	CEP 2.0	Hybrid	Old CEP
Format	Electronic document with electronic signature		Paper document with wet signature
Numbering	2-block code CEP 20XX-XXX-Rev 00		3-block code R0-CEP 20XX-XXX-Rev 00
Information on companies	Name and address of the holder and production sites completed by SPOR OMS LOC &ORG ID		Name and address of holder and production sites
Technical information (Chemical and herbal CEP)	Inclusion of the approved specification and description of additional methods required to control the substance	Limits for additional impurities and inclusion of tests used in addition to the Ph. Eur. monograph tests, required to control the substance	
Expiry date	No reference to a validity date of 5 years (renewal due date, available on public database)		Yes reference to expiry date (before renewal)
Box/Letter of access	Letter of access (template on EDQM website)		Box of access on CEP
Issue date	After 1 September 2023		Until 31 August 2023

The specific features of each and the details of their differences are described below. The three formats may also differ in their layout and some of the statements they include.

4.1. CEP 2.0 and hybrid CEP

4.1.1. Numbering

The number (alphanumerical reference) of a CEP consists of the following two parts:

- invariable part, unchanged root linked to the number assigned to the original CEP dossier: CEP indicator of the procedure + year of receipt of the initial application + chronological number, for example:

C	E	P		X	X	X	X	-	Y	Y	Y

- variable part, revision indicator, which indicates the revision status (incremented each time a revised CEP is granted, whatever the revision is):

-	R	e	v		Z	Z

Together, these two parts constitute the full CEP number, for example:

C	E	P		2	0	2	4	-	0	0	5		-		R	e	v		0	0

year — chronological number — incremented at each revision

4.1.2. CEP letter of access

To allow the use of their CEPs, the CEP holder should authorise its customers to use a CEP by filling in a letter of access to be provided together with a copy of the CEP received from the EDQM. A template for this letter is available on the EDQM website, but alternatively any letter with equivalent content may also be used.

4.1.3. Sites

The CEP holder and all sites involved in the manufacture of the substance covered by the CEP after the introduction of the starting material(s) declared in the CEP dossier are listed on the CEP in an annex with their name, address, SPOR/OMS Organisation (ORG) ID and Location (LOC) ID and role:

- CEP holder;
- site(s) of production of intermediate(s), if any;
- site(s) of production of the substance;
- site(s) of physical treatment, if any grade claimed and accepted;
- site(s) of micronisation, if any grade claimed and accepted;
- site(s) of sterilisation, if any grade claimed and accepted.

If there are minor differences between the address details for sites in CEP applications/dossiers and those registered in the SPOR/OMS database, the EDQM uses the entries from the SPOR/OMS database as a reference for the CEP.

In cases where multiple sites are involved, details of the steps carried out at each site are not stated on the CEP. Testing sites, when different than those involved in the manufacture of the substance, are not stated on the CEP. In any case, CEP holders should provide necessary details to CEP users.

4.2. Old CEP

4.2.1. Numbering

An old CEP number consisted of the following three blocks:

- unchanged root, linked to the number assigned to the original CEP application: CEP procedure number + application year + chronological number

- variable parts of the reference:
  quinquennial indicator, which indicated the renewal status of the CEP (incremented five years after the original CEP was issued):

R	X	-

  This indicator is what differentiates an old CEP number from a CEP 2.0 and a hybrid CEP.

  revision indicator (incremented each time the CEP is revised):

-	R	e	v		Z	Z

Together, these three blocks constituted the full old CEP number, for example:

R	1	-	C	E	P		2	0	1	5	-	4	5	7	-	R	e	v		0	8

4.2.2. Declaration of access box

Only the CEP holder possesses the original paper CEP and can issue a valid (“true”) copy to its customers. The EDQM did not keep any original CEPs as they were generated as unique documents.

To authorise its customers to use a CEP in support of an MAA for a particular medicinal product(s), the CEP holder must make a copy of the original CEP and fill in the Declaration of access ("Box of access") at the end of the CEP document, 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 latest version of the CEP was granted.

4.2.3. Sites

The sites declared in the CEP application were stated on the CEP, according to their respective roles, with their name and address but no SPOR/OMS Organisation (ORG) and Location (LOC) ID. The same rules for the roles of sites as for the CEP 2.0 and hybrid CEP applied to old CEPs.

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.

5. Content of CEPs

CEPs include a number of statements that provide transparency on the items that have or have not been considered during the assessment of the CEP application, and provide useful additional information to CEP users (including competent authorities). The statements depend on the type of evaluation performed and are described below.

5.1. Content of CEP 2.0

5.1.1. Statements on a Chemical CEP

- Specification

The CEP dossier should include the specification of the substance that is to be covered based on the corresponding Ph. Eur. individual monograph as well as European regional requirements from Ph. Eur. general monographs and (V)ICH and EMA guidelines. Compliance with these texts is evaluated and approved during the assessment performed by the EDQM and reflected in the specification that is appended to the CEP. Quality attributes, acceptance criteria and references of test procedures (e.g. Ph. Eur., in-house) are included in the specification table.

For some quality attributes, the CEP holder may decide to set limits tighter than those foreseen by the Ph. Eur. and European regional requirements. This is reflected in the specification.

If a CEP holder decides to include a quality attribute in the specification only to satisfy a regulatory requirement in another region (i.e. non-European regional requirement) or for their own needs, this is presented separately from the other quality attributes and clearly identified as such in the specification (e.g. as "applied but not necessary to satisfy European regional requirements"). These quality attributes, the corresponding test procedures and the validation data are not considered during the assessment, and the test procedures are not appended to the CEP.

The absence of controls/tests for impurities mentioned in the corresponding Ph. Eur. monograph is accepted when justified. In this case, the specific control/test would not be listed in the specification appended to the CEP.

The specification of the substance appended to the CEP may include information on skip testing when approved by the EDQM.

- Test procedures

Manufacturers may use alternative test procedures to those described in the Ph. Eur. monographs, provided these are at least equivalent to the Ph. Eur. ones. When the Ph. Eur. monograph is demonstrated to be suitable to control the impurities or quality attribute, the in-house test procedures are not appended to the CEP. However, the use (and approval) of an alternative test procedure is transparent from the specification appended to the CEP which mentions that an “in-house” test procedure is used.

For quality attributes not covered by the Ph. Eur. monograph for the substance and that are needed to control its quality, in-house test procedures are appended to the CEP (e.g. GC for residual solvents, or ICP-MS for elemental impurities). However, if these are based on test procedures suitably described (i.e. with all details) in an appropriate Ph. Eur. “Methods of analysis” general chapter, the chapter can be referenced in the specification and no description of the test procedure is appended to the CEP.

- Subtitle

A CEP can cover specific physico-chemical characteristics of a substance (e.g. specific polymorphic form or particle size distribution) or its sterility. These are indicated as “grades” and are mentioned on the CEP as a subtitle.

A subtitle is meant to specify a grade of the substance but can also be used to differentiate CEP applications for the same substance submitted by the same holder (e.g. “process b” or “produced at site X”). In addition, the subtitle is also used to reflect on the CEP the requirements of the "labelling” section of the monograph, where applicable.

This applies to the particular case of a CEP for an API-mix (e.g. presence of antioxidant mentioned as a subtitle). The names and target value of any excipients used and, where applicable, the limit and method for the excipient are included in the appended specification. If a carrier oil is used, this is transparent on the CEP with a specific statement.

If a subtitle is requested and accepted by the EDQM, it is covered by the CEP and the corresponding quality attribute is included in the specification appended to the CEP.

Some CEPs cover sterile substances and include an evaluation of sterility aspects together with the chemical purity evaluation. This involves the full assessment and approval of the sterilisation process (including sterilisation of the container closure system) and its validation. It should be noted that validation data should be given to the MAH for submission in the MAA.

CEPs covering a sterile substance include statements for a Chemical CEP (as applicable) and additional statements related to sterility:

- the subtitle “Sterile”;
- a sentence specifying that the substance is sterile and describing the sterilisation method used;

- a test for sterility in the specification for the substance and potentially additional tests such as the control of bacterial endotoxins, if applicable.

- Impurities

The specification includes limits for related substances as foreseen by the individual monograph but can also include limits for “additional related substances” (those not already mentioned in the Ph. Eur. monograph). The CEP holder is encouraged to use unequivocal chemical names for these additional impurities in the specification but, if this is not the case, it is their responsibility to share the relevant information with the users of their CEPs.

Where necessary, elemental, mutagenic and nitrosamine impurities are included in the specification appended to the CEP.

- Residual solvents

Test procedures and limits for the residual solvents stated in the specification appended to the CEP are those proposed by the CEP holder as accepted by the EDQM following assessment.

If class 3 solvents used in the last steps of the manufacturing process are controlled by a suitable loss on drying test, a sentence to this effect is included on the CEP. If there is no test for loss on drying in the Ph. Eur. monograph, such a test may be included in the specification of the substance, with reference to Ph. Eur. general chapter *2.2.32*. In this case, this is stipulated in the specification appended to the CEP without any test procedure being appended.

For class 2 solvents, any justified limit defined according to option 2 calculation (i.e. higher than that of the ICH Q3C or VICH GL18 option 1 limit), is transparent in the specification appended to the CEP.

For class 3 solvents, in exceptional cases, if higher amounts than those allowed by the ICH Q3C or VICH GL18 option 1 limit have been considered acceptable, this is also transparent in the specification appended to the CEP.

- Use and quality of water in the manufacturing process

The use of water in the last steps of the manufacturing process (as a solvent or during isolation and/or purification) and its quality in line with the EMA “Guideline on the quality of water for pharmaceutical use” EMA/CHMP/CVMP/QWP/496873/2018 (i.e. potable water, purified water, water for injections) is reported on the CEP to enable CEP users to confirm the suitability of the quality of the substance for its intended use.

- Residual elemental impurities

The information on elemental impurities provided on the CEP depends on the option chosen by the CEP holder, as follows:

a) if a Risk Management Summary has been provided by the CEP holder, the summary is appended to the CEP, with the necessary information on the level of contamination of the substance, in order to implement a component approach to the finished medicinal product;
b) if no risk assessment has been performed by the CEP holder, elemental impurities (classified in ICH Q3D or EMA/CVMP/QWP/631010/2017) that 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 substance. Alternatively, for substances in the scope of the aforementioned documents (e.g. excluding substances obtained by

fermentation), if no elemental impurities are intentionally added during the process, this is stated on the CEP.

- Microbial quality

This aspect is generally not covered in the CEP procedure since the final use of the substance is not known and this should be assessed in the MAA. However, if applicable, this quality attribute may be part of the specification appended to the CEP.

- Container closure system

The full packaging material (immediate and outer) is described on the CEP even when no re-test period is requested by the CEP holder.

- Re-test period

In line with the current regulatory requirements, a re-test period is mentioned on the CEP if requested by the CEP holder and agreed by the EDQM. Therefore, not all CEPs carry a re-test period.

If a re-test period is mentioned,

- the absence of any specific temperature conditions means that the substance is stable under climatic conditions for zone I/II (combination of long-term and accelerated conditions).
- specific storage conditions reported on the CEP mean:
    - either that they are needed to ensure the stability of the substance in the described container closure system;
    - or that the CEP holder/applicant is applying stricter storage conditions than those recommended by EU/ICH guidelines.

In any case, the re-test period is supported by stability data obtained in the appropriate conditions.

- Use of materials of human or animal origin

A statement on the use or absence of materials of animal or human origin in the manufacture of the substance covered by the CEP is included in the CEP.

Viral safety is not assessed by the EDQM. However, there are cases where, based on the information given in the CEP dossier, it can be concluded that the process includes rigorous viral inactivation steps which minimise risks of contamination, and this is specified on the CEP. If a decision cannot be taken, the CEP contains a statement mentioning that viral safety must be assessed in the context of the medicinal product containing this substance (and relevant data must be submitted in the MAA).

The statement regarding the use of materials of animal or human origin is not limited to TSE-risk materials. If the substance involved is likely to present a TSE risk, the relevant TSE assessment is systematically carried out (see section on “Statements on a TSE CEP”) and the relevant information, including reference to Ph. Eur. general monograph *1483* is mentioned on the CEP (“double CEP”). In the absence of such information, users know that the substance does not pose any TSE risk.

- Production section

According to the Ph. Eur. General Notices, statements on a Ph. Eur. monograph under the heading “Production” draw attention to particular aspects of the manufacturing process but are not necessarily exhaustive. 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.

Compliance with the requirements of the Production section of the substance monograph is checked during assessment. As this section is part of the monograph, no specific statement is added to the CEP regarding this aspect. The CEP holder may, however, decide to include quality attributes in their specification although they are not required by the Production section.

In the few cases in which the specific Production requirements are outside the scope of the certification (e.g. where the production statement concerns biological quality), a statement on the CEP makes it clear that compliance with the Production section of the Ph. Eur. monograph must be addressed in the MAA.

5.1.2. Statements on a Herbal CEP

- Specification

The same principles and approach as described for Chemical CEP 2.0 apply. In addition to the requirements of the corresponding individual Ph. Eur. monograph, the specification may include quality attributes such as microbiological purity, pesticides, aflatoxins and ochratoxins where applicable.

- Test procedures

The same principles and approach as described for the Chemical CEP 2.0 apply.

- Subtitle for extracts

The Drug Extract Ratio (DER) is included on CEPs for extracts. It corresponds to the DER calculated on the genuine extract (extract without excipients).

- Extraction solvent(s)

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

- Use and quality of water

The use of water in the last steps of the manufacturing process (as a solvent or during isolation and/or purification) and its quality, namely “water for preparation of extracts”, is reported on the CEP.

- Standardised extracts

A single content of the assayed constituents stated in the Ph. Eur. monograph and defined by the CEP holder is mentioned on the CEP.

- Excipient(s)

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

- Container closure system

The same principles and approach as described for Chemical CEP 2.0 apply.

- Re-test period

The same principles and approach as described for Chemical CEP 2.0 apply.

- Use of materials of human or animal origin

The same principles and approach as described for Chemical CEP 2.0 apply.

5.1.3. Statements on a TSE CEP

As mentioned above, a TSE CEP only certifies compliance with Ph. Eur. general monograph *1483 Products with risk of transmitting agents of animal spongiform encephalopathies* and does not refer to any individual monograph for a substance.

- Subtitle

TSE CEPs may carry a subtitle, in particular to characterise several grades of the same product, product codes, etc. Where applicable, the manufacturing process is included as a subtitle on the CEP (e.g. for gelatin).

- 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 product 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 and as foreseen by Ph. Eur. general chapter *5.2.8* (e.g. for gelatin), the manufacturing process applied is stated on the CEP.

A double CEP (Chemical + TSE) includes the statements from both types of CEP, as necessary.

5.2. Content of Old CEPs

5.2.1. Statements on an old Chemical CEP

As with the CEP 2.0, the CEP dossier had to include specification for the substance to be covered based on the corresponding Ph. Eur. individual monograph as well as European regional requirements from Ph. Eur. general monographs and ICH and EMA guidelines. Compliance with these texts was evaluated and approved by the EDQM and was reflected in the specification. However, for old CEPs, only the tests required in addition to the corresponding monograph were reported on the CEP and test procedures appended and not the full specification of the substance. Details are given below for various aspects.

- Subtitle

The same principles and approach as described for the CEP 2.0 applied.

In addition to the statements for a Chemical CEP (as applicable), an old CEP for a sterile substance included the following statements related to sterility:

- the subtitle “Sterile”;
- the quality of water in cases where water was used in the sterilisation steps;
- a sentence specifying that the substance was sterile, describing the sterilisation method used and that the sterilisation process had been assessed and accepted;

- a sentence on the compliance of the substance with the relevant test for sterility of the Ph. Eur.;
- the control of bacterial endotoxins if applicable.

- Impurities

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

a) If additional related substances were present in the substance in levels above the identification threshold set by the Ph. Eur. general monograph *Substances for pharmaceutical use* (*2034*) and were detected by the test for related substances described in the monograph, they were stated on the CEP with specified limits. In this case, no test procedure was appended to the CEP.

b) If additional related substances were present in the substance above the reporting threshold set by the Ph. Eur. general monograph *Substances for pharmaceutical use* (*2034*), and the monograph method was not suitable to control these impurities, they had to be controlled by a validated in-house test procedure. The limits for these impurities were mentioned on the CEP and the in-house test procedure was appended to the CEP (it was considered an additional test procedure).

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

Limit for unspecified impurities

When the individual monograph for the substance did not include a limit for unspecified impurities, such a limit had to be introduced in the specification for the substance and was included on the CEP.

Mutagenic and nitrosamine impurities

Where necessary, they were stated on the CEP together with the accepted limit and the corresponding test method and the test procedure was appended to the CEP.

Non-quantitative methods

If the Ph. Eur. individual monograph described a non-quantitative method for related substances (e.g. TLC with a general limit), the test for related substances was replaced by a quantitative method that was appended to the CEP where it was indicated as replacing the Ph. Eur. method.

Alternative test procedures

The same principles and approach as described for the CEP 2.0 applied. Alternative test procedures to those described in the Ph. Eur. monographs were not appended to the CEP.

- Residual solvents

The solvents that were stated on an old CEP were 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 were used in earlier manufacturing steps that were not removed consistently by a validated process and whose levels in the substance were above 10% of the concentration (option 1) limit established by ICH Q3C or VICH GL18. The limits stated on the CEP were the manufacturer's proposed limits as accepted by the EDQM.

Some CEP holders could decide to test all solvents used in the synthesis, including those demonstrated to be absent. In these cases, the CEP cited fewer solvents than were included in the CEP holder's specification for the substance.

For class 2 solvents, when option 2 was applied by the CEP holder, this was made transparent on the CEP.

For class 3 solvents, in exceptional cases, if higher limits than those allowed by ICH Q3C or VICH GL18 option 1 limit (5000 ppm or 0.5%) were accepted, this was made clear on the CEP.

Where only class 3 solvents were likely to be present in an active substance, a loss on drying test could be used. If a loss on drying test was already included in the Ph. Eur. individual monograph with a limit of not more than 0.5%, this was reflected on the CEP with the names of the solvents used, and no test procedure was appended.

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

Even if not described in the Ph. Eur. individual monograph, a test for loss on drying could 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 was stipulated on the CEP and no test procedure was appended.

- Use of water

When water was used in the last steps of the manufacturing process, this was stated on the CEP. The quality of water was not stated on an old CEP except when a particular grade/quality of a substance was claimed (e.g. sterile).

- Residual metal catalysts and reagents/elemental impurities

The same principles and approach as described for the CEP 2.0 applied, depending on whether a Risk Management Summary was provided or not by the CEP holder.

However, CEPs issued before 1 September 2016 (or before 1 June 2021 for substances for veterinary use only) might not include information on the intentional use of elemental impurities in the process. This should be taken into consideration by the CEP users who must request this information from the CEP holder.

Where necessary, the limit(s) proposed by the CEP holder and accepted by the EDQM were stated on the CEP and the test procedure(s) were appended to it.

- Omitted tests

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

- Microbial quality

This aspect was generally not covered in the CEP procedure since the final use of the substance was not known and this should be assessed in the MAA. However, if necessary, this quality attribute could be stated on the CEP.

- Container closure system

The full packaging material (immediate and outer) was described on the CEP even when no re-test period was requested by the CEP holder.
However, CEPs issued before 1 September 2011 might not include this information. This should be noted by the CEP users who must request the missing information from the CEP holder.

- Re-test period

A re-test period was mentioned on the CEP if requested by the CEP holder and agreed by the EDQM.
If a re-test period was mentioned:

- the absence of any specific temperature condition meant that the substance was stable under zone I/II climatic conditions (combination of long-term and accelerated conditions);
- temperature restrictions reported on the CEP meant that they were needed to ensure the stability of the substance in the described container closure system.

- Use of materials of human or animal origin

The same principles and approach as described for the CEP 2.0 applied, although the statement mentioned on the CEP differed slightly.

- Production section

The same principles and approach as described for the CEP 2.0 applied, i.e. compliance with the requirements of the Production section of the substance monograph was evaluated during assessment. As this is part of the monograph, no specific statement was added to the CEP regarding this aspect and, in few cases only, a statement on the CEP made it clear that compliance with the Production section has to be addressed in the MAA.

5.2.2. Statements on an old Herbal CEP

- Subtitle for extracts

The DER was included on CEPs for extracts granted after May 2012. This corresponded to the DER calculated on the genuine extract (extract without excipients).

- Residual solvents

The same principles and approach as described for the old Chemical CEP applied.

- Extraction solvent(s)

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

- Excipient(s)

The excipient(s) included in the extract and their percentage content were stated on the CEP.
If the extract did not include any excipients, this was also made clear on the CEP.

- Container closure system

The same principles and approach as described for the old Chemical CEP applied.

- Re-test period

The same principles and approach as described for the old Chemical CEP applied.

- Use of material of human or animal origin

The same principles and approach as described for the CEP 2.0 applied, although the statement mentioned on the CEP differed.

5.2.3. Statements on an old TSE CEP

For below points, the same principles and approach as described for the CEP 2.0 applied:
- Subtitle
- Country(ies) of origin of source materials
- Nature of animal tissues used in manufacture
- Manufacturing process applied.

5.3. Content of a Hybrid CEP

The principles and approach taken for the statements to be reported on a hybrid CEP are in line with those of the old CEP although some of the sentences are editorially reworded as for the CEP 2.0.

5.3.1. Statements on a Chemical CEP

The same principles and approach as described for the old Chemical CEP apply.

5.3.2. Statements on a Herbal CEP

The same principles and approach as described for the old Herbal CEP apply.

5.3.3. Statements on a TSE CEP

The same principles and approach as described for the old TSE CEP apply.

List of abbreviations

API-mix	Mixture of an Active Pharmaceutical Ingredient with one or more excipients
CEP	Certificate of suitability to the Monographs of the European Pharmacopoeia
DER	Drug Extract Ratio
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
EU	European Union
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDD	Maximum Daily Dose
Ph. Eur.	European Pharmacopoeia
QWP	Quality Working Party
TSE	Transmissible Spongiform Encephalopathy