

Certification of Substances Department

NF-AMEL-HB/CB

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Certification of suitability to the Monographs of the European Pharmacopoeia

**New requirements for the content of the CEP dossier for chemical purity and for herbal
drugs/herbal drug preparations according to the CEP 2.0**

Revision history of the document

| Revision N° | Date | Reason |
|-----------------|--------------|---|
| Initial version | April 2023 | n/a |
| R1 | October 2023 | Updated requirements and clarifications related to sections 3.2.S.4.1 and 3.2.S.4.2. Updated Annex 1. |
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1. Scope and impact

As part of the implementation of the CEP 2.0, some changes are introduced, which affect the requirements for the content of CEP applications for chemical purity and for Herbal Drugs/Herbal Drug preparations.

In this document, revised requirements as well as recommendations for the corresponding sections are described. For each relevant section of the CEP dossier, useful information on the content expected in that section of the dossier is given. However, this document should be used in addition to other [Certification Policy Documents & Guidelines](#) available on the EDQM website for the topics not covered in it since not impacted nor changed with the implementation of the CEP 2.0.

The revised requirements apply to newly submitted applications for a new dossier, a sister file and a renewal.

At the end of the assessment process, the submitted dossier, the assessment performed and the approved dossier should be fully aligned and relevant information reflected on the CEP document accordingly. This implies that the different sections within a CEP dossier should be harmonised with each other and the CEP dossier should contain only information corresponding to the quality claimed (data on particle size, microbiological controls, etc. should not be included in the dossier if no corresponding specific grade is requested).

As a result, any information not approved will have to be deleted from the dossier. EDQM may raise additional questions for the applications concerned by the implementation of the CEP 2.0 regarding the compliance of sections 3.2.S.4.1 and 3.2.S.4.2 with the requirements presented below for new, sister files and renewal applications on-going at the time of implementation of the CEP 2.0.

2. Requirements for the content of the CEP dossier

Manufacturer(s) (3.2.S.2.1) / Producer(s) (3.2.S.2.1) / Application form (box 2 “Companies details”):

All sites involved in the manufacture of the substance covered by the CEP application after the introduction of the starting material(s), including quality control and in process testing sites, should be listed in the application form and in section 3.2.S.2.1 with their name, address and role but also with the SPOR/OMS Organisation (ORG) and Location (LOC) ID (more information on the EMA website). These validated organisation data become mandatory for the submission of CEP applications.

Only if a grade is claimed, sites in charge of the applicable physico-chemical treatments such as milling, micronisation and sterilisation should be listed. If no grade is requested, the information for the related sites should not be included in the application form nor in the CEP dossier.

General properties (3.2.S.1.3) / Application form (box 1.5):

A CEP can cover specific physico-chemical characteristics for a substance (e.g. specific polymorphic forms or particle size distributions) or its sterility. These are indicated as “grades” and only if approved they are mentioned on the CEP as a subtitle. A subtitle is meant to specify a grade

of the substance but can also be used differentiate CEP applications for the same substance from the same holder.

If a CEP holder/applicant wishes to claim a grade, the corresponding subtitle to the CEP should be proposed in the application form (box 1.3) and also in section 3.2.S.1.3 of the CEP dossier. Requesting a grade is optional but when it is claimed, each section of the CEP dossier should be consistent with the grade requested (e.g. manufacturing sites, process description, specification, analytical procedures, stability data etc). If no grade is claimed, related information should not be included in the dossier. If such data would be included in a CEP application when no grade is claimed, the EDQM would request the data to be removed.

For active substances, CEP holders/applicants are requested to include in section 3.2.S.1.3 of the CEP dossier the Maximum Daily Dose (MDD), route of administration and treatment duration used for the development of their control strategy and specification presented. This information should be based on Human medicine European public assessment report (EPAR), summary of product characteristics (SmPCs), or agreed literature such as Martindale.

Description of manufacturing process and Process Controls (3.2.S.2.2):

The process description should contain only information corresponding to the quality/grade claimed. Details on steps such as micronisation or sterilisation, etc should not be included as part of the description of the manufacturing process in the dossier if the corresponding grade is not requested.

Control of materials (3.2.S.2.3):

The quality of the water used within the manufacturing process shall be in line with the EMA "Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018)" which specifies the acceptable grades of water used during manufacture of active substances. The quality of water used should be defined referring to the Ph. Eur. (e.g. purified water, water for injections, water for preparation of extracts etc). The quality of the water used in the last manufacturing steps (as a solvent or during isolation and/or purification) will be reported on the CEP when granted.

Specification (3.2.S.4.1):

The specification applied by the CEP holder/applicant (section 3.2.S.4.1) and the additional methods to the Ph. Eur. which are needed to control the quality of the substance will be appended to the CEP. This has an impact on the way the specification should be presented, as described below.

The specification required to control the substance should be presented in tabular format. Parameters, acceptance criteria and reference of the method should be clearly reported in the table (e.g. Ph. Eur., in-house). In case of in-house impurities controlled in the substance, an unequivocal chemical name of the compound should be used (in-house code may be added if relevant). The given text should be legible (e.g. free of highlighting, tracked changes, coloured text, and watermarks) and the use of scanned documents is to be avoided.

The specification for the substance should focus on compliance with the Ph. Eur. monograph as well as European regional requirements. Therefore, it should not include parameters, which are only implemented to demonstrate compliance with pharmacopoeias other than the Ph. Eur. (e.g. USP). The inclusion of such tests is considered by EDQM to unnecessarily pose the risk of;

- a) Delaying the granting of the CEP or the acceptance of revisions.
- b) Opening the CEP to the possibility of more frequent revision.

However, if a CEP holder decides to include a parameter in their specification, that is present only to satisfy a regulatory requirement in another region (i.e. non-European regional requirement), they are strongly encouraged to separate them from the other parameters and to clearly identify them as such in their specification (e.g. as “applied but not necessary to satisfy European regional requirements”, see Annex 1 for an example).

In addition, the specification of the substance should contain only information corresponding to the quality claimed (specification for particle size, microbiological controls, etc. should not be included in the dossier if no corresponding specific grade is requested).

EDQM does not take position on skip testing unless if specifically foreseen in guidelines e.g. ICH Q3D for elemental impurities, ICH M7 for mutagenic impurities and EMA/425645/2020 for nitrosamine impurities. Therefore, any other reference to skip testing should not be reported in section 3.2.S.4.1.

Reference to a specific supplement number of a Ph. Eur. monograph should be avoided. For any in house test, where the associated method is suitably described by an appropriate Ph. Eur. General Chapter “Methods of analysis”, the chapter can be referenced.

An example of specification is reported as Annex 1 of this document.

Analytical procedures (3.2.S.4.2):

Only the additional methods to the Ph. Eur. methods, which are needed to control the quality of the substance according to European requirements, will be appended to the CEP. Those in-house methods which are alternative and demonstrated equivalent to the Ph. Eur. ones, as well as methods related to tests only present to satisfy a regulatory requirement in another region, will not be appended to the CEP.

Analytical procedures should be described in such a way that they can be repeated by a competent analyst to obtain results within the proposed acceptance criteria. The level of details given in the Ph. Eur. monographs can be used as an example.

To facilitate the preparation of CEPs, CEP holders/applicants are therefore expected to divide the analytical test procedures for their substance into two distinct subsections and to provide “clean” documents.

Subsection 1 - Alternative in house analytical test procedures to those of the Ph. Eur. monograph

This section should include any in house analytical test procedures, which following validation and cross validation with the method of the Ph. Eur. monograph, have been determined to be equivalent. All analytical test procedures provided in subsection 1 should be fully described.

Subsection 2 – Additional in house analytical test procedure(s)

This section should include any additional in house analytical test procedures that are required to control the quality of the substance. Those additional methods are methods, which are either not detailed in the Ph. Eur. monograph for the substance or which are applied when the Ph. Eur. monograph methods are not suitable to control impurities or which are used to control additional parameters (e.g. particle size distribution).

These analytical test procedures should be fully described in this section, and should be appropriately validated.

The method description should be legible and the use of scanned documents is to be avoided. CEP holders/applicants are encouraged to avoid the addition of headers, footers and supportive chromatograms in section 3.2.S.4.2 of their submissions as they would be removed by EDQM during the preparation of the CEP.

An example on how to present additional in house analytical test procedures is reported as Annex 2 of this document.

Analytical methods of the Ph. Eur. monograph

Details of the methods of the Ph. Eur. monograph should not be reproduced in section 3.2.S.4.2. This applies also in case chromatographic adjustments are made to the Ph. Eur. method within the scope of Ph. Eur. chapter 2.2.46.

How to implement this in the e-submissions

In order to address the aforementioned requirements CEP holders/applicants are requested to separate module 3, section 3.2.S.4.2 into two distinct sections as follows.

```
m3
  32-body data
    32s-drug-sub
      32s42-analy-proc
        analytical-procedures-equiv_ih-subsection 1
        analytical-procedures-add_ih-subsection 2
```

Stability (3.2.S.7) / Application form (box 1.5):

CEP holders/applicants are highly encouraged to claim a re-test period and to include stability data even if limited (e.g. 3 or 6 months) in their CEP applications, in order to benefit from the centralised assessment of these data at EDQM. To facilitate this, the EDQM will bring flexibility with regard to stability information in a new CEP application. Despite the fact that changes to on-going applications are usually not accepted, the submission of additional stability data during the course of assessment will be possible, i.e. data obtained for subsequent time points may be provided with replies to a request for additional information to support a (longer) re-test period.

CEP holders/applicants should clearly express their intention to have a re-test period evaluated both in the application form (box 1.5) and in section 3.2.S.7.1. The proposed re-test period, the container closure system and any applicable storage conditions should be clearly stated. However, if a re-test period is not claimed, no stability data or stability protocol should be included in the dossier. If data are presented in a new CEP dossier, this will be understood as a request to have a re-test period.

Stability testing should be performed in accordance with applicable (V)ICH guidelines and the EU guideline on *Stability testing of existing active substances and related finished products* (CPMP/QWP/122/02 and EMEA/CVMP/846/99) and the re-test period should be determined based on the available data.

In addition, as an option, CEP holders/applicants are given the possibility to refer to other climatic zones, known as zones III and IVA and IVB, in addition to zones I and II. It is up to CEP holders/applicants to decide and state the climatic zone they refer to. The *WHO Technical Report Series, No. 1010, 2018* should be used for the definition of storage conditions.

Restrictive storage conditions with respect to temperature may be accepted and reflected on the CEP together with the re-test period, provided they correspond to the conditions in which stability data have been obtained.

Different re-test periods and storage conditions can be proposed within one CEP application (e.g. different re-test period depending on the container closure system or climatic zone).

If a specific grade is claimed, the substance with that quality and grade should be included in the stability testing programme and the stability of the corresponding parameter should also be demonstrated over the proposed re-test period as needed.

Annex 1 - Example of presentation of specification in section 3.2.S.4.1

| Parameters | Acceptance criteria | Reference |
|---|--|--------------------------|
| Characters | White or almost white, crystalline powder | Ph. Eur. current edition |
| Solubility | Practically insoluble in water, slightly soluble in anhydrous ethanol and in methylene chloride. | Ph. Eur. current edition |
| Identification Test A (IR) Test B (HPLC) | Complies to reference Positive | Ph. Eur. current edition |
| Specific optical rotation (o.d.b.) | +158° to + 167° | Ph. Eur. current edition |
| Loss on drying | ≤ 0.5% | Ph. Eur. current edition |
| Related substances | | Ph. Eur. current edition |
| Impurity A | ≤ 0.5% | |
| Impurity B | ≤ 0.3% | |
| Impurity C | ≤ 0.15% | |
| Impurity D | ≤ 0.15% | |
| Unspecified impurities | ≤ 0.10% | |
| Total | ≤ 1.5% | |
| Assay (o.d.b.) | 97.0% to 102.0% | Ph. Eur. current edition |
| Residual solvents (by GC) | | In-house |
| Ethanol | ≤ 5000 ppm | |
| <i>N,N</i> -dimethylformamide | ≤ 880 ppm | |
| <i>N</i> -Nitrosodimethylamine (NDMA) (by GC-MS) | ≤ 3.0 ppm | In-house |

| Specification parameters not necessary to satisfy European regional requirements | | |
|---|-----------------|----------------|
| Assay by titrimetry (o.d.b.) | 99.0% to 101.0% | USP |
| Heavy metals | ≤ 10 ppm | Ph. Eur. 2.4.8 |
| Water content (KF) | ≤ 0.5% | JP |

Annex 2 - Example of presentation of **additional methods** in section 3.2.S.4.2

Residual Solvents by Gas chromatography

Blank solution.

Test solution. Dissolve (*weight*) g of the substance to be examined into (*solvent*) and dilute to (*volume*) mL with the same solvent.

Reference stock solution. Dissolve (*weight*) g of (*reference*) into (*solvent*) and dilute to (*volume*) mL with the same solvent.

Reference solution. Dilute (*volume*) mL of reference stock solution to (*volume*) mL with (*solvent*). Pipette (*volume*) mL of this solution into a headspace injection vial to obtain a solution containing about (*concentration*) of reference standard.

Chromatographic conditions:

Column material:

–size:

–stationary phase:

Carrier gas:

Flow rate: Split ratio:

Injection mode:

Temperature:

Injection method:

Headspace equilibrium temperature:

Headspace equilibration time: Loop temperature:

System suitability requirements:

Test method:

Injections order.

Calculation:

N-Nitrosodimethylamine (NDMA) by GC-MS

Chromatographic conditions:

Column material:

–size:

–stationary phase:

Carrier gas:

Flow rate: Split ratio:

Injection mode:

Temperature:

Injection method:

Mass spectrometer conditions:

Electron impact ionisation mode:

Ion source temperature:

Analyser temperature:

Dwell time:

Gain factor:

Detection mode:

Solutions preparation:

Internal standard solution. Dissolve (*weight*) g of standard into (*solvent*) and dilute to (*volume*) mL with the same solvent.

Spiking solution. In a single volumetric flask, dilute (*volume*) µL of each of CRS to (*volume*) mL with (*solvent*). Dilute (*volume*) µL of this solution to (*volume*) mL with (*solvent*).

Test solution. Dissolve (*weight*) g of the substance to be examined into (*solvent*) and dilute to (*volume*) mL with the same solvent.

Spiked solution. Dissolve (*weight*) g of the substance to be examined into (*solvent*), add (*volume*) mL of spiking solution and dilute to (*volume*) mL with the same solvent.

Reference solution. Dilute (*volume*) mL of spiking solution to (*volume*) mL with (*solvent*). Pipette (*volume*) mL of this solution into an injection vial to obtain a solution containing about (*concentration*) of reference standard.

System suitability requirements:

Test method:

Injections order.

Calculation: