

Certification of Substances Department

AMM/CB

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Certification of suitability to the Monographs of the European Pharmacopoeia

**Management of applications for new Certificates of Suitability, Requests for Revision
or Renewal of Certificates of Suitability and applications using the 'sister files'
procedure**

1. Introduction

This document describes the process applied to manage the applications for new certificates of suitability (CEPs), applications for revisions/renewals of existing certificates of suitability and via the 'sister files' procedure.

This document should be read in conjunction with:

- RESOLUTION AP-CSP (07) 1, Certification of suitability to the monographs of the European Pharmacopoeia, which describes the procedure to grant and revise CEPs.
- EDQM "Guideline on Requirements on Revision/Renewal of Certificates of Suitability to the European Pharmacopoeia monographs" (PA/PH/CEP (04) 2), which describes the categorisation of requests to revise CEPs and the conditions to be fulfilled as well as the documentation to be submitted for each request for revision.
- EDQM "Guidance on applications for sister files" (PA/PH/CEP (09) 141), which describes the conditions to be fulfilled as well as the documentation to be submitted for applications using the sister files procedure.

2. Applications for new CEPs, revision or renewal of CEPs or applications via the 'sister files' procedure - excluding notifications and transfer of holdership

2.1 Overview

EDQM acknowledges reception of applications and responses to requests for information submitted with respect to applications within **5 working days** of receipt. An official acknowledgement of receipt is sent, which specifies that the clock has started together with the deadline for the treatment of the request.

As shown in annex 1, Process Flows, once the application is validated for evaluation and the clock has started, the assessment of applications is handled by:

- the evaluation of the original application and,
- if necessary, the evaluation of additional information submitted upon request from the EDQM, and
- if necessary, the evaluation of another, last, package of additional information submitted upon a **last request** from the EDQM.

The timings allowed for the EDQM and for the applicant at the different steps in the process are included in the table in annex 2 and these vary depending on the type of application (e.g. new application, type of revision etc.).

Where the assessment is successful and the application is accepted as complete, a CEP (new or revised) is granted or for some revisions, a letter is sent to advise that the application has been accepted and the current CEP remains valid. The type of revision has an impact on whether the CEP is revised or not following acceptance of a revision as shown in annex 2.

Applications lacking sufficient information after evaluation of the applicant's response to a second deficiency letter from EDQM are definitively closed and the applicant is advised by letter.

For new applications and sister file applications, this means the application is rejected without a CEP being granted. For revision applications, this means that the request for revision is rejected and the current version of the CEP (without the requested changes) remains valid. For renewal applications this will have an impact on the validity of the existing CEP which may be suspended or withdrawn (see section 6).

2.2 Outcome of the assessment of the initial submission

When the initial assessment of the application is complete there are 4 possible conclusions as described in below:

2.2.1 The information provided is complete and the certificate can be granted or the request for revision is accepted.

A CEP (new, revised or renewed) is granted or the applicant is informed that the revision request has been accepted, see annex 2.

2.2.2 The information provided is unsatisfactory and the certificate cannot be granted or the request for revision/renewal accepted until the issues identified are resolved.

The EDQM sends a letter to the applicant requesting additional information in which there is a list of questions relating to the issues outstanding with the submission which prevent the request being accepted.

The applicant/holder has a defined time (see annex 2) to reply to this request and provide the information required.

The applicant/holder should reply to this request and provide full information required by the deadline or the assessment may be stopped due to this failure to respond (see section 5).

On reception of the response by EDQM, an acknowledgement of receipt is sent to the applicant. The submitted information requires assessment and the deadline for the assessment of the response and the provision of a response to the applicant are as described in the acknowledgment of receipt and in annex 2.

2.2.3 The information provided is in general satisfactory but clarification is required on some issues before the certificate is granted

This option is available only for new applications and sister files. It does not apply to revision or renewal applications.

This refers to the situation when there are some minor remaining point(s)/needs for clarification which have to be addressed.

Following this conclusion, the EDQM sends a letter to the applicant requesting clarification of the issues outstanding with the submission which prevent the request being accepted.

The applicant/holder has a defined time (see annex 2) to reply to this request and provide the information required.

The applicant/holder should reply to this request and provide full information required by the deadline or the assessment may be stopped due to a failure to respond (see section 5).

On reception of the response by EDQM, an acknowledgement of receipt is sent to the applicant. The submitted information requires checking and the deadline for the checking of the response and the provision of a response to the applicant are as described in the acknowledgment of receipt and in annex 2.

2.2.4 The information provided is satisfactory but sections of module 3 require to be updated to reflect the approved dossier before the certificate can be granted or the request for revision/renewal is accepted.

This refers to the situation when there must be an update of the information provided in module 3 to reflect the approved data. For example, where information provided in the module 1 response has not been incorporated into the appropriate section(s) of module 3.

Following this conclusion, the EDQM sends a letter to the applicant requesting update of the sections of module 3 to reflect the approved dossier.

The applicant/holder has a defined time (see annex 2) to reply to this request and provide the information required.

The applicant/holder should reply to this request and provide full information required by the deadline or the assessment may be stopped due to a failure to respond (see section 5).

There is no acknowledgement of receipt issued by EDQM and there is no assessment of the response received for a request to update a dossier. The module 3 is reviewed to ensure it has been updated as required and if so, then the process to prepare the certificate or to confirm acceptance of a request for revision begins. It is anticipated that the CEP or letter of approval will be issued within **1 month** of the receipt of the updated dossier.

2.3 Outcome of the assessment of the response to the 1st request for additional information.

After validation of the response provided by the applicant to the 1st request for additional information, EDQM has a period of time to perform the assessment and inform the applicant/holder of the conclusion of the assessment. The timings allowed are described in annex 2.

When the assessment of the response is complete there are 5 possible conclusions comprising the four conclusions described in 2.2.1 to 2.2.4 and the additional conclusion described in 2.3.1.

2.3.1 Based on the information provided, the conclusion is that no certificate can be granted or the request for revision is rejected with no further request for information.

For an application for a new certificate (including those using the sister file procedure), the outstanding points are identified and the EDQM sends a letter to the applicant, informing them that the application is being closed and providing a list of the outstanding issues which prevent the granting of a certificate and have led to the rejection.

The application is definitely closed. However, the applicant may submit a new application for the same substance. It is expected that the outstanding issues from the assessment of the original closed dossier will be addressed in the new submission.

For requests for revision, the outstanding points are identified and the EDQM sends a letter to the applicant informing that the revision request is rejected and including a list of the issues outstanding which prevent the approval of the request for revision. This also means that the current version of the CEP (without the requested changes) remains valid.

The applicant may submit another revision request for the CEP dossier for the same changes. It is expected that the outstanding issues from the assessment of the original request for revision will be addressed in the new request.

2.4 Outcome of the assessment of the response to the 2nd request for additional information.

After validation of the response provided by the applicant to the 2nd request for additional information, EDQM has a period of time to perform the assessment and inform the applicant/holder of the conclusion of the assessment. The time periods are described in annex 2.

When the assessment of the response is complete there are only 3 possible conclusions:

2.4.1 The information provided is complete and the certificate can be granted or the request for revision/renewal is accepted.

A CEP is granted or the applicant/holder is informed that the revision has been accepted, and the current CEP remains valid (see annex 2).

2.4.2 Based on the information provided, the conclusion is that no certificate can be granted or the request for revision is rejected.

For an application for a new certificate (including those using the sister file procedure), if there are outstanding points, the application is rejected with no further request for information. The EDQM sends a letter to the applicant informing them that the application is being closed and providing a list of the outstanding issues which prevent the granting of a certificate and have led to the closure.

The application is definitely closed. However, the applicant may submit a new application for the same substance. It is expected that the outstanding issues from the assessment of the original closed dossier will be addressed in the new submission.

For requests for revision, the EDQM sends a letter to the applicant informing that the revision request is rejected and including a list of the issues outstanding which prevent the approval of the request for revision. If appropriate, the letter also includes a request to update the sections of module 3 to remove the information which has been rejected and therefore to reflect the

approved dossier. This also means that the current version of the CEP (without the requested changes) remains valid.

The applicant may submit another revision request for the CEP dossier for the same changes. It is expected that the outstanding issues from the assessment of the original request for revision will be addressed in the new request.

When a renewal application cannot be accepted then there may be an impact on the validity of the CEP, see section 6.

2.4.3 The information provided is satisfactory but sections of module 3 require to be updated to reflect the approved dossier before the certificate can be granted or the request for revision/renewal accepted.

This refers to the situation when there must be an update of the information provided in module 3 to reflect the approved data.

For example, where information provided in the module 1 response has not been incorporated into the appropriate section of module 3.

Following this conclusion, the EDQM sends a letter to the applicant requesting update of the sections of module 3 to reflect the approved dossier.

The applicant/holder has a defined time (see annex 2) to reply to this request and provide the information required.

The applicant/holder should reply to this request and provide full information required by the deadline or the assessment may be stopped due to a failure to respond (see section 5).

There is no acknowledgement of receipt issued by EDQM and there is no assessment of the response received for a request to update a dossier. The module 3 is reviewed to ensure it has been updated as required and if so, then the process to prepare the certificate or to confirm acceptance of a request for revision begins. It is anticipated that the CEP or letter of approval will be issued within **1 month** of the receipt of the updated dossier.

3. Management of Notifications

Immediate Notifications have to be reported immediately after implementation within the company whilst annual notifications may be reported by way of a report compiling all the changes, which meet the conditions to be classified as annual notifications, which have been implemented within 12 months of the implementation of the first such change.

The reporting of annual notifications is based on the implementation date of the changes and not the anniversary of the CEP application.

Notifications are either accepted or rejected (if the conditions for a notification are not met). EDQM informs the applicant of the decision regarding the notification within **1 month** of its reception. If a notification is accepted then either a revised certificate is granted or a letter is sent from EDQM to the holder advising that the notification has been found valid. Notifications which are accepted will result in revision of the CEP only where the information on the CEP requires to be changed.

When a notification is rejected a letter is sent from EDQM to the holder advising that it has not been accepted and there is no possibility to submit additional information.

Changes which have been rejected as notifications should be submitted again and depending on the reasons for rejection (which should be addressed in the new request) the type of revision submitted should be adapted (generally a minor revision by default)

4. Transfer of holdership

The evaluation of validity of a transfer of holdership is completed within **1 month** after receipt of a request, and a revised certificate is granted.

If the request is incomplete at receipt, it is rejected without asking for any additional information and a letter of rejection is sent to the holder.

5. Administrative closure of an application for a new CEP or a revision or renewal or a sister file due to lack of response within the required time

At each point in the assessment process, where a request for information is sent by the EDQM to the applicant/holder, the time by which the response should be received is clearly indicated in the letter.

For an application for a new certificate or a sister file, if no response is provided by the applicant within the time allocated then the dossier is closed without further notice and a letter is sent by EDQM to the applicant informing them that the dossier has been closed. The dossier is definitively closed. However, the applicant may submit a new application for the same substance. It is expected that the outstanding issues from the assessment of the original closed dossier will be addressed in the new submission.

For requests for revision, the EDQM sends a letter to the applicant informing them that the lack of response has prevented the approval of the request for revision, which is therefore closed. This also means that the current version of the CEP (without the requested changes) remains valid. There may also be a requirement to update the module 3 to remove the proposed changes (see 2.2.4).

The applicant may submit another revision request for the certificate for the same changes. It is expected that the outstanding issues from the assessment of the original request for revision will be addressed in the new request.

For requests for renewal, the EDQM sends a letter to the applicant informing them that the lack of response has prevented the approval of the request for renewal. This will affect the validity of the current CEP (see section 6).

6. Suspension or Withdrawal of a CEP following rejection of a revision or renewal

In specific situations of renewal of a CEP or update of CEP application after a Ph. Eur. monograph revision, if the application is rejected because the CEP dossier is not in compliance

with the current regulatory requirements, the validity of the CEP cannot be maintained. One example of when this may happen are when a monograph revision includes a new control/limit which has been added for safety considerations and where the substance covered by the CEP is not compliant with the requirement of the monograph. The outstanding points are identified and the EDQM sends a letter to the applicant informing them of all the issues outstanding which prevent the approval of the request. The holder should take the necessary actions to address the issues.

Where the holder of the CEP fails to respond to EDQM requests or is not able to produce a substance which is compliant with the monograph then the CEP may be suspended or withdrawn.

Similarly, if the holder fails to meet the requirements for the renewal of an application, the CEP will be considered as definitely expired and cannot be restored.

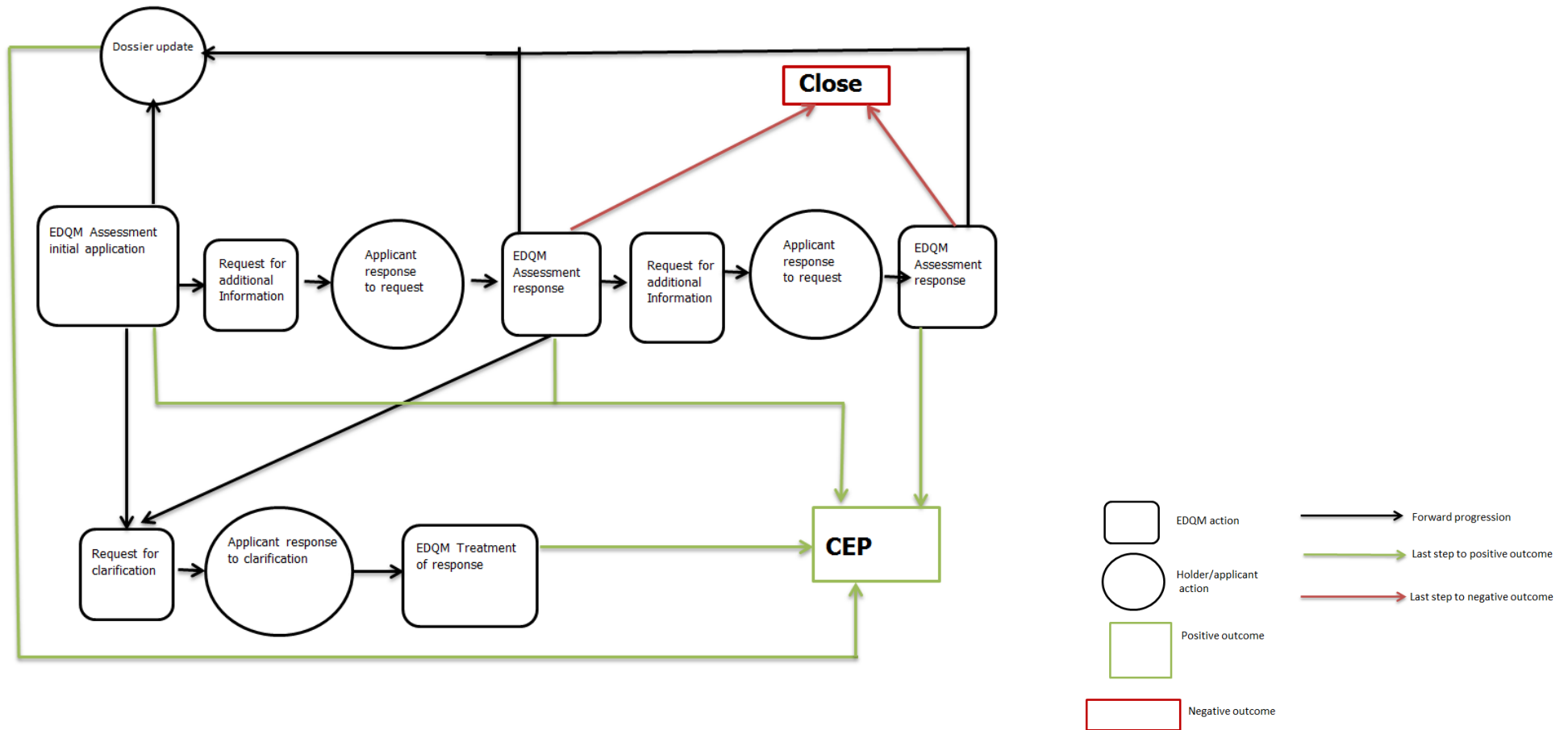
In such cases where the CEP is suspended or withdrawn by EDQM the procedure is described in "Suspension or Withdrawal of a Certificate of Suitability, Closure Of an Application", PA/PH/CEP (08) 17.

7. Documents referenced:

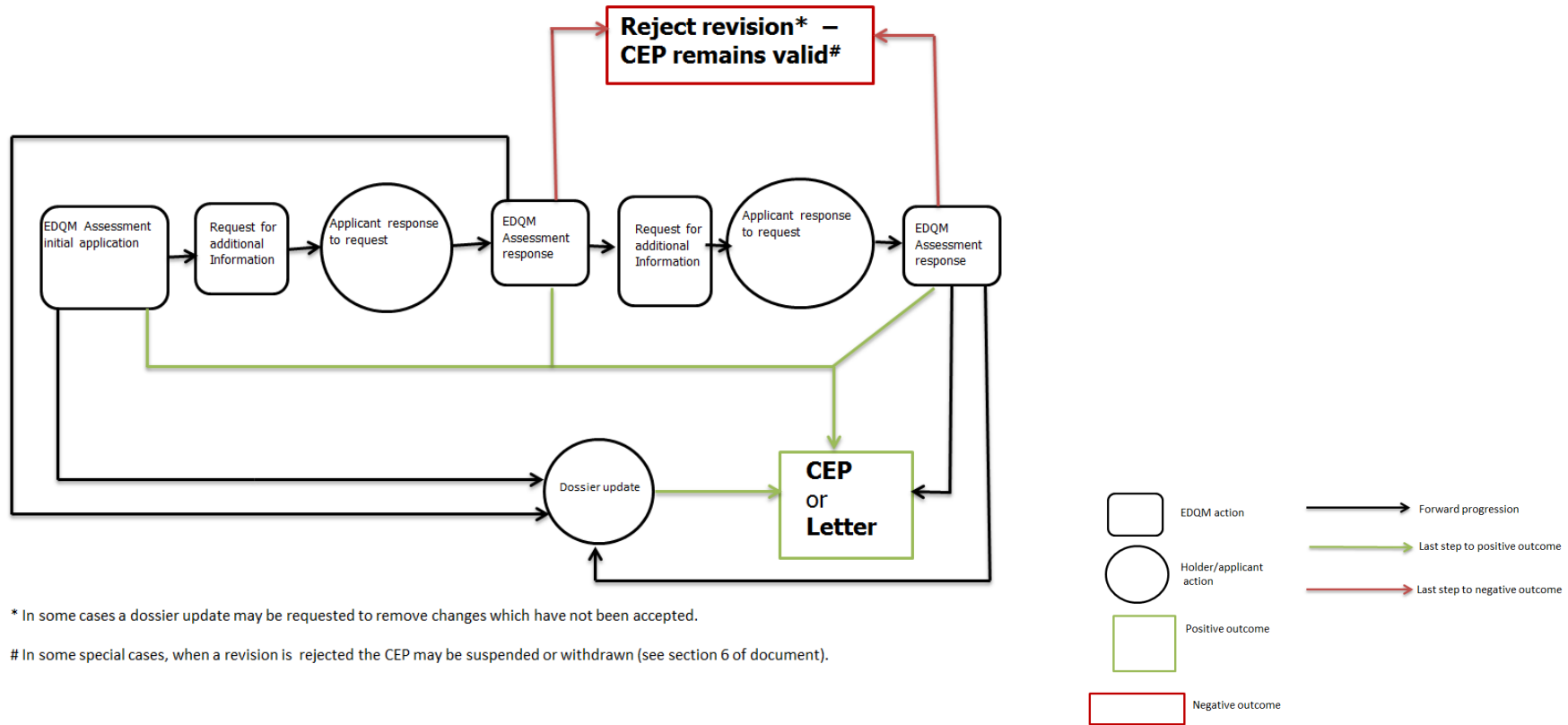
Resolution AP CSP (07) 1	Certification of suitability to the monographs of the European Pharmacopoeia
PA/PH/CEP (04) 2	Guideline on Requirements on Revision/Renewal of Certificates of Suitability.
PA/PH/CEP (09) 141	Guidance on applications for sister files
PA/PH/CEP (08) 17	Suspension or Withdrawal of a Certificate of Suitability, Closure Of an Application

Annex 1 –Process Flows

Applications for New CEP and sister file



Applications for Revisions or Renewals



* In some cases a dossier update may be requested to remove changes which have not been accepted.

In some special cases, when a revision is rejected the CEP may be suspended or withdrawn (see section 6 of document).

Annex 2 – Timings and details of whether CEPs are revised/granted if application accepted

Type of application	EDQM Timelines for assessment of initial application	Applicant Timeline to reply to first request for additional information	EDQM Timelines for assessment of reply to request for information	Applicant Timeline to reply to second request for additional information	EDQM Timelines for assessment of reply to request for information	CEP revised if application accepted ?
New	5 months	6 months*	4 months*	3 months*	4 months*	New CEP issued
		1 month #	1 month #	1 month #	1 month #	
Sister file	2 months	1 month	1 month	1 month	1 month	New CEP issued
Minor revision(s)	1 month	1 month	1 month	1 month	1 month	Revised CEP issued <u>only</u> if information on CEP requires to be changed otherwise a letter accepting the revision is issued
Major revision	2 months	1 month	1 month (TSE or Herbal: 2 months)	1 month	1 month (TSE or Herbal: 2 months)	Revised CEP issued
Monograph revision	3 months	1 month	1 month (TSE or Herbal: 2months)	1 month	1 month (TSE or Herbal: 2 months)	Revised CEP issued <u>only</u> if information on CEP requires to be changed otherwise a letter accepting the revision is issued
Renewal	3 months	1 month	1 month (TSE or Herbal: 2 months)	1 month	1 month (TSE or Herbal: 2 months)	Renewed CEP issued

* if the request from EDQM relates to significant information required to address the issues identified

if the request from EDQM relates to clarification of minor issues or update of the dossier