Every step counts. Make it matter.
#OneQualityVoice

Universitá di Pavia
November 17, 2023

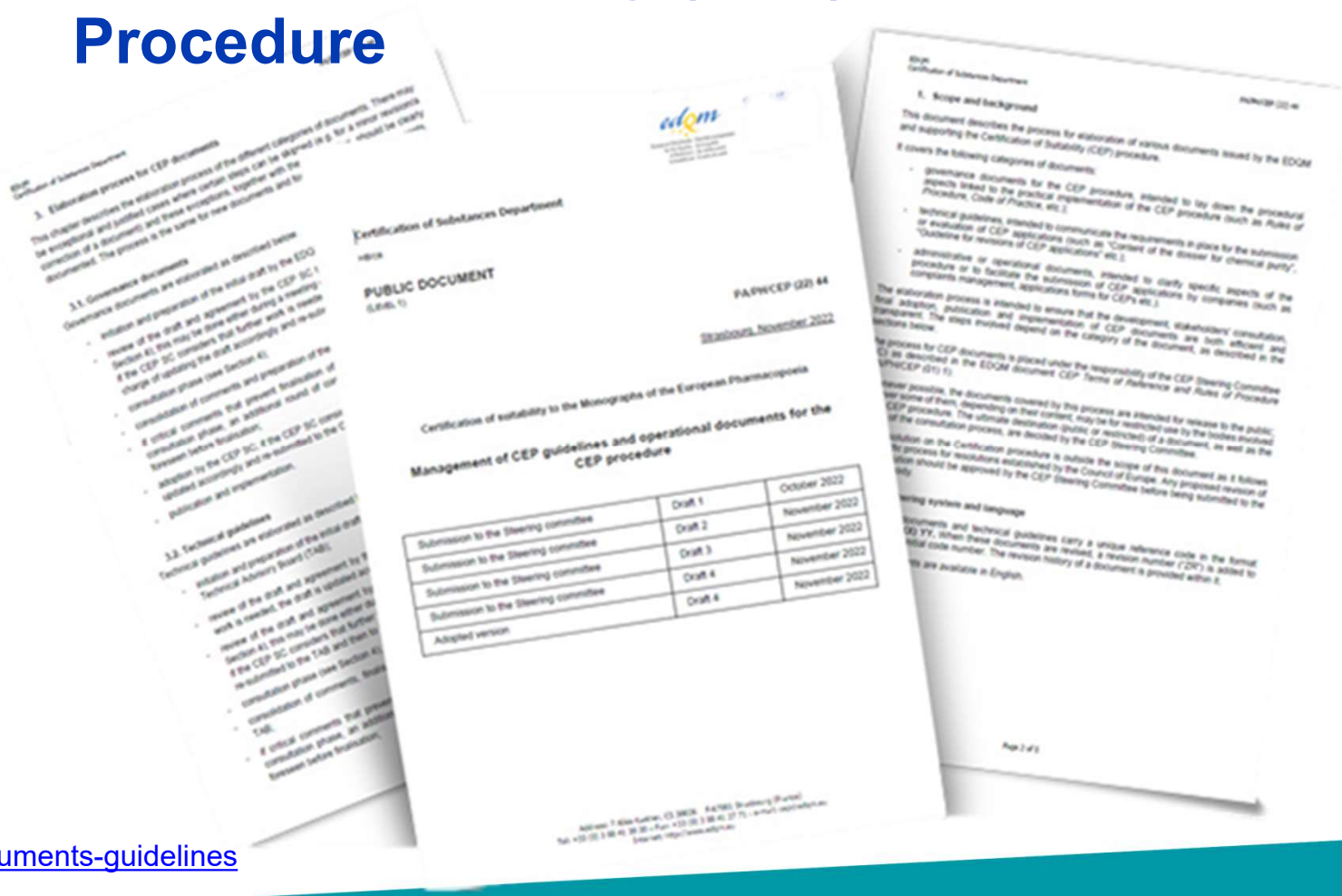
40 mins

Antonella Volpe
Global API Quality and Regulatory Director

INSUD PHARMA

The EDQM Certificate of Suitability (CEP) Procedure

- Background & legal framework
- How to read a CEP
- CEP accepted countries
- The CEP Procedure
  - How to apply to a CEP
  - Content of the Dossier
  - CEP structure vs ASMF procedures
  - Sister Files
  - Notifications/Revisions/Renewals
- Technical Advice Meeting & one-to-one
- Inspection program
- CEP 2.0



https://www.edqm.eu/en/certification-policy-documents-guidelines

Background & legal framework

INSUD PHARMA

The procedure for "Certification of Suitability to the monographs of the European Pharmacopoeia" was established in **1994** and was in **the beginning restricted to controlling the chemical purity of pharmaceutical substances**.

In **1999**, the **procedure was extended to include products with a risk of transmissible spongiform encephalopathy (TSE)**, thus enabling their certification on the basis of the European Pharmacopoeia general chapter 5.2.8 'Minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products' and of the new monograph on "Products with risk of transmitting agents of animal spongiform encephalopathies (1483)".

- Resolution AP-CSP (07) 1 on the "Certification of Suitability to the Monographs of the European Pharmacopoeia (Revised Version)" (Adopted by the Public Health Committee (CD-P-SP) on 21/02/2007)
- Directives 2001/82/EC and 2001/83/EC, as amended, of the European Council and of the Parliament.

OPPORTUNITY

CEPs are recognized by the signatory parties of the Convention on the Elaboration of a European Pharmacopoeia, i.e. all member states and the European Union. They are **also recognized by other countries, e.g. Canada, Australia, New Zealand, Tunisia and Morocco**. EDQM has established a list of authorities and organisations with which the EDQM has a Memorandum of Understanding and/or Confidentiality Agreement in place allowing them access to assessment and/or inspection reports. These reports are also shared with the National Competent Authorities of the Ph. Eur. member states and with the EMA (including EMA committees and working parties/groups and the members and experts thereof).

CEP accepted countries

OPPORTUNITY

INSUD PHARMA

Certificates of suitability (CEPs) are ***accepted in all EU member states*** and in signatories to the Convention on the elaboration of a European Pharmacopoeia (including the United Kingdom but not including Ukraine). Some non-EU states may have additional requirements. A current list of the Ph. Eur. members is available on the EDQM website.

CEPs may be accepted in other countries (outside the EU or Ph. Eur. members) at the discretion of the authorities in those countries. In such cases, the competent authorities will decide on the scope of the acceptance of CEPs and the conditions they may apply to them. For example, in addition to the CEP, there may be a requirement to provide a Drug Master File (open part or full content) or other supporting documents. It is therefore important to check the acceptability and conditions associated with the use of a CEP in these countries in advance. We recommend that you contact the competent authority in the relevant country for details of their requirements, as these could change without prior notice.

Based on information received from regulatory authorities and trade associations, the following countries accept CEPs, some with conditions:

Albania, Algeria, Australia, Azerbaijan, Canada, Georgia, Ghana Israel, Kyrgyzstan, Malaysia, Moldova, Morocco, New Zealand, Saudi Arabia, Singapore, South Africa, Tunisia, and Uzbekistan.

CEPs are also accepted (with conditions) by the Taiwan Food and Drug Administration.

Please note that this is not an exhaustive list.

EU Directives 2001/83/EC (human) states that for active substances

They should comply with the Ph.Eur monograph ***if there is one***

Directive2001/83/EC amended by 2003/63/EC
In cases where a specification contained in a European Pharmacopeia monograph might be insufficient to ensure the quality o the substance (new impurities), the competent authorities may request more appropriate specifications from the marketing authorization holder

- A CEP does not replace a certificate of analysis
- A CEP does not replace the QP declaration
- A CEP is not a GMP certificate

Resolution AP-CSP(07)1 adopted by the Public Health Committee of the Council of Europe

- describes the process for the procedure
- available on the EDQM website www.edqm.eu

A STANDARD WAY to read

OPPORTUNITY

CEP unique reference

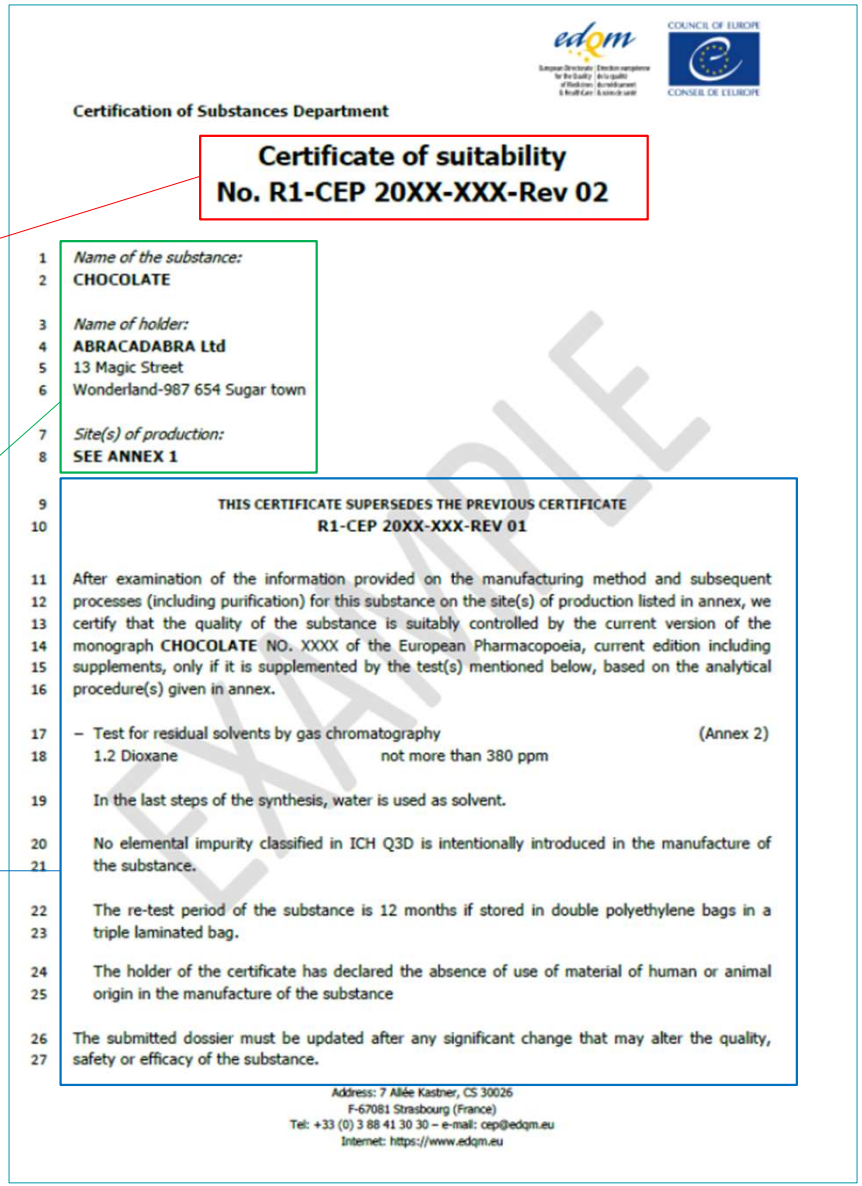
The alphanumerical reference of a CEP consists of the following three blocks:
1) EP procedure number + application year + chronological number.
2) Quinquennial indicator (Variable part)
3) Revision indicator (Variable part)

Name and site(s)

The sites declared in the CEP application are stated on the CEP.
The following sites are stated on a chemical CEP:
- CEP holder
- Substance manufacturing site(s)
- Intermediates manufacturing site(s)

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.



Certification of Substances Department

Certificate of suitability
No. R1-CEP 20XX-XXX-Rev 02

Name of the substance:
CHOCOLATE

Name of holder:
ABRACADABRA Ltd
13 Magic Street
Wonderland-987 654 Sugar town

Site(s) of production:
SEE ANNEX 1

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 20XX-XXX-REV 01

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production listed in annex, we certify that the quality of the substance is suitably controlled by the current version of the monograph **CHOCOLATE** NO. XXXX of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

– Test for residual solvents by gas chromatography (Annex 2)
1.2 Dioxane not more than 380 ppm

In the last steps of the synthesis, water is used as solvent.

No elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance.

The re-test period of the substance is 12 months if stored in double polyethylene bags in a triple laminated bag.

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacture of the substance

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

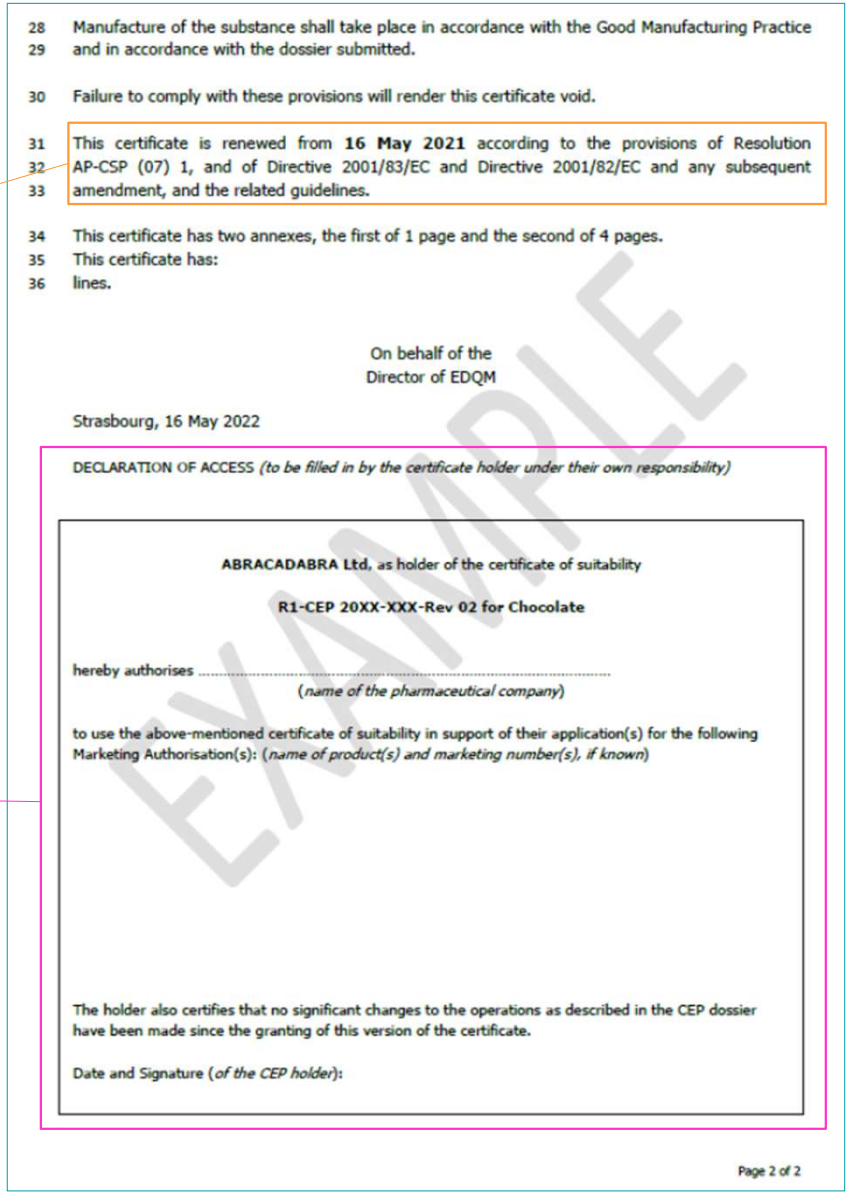
Address: 7 Allée Kastner, CS 30026
F-67081 Strasbourg (France)
Tel: +33 (0) 3 88 41 30 30 – e-mail: cep@edqm.eu
Internet: https://www.edqm.eu

Renewal of a CEP

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.

Declaration of Access

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.



Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

This certificate is renewed from **16 May 2021** according to the provisions of Resolution AP-CSP (07) 1, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has two annexes, the first of 1 page and the second of 4 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 16 May 2022

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

ABRACADABRA Ltd, as holder of the certificate of suitability

R1-CEP 20XX-XXX-Rev 02 for Chocolate

hereby authorises .....
(*name of the pharmaceutical company*)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): (*name of product(s) and marketing number(s), if known*)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (*of the CEP holder*):

EXAMPLE

Page 2 of 2

European Directorate for the Quality of Medicines & HealthCare
Certification of Substances Department

Application Form
REQUEST FOR
NEW CERTIFICATE OF SUITABILITY

(to be completed for each request for a new Certificate of Suitability to the monographs of the European Pharmacopoeia, in accordance with Resolution AP-CSP (07) 1)

Date of submission: ...../...../.....

Please note that the format of the submission should be eCTD.
NB: exceptions are for substances for veterinary use only (VNeeS or eCTD accepted) or for TSE risk assessment (PDF required).

1. General Information:

1.1. Type of application for a new Certificate of Suitability:

☐ *Chemical* ☐ *Chemical and sterile* ☐ *TSE*
☐ *Double (Chemical and TSE)* ☐ *Double and sterile* ☐ *Herbal*

1.2 Name of the substance using the Recommended International Nonproprietary Name (rINN):

1.3 *If needed* **(subtitle)**: specify any subtitle requested such as 'micronised', 'process B', ...:
NB: acceptability of the proposed subtitle will be confirmed during assessment

1.4 Monograph(s) you are referring to:
(*Name, Number, Year of publication*)

1.5 Re-test period requested:	*(not applicable for TSE Certificate of Suitability)*
Proposed re-test period (in months)	
If applicable: required storage conditions (e.g. T°, nitrogen atmosphere, others, ...)	
Tick this box if you do **not** wish a re-test period ☐	

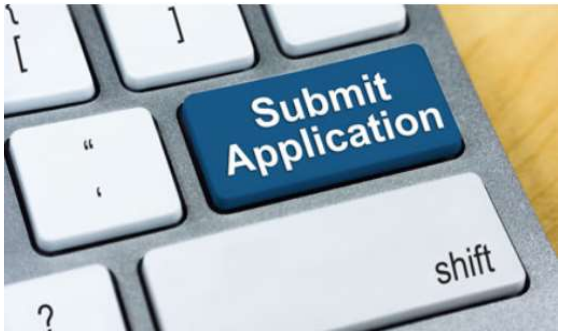
INSUDPHARMA

how to apply for a CEP

a very clear path to proceed with

OPPORTUNITY

- To obtain a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP), applicants should send in electronic format the following documentation to the Certification of Substances Department (DCEP) of the EDQM
  - a completed application form;
  - a dossier in CTD format written in English* (Modules 1, 2 (QOS) & 3)



- Upon receipt, the application is validated and listed for assessment.
- After assessment, the EDQM may send queries to the applicant.
- When they are resolved, the EDQM sends a CEP to the applicant.
- The evaluation of new applications is handled with three rounds of assessment.
- A document describes this policy and provides clarification on the potential outcomes of assessment. Applications lacking sufficient information after evaluation of the applicant's response to a maximum of 2 EDQM deficiency letters are definitively closed.

Content of the dossier

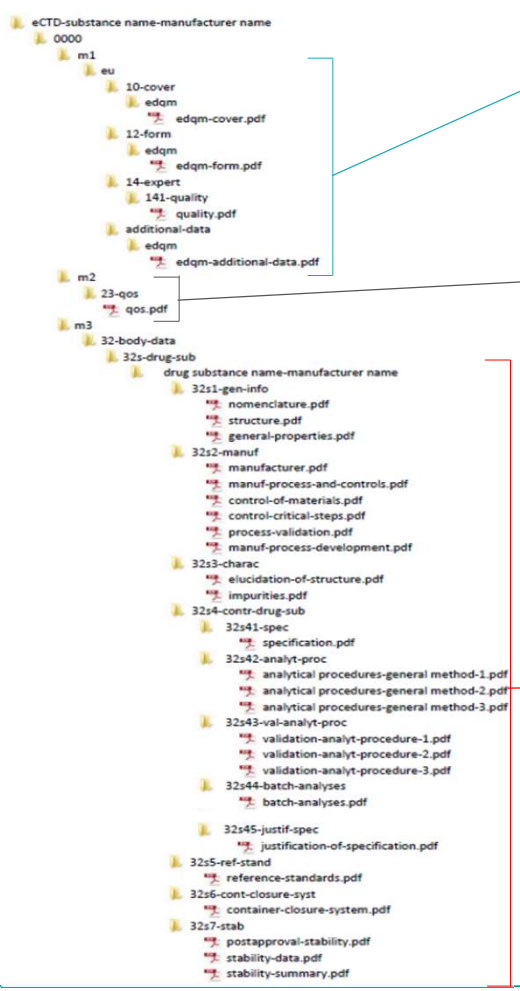
Detailed information on what an application should contain is described in the documents below.

- Content of the dossier for chemical purity and microbiological quality, PA/PH/CEP (04) 1, 6R
- Content of the Dossier for a Substance for TSE Risk Assessment (PA/PH/CEP (06) 2 1R)
- Content of the Dossier for Herbal Drugs and Herbal Drug Preparation Quality Evaluation PA/PH/CEP (02) 6 1R

For applications related to sterile API, you should also read the:

- Clarification on the Acceptability of CEP Applications for Sterile Grade Material (PA/PH/CEP (08) 60, 1R, July 2016)
- Certificates of Suitability for Sterile Active Substances (PA/PH/Exp. CEP/T (06) 13, 1R)

How is structured a CEP dossier? the eCTD



Module 1

Administrative Information:

- Cover Letter
- EDQM application form
- Curriculum of the expert

Module 2

Quality Overall Summary

Module 3

- General info
- Manufacturing process
- Characterization
- Control of drug substance
- Reference standard
- Container closure system
- Stability data

CEP and ASMF procedures

The applicant can choose the **way to provide data on the quality of an active substance:**

- CEP
- Active substance Master File (ASMF)

The data to be submitted are the same, regardless of the route selected
CEPs are not mandatory, but generally avoid any subsequent reassessment

OPPORTUNITY

European Medicines Agency

CHMP/QWP/297/97 Rev 1 corr
EMEA/CVMP/1069/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)
COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
(CVMP)

GUIDELINE ON
SUMMARY OF REQUIREMENTS FOR ACTIVE SUBSTANCES IN
THE QUALITY PART OF THE DOSSIER

2. FEASIBLE WAYS TO SUBMIT THE REQUIRED INFORMATION

Depending on the kind and classification of the active substance, the required data may generally be submitted in one of the following three ways – see sections 2.1, 2.2 and 2.3.

2.1 Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP)

2.2 Active Substance Master File (ASMF) Procedure

2.1 Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP)

The active substance manufacturer should submit documentation to the European Pharmacopoeia Secretariat with a view to evaluating the suitability of the pharmacopoeial monograph in relation to the manufacturing method actually used, cf. Appendix I of the Council of Europe Resolution AP-CSP (99) 4 *Certification of Suitability to the Monographs of the European Pharmacopoeia.*

The Applicant should include a copy of the most current CEP in the dossier, together with a written assurance that no significant changes in the manufacturing method have taken place following the granting of the certificate or its last revision.

Along with the CEP, the Applicant should supply results of batch analysis demonstrating compliance with the Ph.Eur. monograph and including any additional tests/limits listed on the CEP (e.g. residual solvents, additional impurity tests).

In the case of sterile substances, the Applicant should make sure that a full of the sterilisation process as specified on the CEP as well as results of any tests applied (in particular the test of the monograph) and validation data are provided in the application file.

The CEP may not necessarily address all relevant parameters and in these cases the Applicant should supply additional data, e.g. stability data to support a retest period (only if retest date not mentioned on the CEP), physico-chemical characteristics such as particle size and polymorphism.

2.2 Active Substance Master File (ASMF) Procedure

Full details of chemistry, manufacturing process, quality controls during manufacture and process validation for the active substance may be submitted in a Active Substance Master File as outlined in the Guideline *Active Substance Master File Procedure EMEA/CVMP/134/02 or CPMP/QWP/227/02).* In such cases, The Applicant's Part needs to be included in the marketing authorisation (MA) application.

Proof of structure may not be necessary where this can be shown by specific identification tests in relation to reference substances sufficiently described in the dossier.

In the case of *pharmacopoeial active substances:*

- Stability data may not be necessary where adequate literature evidence can be cited and summarised and where the monograph covers the degradation products for which suitable limits have been set as indicated in the Note for Guidance *Stability testing on Existing Active Substances and Related Finished Products (EMEA/CVMP/846/99 or CPMP/QWP/122/02).*
  In this situation the Applicant should demonstrate that the substance complies with the monograph immediately before use.
- Special emphasis should be given to demonstrating that those potential impurities, most likely to arise during synthesis, from the actual manufacturing process can be controlled by the manufacturer, particularly where these differ from any included in the monograph. In case that not all potential impurities are mentioned in an impurity section of the monograph, the Applicant should demonstrate whether the tests of the monograph can control these additional impurities. If the manufacturer uses different methods to control specified impurities, equivalence to the pharmacopoeial method should be demonstrated. The toxicological implications of impurities not included by the monograph should be

Comparison between CEP & ASMF

INSUD PHARMA

	CEP procedure	ASMF system
Scope	pharmacopoeial substances only -> active substances or excipients -> any substance for TSE CEP	active substances only -> new or pharmacopoeial
Dossier  OPPORTUNITY	Content identical (CTD 3.2.S) Full dossier sent directly by the manufacturer to EDQM (will be the holder of the CEP)	Content identical (CTD 3.2.S) Full dossier sent by API manufacturer to Competent Authorities AP sent by API manufacturer to marketing authorisation applicant or holder of medicinal product
Additional data	Holders commitments	Letter of access (to be sent by API manufacturer)
Link with a medicinal product	Independent from marketing authorisation applications	In the context of a specific marketing authorisation application or variation for medicinal products


OPPORTUNITY

	CEP procedure	ASMF system
Evaluation  OPPORTUNITY	Single evaluation centralised at EDQM by assessors nominated by Competent Authorities / Certification Steering Committee	Assessment of ASMF by each competent authority in the context of assessing a specific marketing authorisation application or variation for medicinal products
	Principles identical: Assessment against ICH/EU guidelines for quality + Ph. Eur monograph + EDQM specific guidance	Principles identical: Assessment against ICH/EU guidelines for quality + Ph. Eur monograph if applicable

INSUDPHARMA

	CEP procedure	ASMF system
Deliverable	Certificate including annexes (additional tests to be performed) granted to manufacturer who supplies a copy to customers (users of the API)	A Marketing Authorisation for the medicinal product using this particular API
Variations  OPPORTUNITY	Changes to the CEP dossier centralised at EDQM Submission of revised CEPs according to EU Variations regulation	Submission of changes to marketing authorisation applications, according to EU Variations regulation
Use	Ph. Eur member states & others (Australia, Canada, New Zealand, Tunisia, Morocco, Singapore, South Africa, Saudi Arabia, etc)	EU/EEA member states + Australia + Canada

INSUDPHARMA

What is the difference between Asmf and CEP?

ASMF is never approved nor disapproved, but is reviewed everytime it is referenced in the MAA application unlike CEP is approved. ASMF constitutes of two parts, Applicants Part (AP) and Restricted Part (RP).

Sister files

OPPORTUNITY

INSUD PHARMA

The sister file procedure is intended to **facilitate the submission of similar dossiers** within the Certification Procedure, and to allow applicants to benefit from a **fast-track procedure** and harmonized assessments.

A company which has been granted a certificate of suitability (CEP) may wish to apply for another CEP for the same substance. This may be because it is not possible to apply for a revision of the initial CEP or when the company wishes to have separate CEPs for different conditions of preparation or qualities (for example, to cover an alternative manufacturing process, manufacturing site or an alternative grade).
This new application can be submitted as a "sister file", provided that the conditions listed in the guideline **PA/PH/CEP (09) 141,** are fulfilled.
Holders of a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) should send, in electronic format, the following documentation to the Certification of Substances Department (DCEP) of the EDQM:

- Filled specific application form, which includes invoicing details and a comparative table of the differences between the existing CEP and the new application for a sister file,
- A complete dossier in eCTD format,
- A risk assessment relating to the potential for nitrosamine impurities in the substance should be submitted for the sister file application.

These applications are managed as described in the guidance PA/PH/CEP (09) 141 and PA/PH/CEP (13) 110.

Notifications/revisions/renewals

Holders of a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) **must inform the EDQM of any change(s)** to the information provided in the initial application.

In addition, a **CEP must be renewed once**, 5 years after the issue date of the original CEP for it to remain valid (regardless of revisions in the interim period).

The themed topics below help companies to understand how to notify EDQM of changes, get them approved and how to renew their CEP.

A very clear changes classification

OPPORTUNITY

INSUD PHARMA

In accordance with the current European Regulation on variations to marketing applications, **changes are classified into three categories**:

- **notifications** (for changes not expected to impact quality),
- **minor changes** (for changes which may impact quality) and
- **major changes** (for changes which are likely to impact quality).

The EDQM **Guideline on Requirements for Revision/Renewal of Certificates of Suitability to the European Pharmacopoeia Monographs (PA/PH/CEP (04) 2)** ***describes in detail the classification of changes for CEPs and the conditions to be met as well as the documentation to be provided for each type of change.***

Where a change is not classified in the Guideline as a notification, minor or major change, it should be classified as a minor change by default and this information should be included on the application form. Specific guidance is also given in this guideline for editorial changes.

- When a new substantially different route of synthesis is introduced (even when the impurity profile of the final substance is equivalent): an application for a separate CEP should be made. This applies to both alternative and replacement routes of synthesis. The sister file procedure may be used if the conditions are met (**PA/PH/CEP (09) 141**).

- Different grades (e.g. particle sizes) may be included in the same CEP application when the impurity profile is shown equivalent, and the different grades may be mentioned on the CEP when granted, with controls for each grade. Separate CEPs for the grades are needed if the impurity profiles are not equivalent or if preferred by the applicant and the sister file procedure may be used if the conditions are met (**PA/PH/CEP (09) 141**).

- Revised discussions on impurities in section 3.2.S.3.2 should be submitted as minor revisions. One key reason to revise this section is for the assessment on risk of nitrosamine impurities and for this, there is specific information

OPPORTUNITY

INSUD PHARMA

CEP ***holders can consult EDQM*** on the classification of a change on their CEP dossier prior to submission.

This can be done via the EDQM Helpdesk for general queries or via email to the account mentioned in correspondence for questions about specific CEPs and the CEP dossier should be identified to ensure the most appropriate reply can be provided.

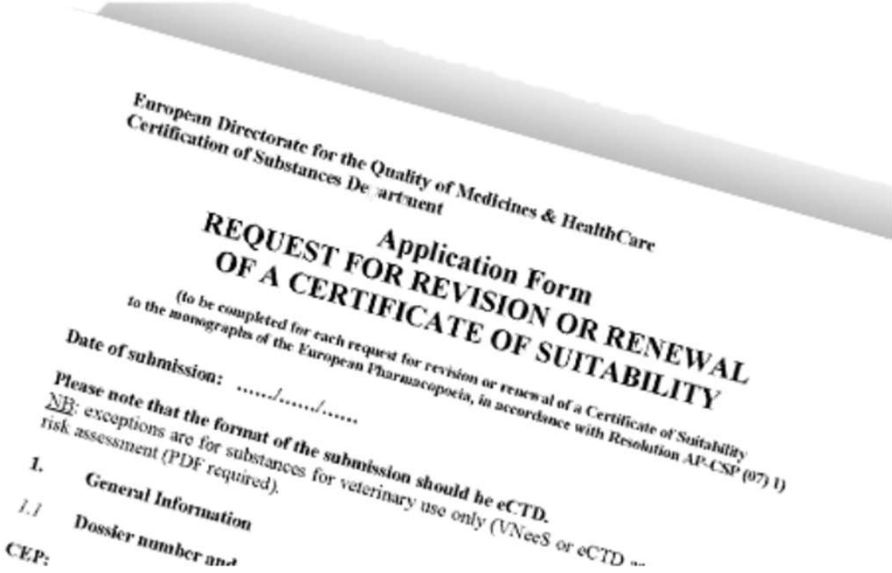
*Where requests have been **misclassified by CEP holders** (e.g.as a minor revision instead of a major revision, or as a notification instead of a minor revision), this will lead to the **rejection** of all submitted changes.*
*The CEP holder will need to **resubmit the changes correctly classified**, together with the settlement of the appropriate fees (i.e. there will be a need to pay twice).*

Holders of a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) should **send, in electronic format,** the following documentation to the Certification of Substances Department (DCEP) of the EDQM:

- Filled application form, which includes classification of the changes, invoicing details and a comparative table of the changes, highlighting approved and proposed text;
- Data supporting the changes;
- Update of the relevant section(s) of the dossier (if the dossier is already in eCTD format), or a baseline dossier in CTD format (including all sections, not only those impacted by the change) if the dossier is not yet in eCTD format.

The EDQM Guideline **PA/PH/CEP (13) 110** details the **policy applied to the management of notifications, revisions and renewals** and makes clear:

- If a notification is not accepted, there is no possibility to submit additional information regarding the notification and the holder will be advised of the rejection;
- Revision application lacking sufficient information after evaluation of the applicant's response to a maximum of two EDQM deficiency letter(s) will be rejected.


European Directorate for the Quality of Medicines & HealthCare
Certification of Substances Department

Application Form
REQUEST FOR REVISION OR RENEWAL
OF A CERTIFICATE OF SUITABILITY

(to be completed for each request for revision or renewal of a Certificate of Suitability to the monographs of the European Pharmacopoeia, in accordance with Resolution AP-CSP (07) 1)

Date of submission: ...../...../.....

Please note that the format of the submission should be eCTD.
NB: exceptions are for substances for veterinary use only (VNeeS or eCTD ...
risk assessment (PDF required).

1. General Information

1.1 Dossier number and

CEP:

OPPORTUNITY

INSUDPHARMA

Technical advice meetings are intended to provide advice to applicants on questions related to the requirements for the submission of a new application for Certificate(s) of Suitability to the monographs of the European Pharmacopoeia (CEPs), or for their subsequent revision or renewal. Questions can be of a technical nature, on matters concerning the content of an application or on the submission of a revision application with complex or multiple changes. Meetings last one hour and can take place on the EDQM's premises or by a teleconference. Technical advice meetings do not replace the submission and assessment processes for applications. They neither grant CEPs nor relieve applicants from their legal obligations.

Applicants should submit the Technical Advice Meeting Form. Remember to propose 2 or 3 dates for a meeting and to submit **all the relevant documentation supporting the request**. If the required documentation is not provided, the request cannot be accepted nor progressed.

Requests should be sent by e-mail to: cep@edqm.eu.

The fee for a technical advice meeting can be found in the document "Fees and inspection costs".

The meeting minutes shall be prepared by the applicant and submitted to the EDQM for approval within one month after the meeting. The advice provided during a technical advice meeting may not be considered valid if they are not implemented within 1 year after the date of the meeting, and the final acceptability will lie with the assessors who evaluate the application.

OPPORTUNITY

One-to-One Meetings: these face-to-face discussions allow participants the opportunity to meet with Certification of Substances Department staff, exchange points of views and help clarify unanswered questions. They usually take place during EDQM events such as conferences or exhibitions, rather than on the EDQM's premises or by teleconference. One-to-one meetings generally last 15 to 30 minutes.

The CEP 2.0 (new name of the CEP of the future) is **a "new-look"** CEP that will better meet the current needs of stakeholders and offer both enhanced user-friendliness and greater transparency of the information conveyed without, however, increasing the regulatory burden related to revisions of CEPs.

- Area 1: CEPs and information reported
- Area 2: Changes regarding assessment of CEP applications
- Area 3: On-line public certification database
- Area 4: Authorities database
- Area 5: Fostering information sharing between CEP holders & MAH
- Area 6: Reduction of revisions of CEPs
- Area 7: Impact of changes and their implementation
- Area 8: Trainings for CEP holders and CEP users
- Area 9: Revising documents available on the EDQM website

https://www.edqm.eu/en/what-is-the-cep-2.0

The CEP becomes an electronic document with a digital signature,
downloadable as a pdf or printed by CEP holders
to share with their customers, for inclusion in Marketing Authorization Applications (MAA).

The Authorities database is currently intended for the licensing authorities of the member states of the Ph. Eur. convention. It contains confidential information related to the lifecycle of CEP applications as well as copies of the current CEPs and CEP assessment reports. ***It is aimed to ease the decision-making process during the review of the marketing applications for medicinal products where a CEP is included.*** There will be new features in this database in addition to current ones. The EMA SPOR/OMS Org and Loc ID will be mentioned for CEP holders and manufacturing sites. The CEP number and CEP document corresponding to each procedure of a dossier (if any) will be available. It is also foreseen to grant access to regulatory authorities beyond Ph. Eur. which accept CEPs under suitable confidentiality agreements or Memorandum of Understanding (MoU). The EDQM website will describe the list of authorities which have access to the Authorities database. The CEP holder's declarations as part of the CEP application form will be updated to cover this aspect.

The CEPs will no longer be revised if their content is not changed. This means that the approval of changes (even major ones) not impacting the CEP content, will not result in the granting of a revised CEP.

Inspection programme

INSUDPHARMA

The EDQM inspection programme is an integral part of the Certification procedure and is elaborated in the context of the mandate given to the EDQM by the European Commission in the application of Directives 2001/83/EC and 2001/82/EC as amended. It aims to check compliance with both Good Manufacturing Practice (GMP)* and the Certificate of Suitability (CEP) application (and any updates) at the manufacturing/distribution sites covered by CEPs.

As part of the CEP application, the manufacturers involved in the manufacture of active substances (API) and their intermediates are requested to declare that they manufacture according to EU GMP Part II and their willingness to be inspected. Based on these declarations and a risk-based approach, the EDQM may or may not inspect the sites, and if they do, the inspection takes place either before or after the CEP is granted.

Every year, a programme of inspections is elaborated based on risk assessment and in accordance with EU recommendations.

The EDQM Certification Department is responsible for the establishment of the annual programme, the organization and performance of the inspections and their follow-up, including the implementation of any subsequent actions regarding the related CEPs and communication with the authorities concerned.

The EDQM inspections are normally carried out by teams composed of an official inspector from the EU/EEA competent authorities (or from countries having a Mutual Recognition Agreement (MRA) with the EU in the sector of GMP for APIs) and an inspector from EDQM. They typically last 3 days. About 40 inspections are performed every year, including re-inspections

An inspection pilot phase was launched in 1999 with the aim to verify the GMP compliance of manufacturing sites producing/trading substances covered by CEP (active substances or excipients)

- Initially it involved only manufacturers located in Europe then the program was enlarged to extra-EU countries
- Consolidated phase: the European Commission gave a mandate to the EDQM to establish an annual program for inspections

Starting November 2005 new obligations for manufacturing authorizations holders to use only active substances manufactured according to the GMP came into force (directive 2001/83/EC and 2001/82/EC as amended)

- The same year a new EMA guidance on “When it is appropriate for Competent Authorities to conduct inspections at premises of manufacturers of active substances used as starting materials” was issued

An annual program regularly developed, initially based on the requests from assessors and then on the basis of new triggers, as defined by the EMA procedure

- Initially inspection team composed of one or more GMP inspectors from NCAs working with CEP personnel (assessors)
- Recruitment of GMP inspectors in secondment from NCA

Establishment of an EDQM inspection Unit, with GMP inspectors recruited from NCAs thorough a selection process managed by the Council of Europe (temporary or permanent agents = EDQM inspectors)

- Inspection team composed of an EDQM inspector and a NCA inspector, whose NCA is responsible for issuing responsibility to issue the GMP certificate

Legislation: Where are we now?

BEFORE	NOW
Before directive 2011/62/EU each NCA might have had different approaches for API manufacturers oversight, according to the national legislation: • Mandatory registration/authorization • No legal requirements for registration/authorization • Inspections carried out in EU or extra-EU countries for specific category of APIs (i.e. biological origin/sterile APIs)	The directive 2011/62/EU introduces the mandatory registration for manufacturers, importers and distributors of active substances, located in the European Union territory (art. 52a): • EU Member States must take appropriate measures to ensure that manufacture, import and distribution on their territory of active substances, including that are intended for export, comply with GMP and GDP (art. 111, 1b).
Inspections carried out in Europe or extra-EU countries if requested by the manufacturer to grant a GMP certificate: • Inspections carried out if deemed necessary during the assessment (NCA inspections, EMA inspections).	NCAs shall have a system of supervision including inspection at an appropriate frequency, based on risk, at premises of manufacturers, importers or distributors of active substances, located in their territories and effective follow-up thereof. If there are grounds to suspect noncompliance NCAs may carry out inspections at premises of manufacturers or distributors of active substances located in third countries or manufacturers or importers of excipients (in their territory).

BENEFITS COMING FROM THE EDQM INSPECTION PROGRAM

EDQM inspection program: its contribution to the API oversight system

1. Development of a risk-based inspection program
2. Inspections of sites under common interest for the European market
3. Involvement of inspectors working for different NCAs: promotion of harmonized approaches for inspection of API manufacturers
4. Development of a standardized post inspection procedure
5. Sharing/optimization of inspection resources within EU/EEA NCAs

OPPORTUNITY

- For participating inspectors: increase knowledge and understanding of the global API market and have an active role in a challenging regulatory area
- For participating inspectorate: opportunity to contribute to a program where there is mutual interest among EU/EEA NCAs and International Partners
- For EU/EEA citizens (and not only..): a higher and common level of public health protection

Development of a risk-based inspection program

Inspections of sites under common interest for the European market

Harmonization of inspection's approaches

Resources saving

Holder or customer? Who is the beneficiary?

OPPORTUNITY

INSUD PHARMA

1. **Mutual benefit (holder and client):** ***Shorter evaluation/approval time.*** The CEP is only evaluated by one agency (EDQM) while an ASMF, if your molecule does not meet specific requirements to be able to apply to a centralized process, you have to resort to a mutual recognition or decentralized process, which means that your dossier has have to be evaluated by several agencies (this increases time and costs). Lower cost (client): related to the previous point, the number of fees that the client has to pay is also reduced, although in our case as an ASMF holder we would only pay fees in Italy, with changes associated with the ASMF, with the CEP if we have to pay for the variations to the CEP.

2. **Mutual benefit (holder and client):** ***a CEP is evaluated independently*** of the marketing authorizations and a revised one is approved. On the other hand, an ASMF does not begin to be evaluated until the country in question receives a marketing authorization referencing the dossier. Furthermore, the ASMF is never considered “approved” and is reviewed with each associated marketing authorization. Note: Although there may be nuances with this point, when, for example, we have an ASMF 'worksharing', the evaluations are greatly speeded up since the assessments are shared in a common repository for the European agencies and are not completely re-evaluated in countries with other procedures. also associated with that ASMF, but when new countries are included, new questions can be circulated.

3. **Benefit for the client:** The client can change CEP from one manufacturer to another without needing to submit a complete variation, which reduces change evaluation time and allows them to have more access to new suppliers. For us it can be a benefit if we obtain a CEP close to the publication of the monograph, but it can be a disadvantage if we have not obtained it/time is delayed with deficiencies/comments if other competitors have it.

4. **Mutual benefit (ours and the client's):** ***Information on the methods and impurities*** is also published in the monograph, this reduces time and cost in method development, in addition the monograph includes impurities, in the ASMF the studies of theoretical impurities/ probable are usually more extensive, the methods have to be developed and validated. In addition, the EDQM also has standards that can be purchased to save (again time/money/resources) in the complete elucidation of the structure. These standards are not cheap, but from the primary one you can make working standards for API identification.

INSUD PHARMA

CEP ADD VALUE

OPPORTUNITY

- Assessment of the quality of substances for pharmaceutical use (mainly APIs), with reference to monographs of the Ph. Eur.
- Source of information to update Ph. Eur. monographs
- **Centralized assessment**
- **Facilitates management of MAAs and variations Coordination and conduct of GMP inspections of API manufacturers**
- **Having a CEP instil confidence in customers, regulatory authorities, other stakeholders and enhances the reputation and credibility of API manufacturers in the pharmaceutical industry. Moreover, obtaining the CEP allows to be listed in EDQM website database ensuring visibility**

OUT OF THE SCOPE

- Substances not included in Ph. Eur. (except TSE CEP)
- Substances which do not comply with the Definition section of the monograph, if applicable
- Biologicals and products extracted from animal tissues
- Human tissues derivatives, blood derivatives, vaccines
- Finished products

INSUD PHARMA

the key to achieving world-class expertise in any skill, is,
to a large extent,
a matter of practicing the correct way

Malcolm Gladwell

thank you all for the attention

antonella.volpe@insudpharma.com