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Certification of suitability to the Monographs of the European Pharmacopoeia

GUIDELINE ON REQUIREMENTS FOR REVISION/RENEWAL OF CERTIFICATES OF SUITABILITY TO THE EUROPEAN PHARMACOPOEIA MONOGRAPHS

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1. INTRODUCTION:

The holder of a certificate of suitability (CEP) shall inform the EDQM of any change to information in the CEP application by sending an appropriate request for revision demonstrating that the conditions laid down in the present guideline are met.

In addition, this guideline describes the requirements for the renewal of CEPs and for a transfer of holdership.

2. CLASSIFICATION OF CHANGES:

The changes are classified in different categories [annual notification (AN)/immediate notification (IN)/minor (MIN)/major (MAJ)] depending on the potential impact of the change on the quality of the final substance. These categories are based on those (IA-IA$_{IN}$/IB/II) of the European Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

Any change not classified as a notification or a major change (or if all conditions of a change are not respected) should be classified as a **minor change by default**. For the convenience of applicants, some frequent minor changes are listed in this guideline, however this list should not be considered exhaustive.

In the following special cases a request for revision cannot be submitted but a **separate CEP application** should be made:

- Addition of a new manufacturing site of the final substance that does not belong to the same group and even when a qualified contract manufacturer

- Change to the manufacturing process resulting in
  - Sterile grade of a non-sterile active substance
  - Non-sterile grade of a sterile active substance
  - Addition of raw materials resulting in simultaneous use of material from different origin (e.g. TSE risk material vs non TSE risk material/substance from animal/human origin vs non animal/human origin)
  - Different polymorphic forms
  - Introduction of a new substantially different route of synthesis (even when the impurity profile of the final substance is equivalent)

For the same change(s) affecting several dossiers, it is possible to apply for a **grouped submission** provided that:

- the changes do not include any major change
- the different dossiers affected by the same group of changes are held by the same holder
- there is no or limited need for product specific impact assessment (this should be justified by the applicant)
- individual documentation should be submitted at the same time for each affected CEP application.

Updates of CEP applications following Ph. Eur. monograph revisions or any other regulatory requirements are treated separately and generally initiated by the EDQM.

3. DOCUMENTATION TO BE PROVIDED:

For any revision the documentation should consist of the CTD modules 1 & 3:

For module 1, the following information is required:

- A **cover letter**
- A completed **application form (specific for revisions)** identifying the type of revision and listing all the changes applied for, a description of each change, together with appropriate rationale and supporting information to justify the change should be provided.
- The differences between the approved and proposed text of module 3 **must** be presented as a **comparative table** (template of which is in annex of the application form). In this table each change introduced should be clearly identified in the column related to "proposed text". NB: Wording such as "updated"/ "see Module 3" is not appropriate.
- For notifications it must be shown how the conditions have been met.

For module 3, the following information is required:

- Each **complete** updated section which is affected by the change(s) being made.

Each time batch data are needed:
- they should be recent batches (within the last 18 months) in accordance with the specification of the current Ph. Eur. monograph and when relevant with the additional requirements of the CEP
- the manufacturing site, the manufacturing date and the size of the batches should be specified
- quantitative results should be presented numerically (i.e. not in general terms such as "complies") and with the appropriate number of decimal places.

Where necessary, the requirements of the "*Guideline on stability testing for applications for variations to a marketing authorisation" (EMA/CHMP/CVMP/QWP/441071/2011)* should be taken into account and relevant documentation should be provided. This applies namely to the items listed under sections 4.II.1 Manufacture and 4.II.3 Container closure system.

Editorial changes should not be submitted as separate revisions but may be reported at the same time as changes concerning the respective part of the dossier. In any case, a declaration should be provided that the content of the concerned part of the dossier has not been changed by the editorial changes (except for the change itself).

4. LIST OF CHANGES:

The changes are presented in the sections described below:
- Administrative changes
- Quality changes
- TSE changes
- Use of CEP in an application for another CEP
- Transfer of holdership

4.I. ADMINISTRATIVE CHANGES

This type of changes applies to chemical, double, herbal and TSE certificates of suitability.

4.I.1 Change in the name and/or address of the certificate holder	**Conditions**	**Specific documentation**	**Type of change**
	1	**1, 2**	**IN**
Conditions			
1. The certificate holder must remain the same legal entity (exception to this condition: where the company is sold or in the event of a company merger).			
Documentation			
1. A formal document from a relevant official body in which the new name and/or new address is mentioned.			
2. All updated declarations (annexes to the application form).			

4.I.2 Change in the name and/or address of a manufacturing site or a quality control testing site for the final substance	**Conditions**	**Specific documentation**	**Type of change**
	1	**1, 2, 3**	**IN**
Conditions			
1. The location of the manufacturing site or the quality control site must remain the same.			
Documentation			
1. A formal document from a relevant official body in which the new name and/or address is mentioned.			
2. Updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected (annexes to the application form).			
3. If needed, updated annexes to the CEP reflecting the change of name.			

4.I.3 Change in the name and/or address of a manufacturer of a starting material used in the manufacture of the final substance	**Conditions**	**Specific documentation**	**Type of change**
	1	**1**	**AN**
Conditions			
1.The location of the manufacturing site must remain the same.			
Documentation			
1. Updated list (with name and complete address) of approved and proposed manufacturers of starting material.			

4.I.4 Change in the name and/or address of a manufacturer of an intermediate used in the manufacture of the final substance	Conditions	Specific documentation	Type of change
	1	1, 2	IN
Conditions			
1. The location of the manufacturing site must remain the same.			
Documentation			
1. Updated list (with name and complete address) of approved and proposed manufacturers of intermediate.			
2. Updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected (annexes to the application form).			

4.I.5 Deletion of a manufacturer of intermediate or of a manufacturing site or quality control testing site for the final substance	Conditions	Specific documentation	Type of change
	1	1, 2	IN
Conditions			
1. There should at least remain one site/manufacturer, as previously declared, performing the same function as the one(s) concerned by the deletion.			
Documentation			
1. The justification of the deletion.			
2. Updated list (with name and complete address) of approved and proposed sites.			

4.I.6 Deletion of a manufacturer of a starting material used in the manufacture of the final substance	Conditions	Specific documentation	Type of change
	1	1, 2	AN
Conditions			
1. There should at least remain one site, as previously declared, performing the function.			
Documentation			
1. The justification of the deletion.			
2. Updated list (with name and complete address) of approved and proposed manufacturers of starting material.			

4.I.7 Change in the code product/reference number of the final substance or any material used in its manufacture	Conditions	Specific documentation	Type of change
	1	1	AN
Conditions			
1. The change does not regard the quality of the final substance or the concerned material.			
Documentation			
1. Approved and proposed code product / reference number.			

4.II. QUALITY CHANGES

These type of changes apply to chemical/double and herbal certificates of suitability.

4.II.1 Manufacture

4.II.1.1 Change in the manufacturer of a starting material used in the manufacturing process of the final substance	Conditions	Specific documentation	Type of change
a) The proposed manufacturer of the starting material is part of the same group as the currently approved manufacturer	**1, 2**	**1, 2, 3, 4**	**IN**
b) The proposed manufacturer of the starting material is not part of the same group as the currently approved manufacturer	**1,2**	**1, 2, 3, 4**	**MIN**
c) The proposed manufacturer of the starting material uses a different route of synthesis or manufacturing conditions which impact the specifications of the starting material		**1, 3, 4**	**MIN**
d) The proposed manufacturer of the starting material uses a different route of synthesis or manufacturing conditions which impact the specifications of the final substance			**MAJ (*)**
e) The proposed manufacturer of the starting material is used in the manufacturing process of a biological substance		**1, 3, 5**	**MAJ**

Conditions	
1.	The specifications of the starting material are identical to those already approved.
2.	The final substance is not a biological substance or a sterile substance.
Documentation	
1.	A declaration from the Certificate holder that the specifications of the final substance are the same as those already approved.
2.	A declaration from the Certificate holder that the specifications and the quality control procedures of the starting material are the same as those already approved. If a different route of synthesis is retained for the new supplier, the synthetic flowchart of how the starting material is obtained should be provided.
3.	A list (with name and complete address) of all current approved manufacturers/sites versus all proposed manufacturers sites in the current submission.
4.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the approved and proposed manufacturers/sites.
5.	Batch analysis data (in a comparative tabular format) for at least three batches (minimum pilot scale) of the final substance from the approved and proposed manufacturers/sites
(*)	If applicable supportive stability data as listed in current version of the "Guideline on stability testing for applications for variations to a marketing authorisation" (EMA/CHMP/CVMP/QWP/441071/2011).

4.II.1.2 Change in the manufacturer of an intermediate	**Conditions**	**Specific documentation**	**Type of change**
a) The proposed manufacturer of the intermediate is part of the same group as the currently approved manufacturer	**1, 2**	**1, 2, 3, 4, 5**	**IN**
b) The proposed manufacturer of the intermediate is not part of the same group as the currently approved manufacturer	**1, 2**	**1, 2, 3, 4, 5**	**MIN**
c) The proposed manufacturer of the intermediate uses a substantially different route of synthesis or manufacturing conditions which are likely to change the specifications (qualitative and/or quantitative impurity profile) of the final substance (e.g. change in synthetic strategy, new reagents, solvents, materials are introduced into the synthesis)	**3**		**MAJ (*)**
d) The proposed manufacturer of the intermediate is used in the manufacturing process of a biological substance	**3**	**1, 2, 3, 5, 6**	**MAJ**

Conditions	
1.	The specifications and the route of synthesis (including in-process controls, methods of analysis of all materials used) of the intermediate are identical to those already approved.
2.	The final substance is not a biological substance or a sterile substance.
3.	When a substantially different route of synthesis or manufacturing conditions is used the new manufacturer will **replace** the current manufacturer. The **addition** of an alternative process into a file where the synthetic route is different i.e. different synthetic intermediates, and even when the impurity profile of the final substance is equivalent, is not acceptable and a separate application is needed.
Documentation	
1.	A declaration from the Certificate holder that the specifications of the final substance are the same as those already approved.
2.	A declaration from the Certificate holder that the synthetic route/manufacturing process (or in case of herbal material, where appropriate, the method of preparation, geographical source and production), the specifications and the quality control procedures of the intermediate are the same as those already approved.
3.	A list (with name and complete address) of all current approved manufacturers/sites versus all proposed manufacturers/manufacturing sites in the current submission.
4.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the approved and proposed manufacturers/sites.
5	Declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected for the proposed manufacturer/sites (annexes to the application form). Information on sources and specification of starting materials used by the new manufacturer.
6.	Batch analysis data (in a comparative tabular format) for at least three batches of the final substance from the approved and the proposed manufacturers/sites.
(*)	If applicable supportive stability data as listed in current version of the "Guideline on stability testing for applications for variations to a marketing authorisation" (EMA/CHMP/CVMP/QWP/441071/2011).

4.II.1.3 Change in the manufacturer of the final substance (including where relevant quality control testing sites)	**Conditions**	**Specific documentation**	**Type of change**
a) The proposed manufacturer (manufacturing site/workshop) of the final substance is part of the same group as the currently approved manufacturer	**1, 2**	**1, 2, 3, 4**	**IN**
b) The proposed manufacturer is for a biological substance and is part of the same group as the currently approved manufacturer	**1**	**1, 3, 4, 5**	**MIN**
c) Addition or replacement of a quality control testing site for the final substance	**2, 3**	**1**	**IN**
d) Addition or replacement of an alternative sterilisation site for the final substance using a standard	**1, 4**	**1, 2, 6, 7**	**MIN**

	Ph.Eur. listed method of sterilisation			
e)	**Introduction of a new (additional) site of micronisation**	**1, 2, 5, 6**	**1, 2, 3, 4**	**IN**
Conditions				
1.	The specifications (including In-Process Controls, methods of analysis of all materials used), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.			
2.	The final substance is not a biological substance or a sterile substance.			
3.	Method transfer from the current to the new site has been successfully completed.			
4.	The proposed alternative sterilisation site is part of the same group as the current manufacturer of the final substance and is also performing manufacture of the final substance (including pre-sterilisation synthetic steps). When this condition is not met, the proposed new site cannot be accepted.			
5.	The particle size specification of the final substance and the corresponding analytical method remain the same and are already included on the CEP.			
6.	A micronisation site is already approved (included on the CEP).			
Documentation				
1.	A list (with name and complete address) of all current approved sites versus all proposed manufacturers/manufacturing sites in the current submission.			
2.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the approved and proposed manufacturers/sites.			
3.	Declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected for the proposed site/manufacturer (annexes to the application form). Information on sources and specification of starting materials used by the new manufacturer.			
4.	A declaration from the Certificate holder that the synthetic route/manufacturing process (or in case of herbal material, where appropriate the method of preparation, geographical source and production), quality control procedures and specifications of the final substance are the same as those already approved.			
5.	Batch analysis data (in a comparative tabular format) for at least three batches of the final substance from the approved and the proposed manufacturers/sites.			
6.	Declarations that sterilisation is performed in accordance with the dossier and according to EU GMP, Part 1 and of willingness to be inspected for the proposed site/manufacturer (annexes to the application form).			
7.	A declaration from the Certificate holder that the proposed alternative sterilisation site is part of the same group as the manufacturer of the final substance.			

4.II.1.4 Changes in the manufacturing process of an intermediate or the final substance		**Conditions**	**Specific documentation**	**Type of change**
a)	**Minor change in the manufacturing process of an intermediate or the final substance that is not expected to impact the quality, safety or control**	**1, 2, 3**	**1, 3, 4**	**AN**

	strategy of the final substance			
b)	**Any other minor changes in the manufacturing process of an intermediate or the final substance e.g. introduction of recovery procedures, addition of a solvent in a synthesis step excluding final purification and when this solvent is already used elsewhere in the approved process, changes to the process resulting in a new grade of the substance including micronisation, change in source of a material used in the preparation of the final substance from a TSE risk material to a vegetable, synthetic, or non-TSE risk material.**		**1, 3, 4, 5, 6, 7**	**MIN**
c)	**Replacement of the manufacturing process with substantial changes likely to change the qualitative and/or quantitative impurity profile of the final substance also including the introduction of a 'telescoped process' (where multiple chemical transformations are run without isolation of intermediates) or the introduction of new technology (e.g. 'flow chemistry' or 'continuous manufacturing process technology).**	**4**		**MAJ (*)**
d)	**Change in the manufacturing process of an intermediate or the final substance concerning the sterilisation step(s), including changes in batch size of a sterile substance**			**MAJ (*)**
e)	**Changes in the manufacturing process of a herbal substance related to geographical source or production**			**MAJ (*)**

	Conditions
1.	The specifications of the final substance or intermediates are unchanged and there is no adverse change in qualitative and quantitative impurity profile of the final substance.
2.	The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process (eg, non-significant adjustments to operating conditions, non-significant changes in equipment, addition of a reprocessing step, i.e. the direct repetition of an approved step, repetition of washing/purification operations within the same step, changes/upgrades in equipment except for sterile grade material). In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.
3.	The final substance is not a biological substance.
4.	When a substantially different route of synthesis or manufacturing conditions is proposed

	the new route of synthesis will **replace** the current route. The **addition** of an alternative process into a file where the synthetic route is substantially different, and even when the impurity profile of the final substance is equivalent, is not acceptable and a separate application is needed.
Documentation	
1.	Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) of the final substance manufactured according to the approved and proposed process.
2.	Batch analysis data (in comparative tabular format) of at least three batches (minimum pilot scale) of the final substance manufactured according to the approved and proposed process.
3.	A direct comparison of the approved and the proposed process.
4.	A declaration from the Certificate holder that the specifications of the final substance are the same as those already approved.
5.	Specifications of the proposed source of the material.
6	If relevant a declaration from the manufacturer of the material that it is purely of vegetable, synthetic or non-TSE risk origin (specifying the origin, see annex of the application form).
7.	If relevant a declaration from the Certificate holder that there is no change in the manufacturing process of the final substance and that the specifications of the final substance remain the same.
(*)	If applicable supportive stability data as listed in current version of the "Guideline on stability testing for applications for variations to a marketing authorisation" (EMA/CHMP/CVMP/QWP/441071/2011).

4.II.1.5 Change in batch size of final substance or intermediate	**Conditions**	**Specific documentation**	**Type of change**
a) Up to 10-fold increase compared to the original approved batch size	**1, 2, 3, 4, 6, 7**	**1, 2, 3, 4**	**AN**
b) Downscaling down to 10-fold	**1, 2, 3, 4, 5, 6**	**1, 2, 3, 4**	**AN**
c) More than 10-fold increase compared to the originally approved batch size		**2, 3, 5**	**MIN**
d) Change in batch size of a biological substance		**2, 3, 6, 7**	**MIN**

Conditions	
1.	Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.
2.	Test results of at least two batches of the final substance complying with the approved specifications should be available for the proposed batch size.
3.	The substance is not a biological substance or a sterile substance.
4.	The change does not affect the reproducibility of the manufacturing process.

5.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6.	The specifications of the final substance/intermediates remain the same.
7.	The currently approved batch size was not approved via a notification.
Documentation	
1.	The batch numbers of the tested batches having the proposed batch size.
2.	Approved and proposed batch size.
3.	Updated description of the full process specifying the proposed batch size.
4	A declaration from the Certificate holder that the changes to the manufacturing methods are only those necessitated by scale up / downscaling, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the final substance/intermediates remain the same.
5.	Batch analysis data (in comparative tabular format) on a minimum of one production batch of the final substance manufactured according to both the approved and the proposed sizes.
6.	Batch analysis data (in comparative tabular format) of at least three batches (minimum pilot scale) of the final substance manufactured according to the approved and proposed process.
7.	A declaration from the holder of the certificate of suitability that the specifications of the final substance are the same as those already approved.

4.II.1.6 Change in test procedure for in-process tests or limits applied during the manufacture of the final substance or specification limits for a starting material /reagent/intermediate	**Conditions**	**Specific documentation**	**Type of change**
a) Tightening of the limits of in-process tests applied during the manufacture of the final substance or specification limits for a starting material /intermediate / reagent used in manufacture	**1, 2, 3**	**1**	**AN**
b) Addition of a new in-process test applied during the manufacture of the final substance and limit or specification parameter for a starting material / intermediate / reagent	**1, 4, 5, 6**	**1, 2**	**AN**
c) Addition of a new in-process test and limit regarding a critical parameter		**1, 2**	**MAJ**
d) Deletion of a non-significant in-process test or specification parameter for a starting material/intermediate/reagent	**1, 6**	**1, 3**	**AN**

e) Widening of in-process test limits applied during the manufacture of the final substance or specification parameter for a starting material / intermediate / reagent which may have a significant effect on the overall quality of the final substance			**MAJ**
f) Deletion of in-process test limits applied during the manufacture of the final substance, which may have a significant effect on the overall quality of the final substance			**MAJ**
g) Minor changes/updates in a test procedure	**2, 3, 5, 7**	**1, 2**	**AN**
h) Change of a limit for a mutagenic impurity in a starting material/intermediate/reagent according to the principles and limits of the ICH M7 guideline		**1, 2, 4, 5**	**MIN**
i) Changes to a test procedure (including replacement or addition) for a biological substance or changes to a biological method		**1, 2**	**MIN**

Conditions

1	The change does not result from unexpected events arising during manufacture.
2	Any change should be within the range of currently approved limits.
3.	The test procedure remains the same (e.g. a change in column length or temperature, but not a different type of column or method), or changes in the test procedure are minor.
4.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5.	The new test method is not a biological method or a method using a biological reagent for a biological substance (does not apply for standard European pharmacopoeial microbiological methods).
6.	The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance) or controls for mutagenic impurities, controls for elemental impurities, impurities which are not controlled elsewhere in the process, any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water.
7.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

Documentation

1.	Comparative table of approved and proposed in-process tests or limit in starting material/intermediate/reagent.

2.	Details of any new non-pharmacopoeial analytical method and validation data, where relevant.
3.	Justification/risk assessment from the Certificate holder that the in-process tests are non-significant.
4.	Justification/ risk-assessment from the Certificate holder as appropriate showing that the parameter can be deleted or widened according to the principles and limits of the ICH M7 guideline.
5.	Batch analysis data on two production batches of the final substance for all specification parameters.

4.II.2 Control of the final substance

4.II.2.1 Change in the specification parameters and/or limits of the final substance	Conditions	Specific documentation	Type of change
a) Tightening of specification limits for the final substance	**1, 2, 3**	**1**	**IN**
b) Addition of a specification parameter for the final substance	**1, 4, 5, 6, 7**	**1, 2, 3**	**IN**
c) Deletion of a non-significant specification parameter for the final substance (e.g. deletion of an obsolete parameter)	**1, 7**	**1, 4**	**AN**
d) Deletion of a specification parameter which may have a significant effect on the overall quality of the final substance			**MAJ**
e) Widening of the approved specification limits for the final substance to be in line with the limits of the Ph. Eur. monograph /ICH /VICH guidelines		**1, 2, 3**	**MIN**
f) Widening of the approved specification limits for the final substance			**MAJ**
g) Change of a limit for a mutagenic impurity in the final substance specification according to the principles and limits of the ICH M7 guideline.		**1,3, 5**	**MIN**
h) Introduction or revision (non-editorial changes) of a RMS (Risk management summary) regarding elemental impurities	**8**	**6**	**MIN**
i) Addition of a specification parameter dealing with a new grade to be included on the certificate (e.g. a micronised material)		**1, 2, 3, 7, 8**	**MIN**

Conditions	
1.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
2.	Any change should be within the range of currently approved limits.
3.	The test procedure remains the same, or changes in the test procedure are minor.
4.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5.	The test method is not a biological method or a method using a biological reagent for a biological substance (does not apply for standard Ph. Eur. microbiological methods).

6.	The change does not concern a mutagenic or an elemental impurity. Any new impurity control should be in line with the Ph. Eur. where applicable.
7.	The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water.
8.	The route of synthesis of the final substance remains unchanged.
Documentation	
1.	Comparative table of approved and proposed specifications.
2.	Details of any new analytical method and validation data, where relevant.
3.	Batch analysis data on two production batches of the final substance for all specification parameters.
4.	Justification/risk-assessment from the Certificate holder as appropriate showing that the parameter is non-significant.
5.	Justification/risk-assessment from the Certificate holder as appropriate showing that the parameter can be deleted or widened according to the principles and limits of the ICH M7 guideline.
6.	Risk management discussion and summary for elemental impurities.
7.	If new sites are involved, a list (with name and complete address) of all current approved sites versus all proposed manufacturers/manufacturing sites in the current submission. Declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected for the proposed site/manufacturer (annexes to the application form).
8.	A declaration from the Certificate holder that the synthetic route/manufacturing process (or in case of herbal material, where appropriate the method of preparation, geographical source and production), quality control procedures and specifications of the final substance (with the exception for particle size) are the same as those already approved.

4.II.2.2 Change in test procedure for the final substance	**Conditions**	**Specific documentation**	**Type of change**
a) Minor changes to a test procedure for the final substance. Editorial changes to a method description annexed to a certificate of suitability	**1, 2, 3, 4**	**1, 2, 3**	**IN**
b) Changes to a test procedure (including replacement or addition) for a biological substance or changes to a biological method		**1, 2, 3**	**MIN**
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.			

3.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
4.	The test method is not a biological method, or a method using a biological reagent for a biological substance (does not include standard pharmacopoeial microbiological methods).
Documentation	
1.	Description of the analytical method and revised specifications.
2.	Comparative validation results, or if justified comparative analysis results showing that the approved test and the proposed one are equivalent.
3.	Updated description of the method in a format to be appended to the certificate of suitability.

4.II.3 Container closure system

4.II.3.1 Change in the composition of the immediate packaging of the final substance	**Conditions**	**Specific documentation**	**Type of change**
a) Composition (when there is a re-test period mentioned on the certificate of suitability)	**1, 2, 3**	**1, 2, 3**	**IN**
b) Composition (when there is no re-test period mentioned on the certificate of suitability)	**1, 3**	**1, 2**	**IN**
c) Composition for sterile substances			**MAJ (*)**
d) Composition for liquid final substance (non-sterile)		**1, 2, 4, 5**	**MIN**

Conditions	
1.	The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
2.	Relevant stability studies have been started under ICH conditions and relevant stability parameters have been assessed in at least two pilot-scale of industrial scale batches and at least three months satisfactory stability data are at the disposal at time of implementation. NB: if the proposed packaging is more resistant than the existing packaging, the three months stability data do not yet have to be available. These studies must be finalized and the data will be provided immediately to EDQM if outside specifications or potentially outside specifications at the end of the re-test period (with proposed action).
3.	The final substance is not a sterile, liquid or biological substance.
Documentation	
1.	Comparison of the approved and proposed immediate packaging specifications, if applicable.
2.	Appropriate data on the new packaging including a confirmation that the material complies with relevant pharmacopoeial requirements or EU legislation on plastic materials and objects in contact with foodstuffs.

3.	A declaration from the Certificate holder as appropriate that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalized and that data will be provided immediately to EDQM if outside specifications or potentially outside specifications at the end of the approved re-test period (with proposed action).
4.	Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.
5.	If a retest period has been approved, the results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to EDQM if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action).
(*)	If applicable supportive stability data as listed in current version of the "Guideline on stability testing for applications for variations to a marketing authorisation" (EMA/CHMP/CVMP/QWP/441071/2011).

4.II.3.2 Change in the specification parameters and/or limits of the immediate packaging of the final substance	**Conditions**	**Specific documentation**	**Type of change**
Any change in the specification parameters and/or limits	**1, 2, 3**	**1**	**AN**
Conditions			
1. The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the final substance.			
2. The test procedure remains the same, or changes in the test procedure are minor.			
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
Documentation			
1. Comparative table of current and proposed specifications.			

4.II.3.3 Change in the composition / specification of the secondary packaging of the final substance	**Conditions**	**Specific documentation**	**Type of change**
a) Composition		**1**	**IN**
b) Specification	**1**	**1**	**AN**
Conditions			
1. The composition of the secondary packaging of the final substance remains the same.			

Documentation
1. Comparison of the approved and proposed secondary packaging specification/or composition.

4.II.4 Stability

4.II.4.1 Change in the re-test period or storage conditions of the final substance	**Conditions**	**Specific documentation**	**Type of change**
a) Removal or reduction of an approved re-test period	**1**	**1**	**IN**
b) Addition of a re-test period for the final substance and/or change in the storage conditions for the final substance		**2, 3**	**MIN**
c) Extension of the re-test period of the final substance and/or change in the storage conditions for the final substance		**4**	**MIN**
d) Change to more restrictive storage conditions	**1**	**1**	**IN**
e) Change to an approved stability protocol	**1, 2**	**5**	**IN**

Conditions
1. The change should not be the result of unexpected events arising during manufacture.
2. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.

Documentation
1 Justification of the removal/reduction of the re-test period or of more restrictive storage conditions.
2. Results of long-term and accelerated stability studies for at least two pilot or production scale batches.
3. Appropriate data on the packaging material including a confirmation that the material complies with relevant pharmacopoeial requirements or EU legislation on plastic materials and objects in contact with foodstuffs.
4. Updated results of stability studies for at least two pilot or production scale batches.
5. Justification for the proposed changes and updated stability protocol.

4.II.5 Design Space and Post-Approval Change Management Protocols

4.II.5.1 Introduction of a new design space or extension of an approved design space for the final substance, concerning:	**Conditions**	**Specific documentation**	**Type of change**
a) One unit operation in the manufacturing process of the final substance including the resulting in-process controls and/or test procedures		**1, 2, 3**	**MAJ**
b) Test procedures for starting materials/reagents/intermediates and/or the final substance		**1, 2, 3**	**MAJ**
Documentation			
1. The design space has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the final substance has been achieved.			
2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
3. Amendment of the relevant section(s) of the dossier in CTD format.			

4.II.5.2 Introduction of a post approval change management protocol related to the final substance	**Conditions**	**Specific documentation**	**Type of change**
		1, 2, 3	**MAJ**
Documentation			
1. Detailed description for the proposed change.			
2. Change management protocol related to the final substance.			
3. Amendment of the relevant section(s) of the dossier in CTD format.			

4.II.5.3 Deletion of an approved change management protocol related to the final substance	Conditions	Specific documentation	Type of change
	1	1, 2	IN

Conditions

1. The deletion of the approved change management protocol related to the final substance is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol and does not have any effect on the already approved information in the dossier.

Documentation

1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the dossier.

4.II.5.4 Changes to an approved change management protocol	Conditions	Specific documentation	Type of change
a) Major changes to an approved change management protocol			MAJ
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		1	MIN

Documentation

1. Declaration that any change is within the range of currently approved limits.

4.II.5.5 Implementation of changes foreseen in an approved change management protocol	Conditions	Specific documentation	Type of change
a) The implementation of the change requires no further supportive data	1	1, 2, 3	IN
b) The implementation of changes requires further supportive data		1, 2, 3, 4	MIN

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol.

Documentation

1. Reference to the approved change management protocol.
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol.
3. Amendment of the relevant section(s) of the dossier in CTD format.
4. Results of the studies performed in accordance with the approved change management protocol.

4.III. TSE CHANGES

4.III.1 Change in source country/ in source of material	Conditions	Specific documentation	Type of change
a) Deletion of a source country or deletion of a tissue used in the preparation of the final product for TSE risk material	**1**	**1**	**IN**
b) Change/addition of a source country or tissues for TSE risk material			**MAJ**
Conditions			
1. There is no change to the manufacturing process and there should be at least one remaining tissue and one remaining source country.			
Documentation			
1. Direct comparison of the approved/proposed source of material.			

4.III.2 Change or addition of a manufacturing site/manufacturer for a starting material/an intermediate or the final product for a TSE CEP	Conditions	Specific documentation	Type of change
a) The proposed manufacturer for the final product is part of the same group as the approved manufacturer	**1, 2**	**1, 2, 3**	**IN**
b) Change / addition of a manufacturing site for a starting material/an intermediate or where other TSE materials are processed			**MAJ**
Conditions			
1. No change in the manufacturing process, in the materials nor in the origin of the materials used in the process.			
2. The certificate of suitability covers only the TSE risk and does not cover the chemical purity and microbiological quality.			
Documentation			
1. A declaration from the Certificate holder that the manufacturing process is identical to that already approved.			
2. A declaration from the Certificate holder that no other TSE risk material is processed in the new manufacturing site.			
3 Updated declarations of manufacture in accordance with the dossier and according to GMP rules/quality system and of willingness to be inspected.			

4.III.3 Change in the quality assurance system applied in the manufacturing site	Conditions	Specific documentation	Type of change
	1, 2	1	IN
Conditions			
1. The new quality assurance system is at least equivalent to the approved one.			
2. No change in the manufacturing process (including process parameters) or in the specifications of the final substance.			
Documentation			
1. Updated information on the quality assurance system (including traceability).			

4.III.4 Change in the manufacturing process of the final substance	Conditions	Specific documentation	Type of change
a) Minor change in the manufacturing process (including process parameters)	**1, 2**	**1, 2**	**AN**
b) Substantial changes in the manufacturing process that are likely to affect the TSE risk	**3**		**MAJ**
Conditions			
1. The change has no impact on the TSE risk.			
2. The certificate of suitability covers only the TSE risk and does not cover the chemical purity and microbiological quality.			
3. For gelatine the manufacturing remains essentially the same i.e. an alkali process cannot be included in a file where an acid process is described or vice versa. Separate certificates are needed for gelatine according to the used manufacturing process.			
Documentation			
1. Comparison of the approved and proposed process.			
2. A declaration from the holder of the certificate of suitability that the change has no impact on the TSE risk.			

4.III.5 Minor change in the specification of the final substance	Conditions	Specific documentation	Type of change
	1,2	1, 2	IN
Conditions			
1. The change has no impact on the TSE risk.			
2 The certificate of suitability covers only the TSE risk and does not cover the chemical purity and microbiological quality.			
Documentation			
1. Comparison of the approved and proposed specification.			
2. A declaration from the Certificate holder that the change has no impact on the TSE risk.			

4.IV. Use of CEP in an application for another CEP

4.IV.1 Submission of a CEP for a starting material or intermediate used in the manufacturing process of a final substance in an application for a chemical CEP	Conditions	Specific documentation	Type of change
a) A newly introduced CEP used to describe a starting material	1, 2, 3	1, 2, 4	IN
b) A newly introduced CEP used to describe an intermediate	1, 2, 3	1, 3, 4	MIN
c) A newly introduced CEP used to describe a material when the specifications of the material are changed		1, 2 or 3, 4, 5	MIN
d) A revised version of a CEP already referenced to describe a material, when the manufacturing sites mentioned on this CEP are unchanged	3	1	AN
e) A revised version of a CEP already referenced to describe a material when the manufacturing sites mentioned on this CEP are changed	3	1, 2 or 3	IN
f) A revised version of a CEP already referenced for a material when the specifications on this CEP are changed	3	1, 4, 5	MIN
g) A deletion of a CEP used to describe a material when multiple sources of material are used	4	2, 3	IN
h) A deletion of a CEP used to describe a starting material or intermediate and replacement by another source that does not have a CEP			MAJ

Conditions

1. The material must be the substance which is covered by the CEP being submitted
2. The CEP for the material must have been granted and be valid.
3. The specifications of the material are identical to those already approved.
4. At least one other source of the material remains in the dossier.

Documentation
1. Copy of the current CEP for the material with the box of access completed appropriately.
2. The details of the sites involved in the manufacturing process described in the CEP for the starting material should be provided in the section "3.2.S.2.3 Control of materials" of the dossier.
3. The details of the manufacturing sites involved in the manufacturing process described in the CEP for the material should be provided in the section "3.2.S.2.1 Manufacturers" of the dossier.
4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance.
5. A discussion on the impact of the change of specifications of the material on the quality of the final substance.

4.IV.2 Submission of a TSE CEP for a material referenced in an application for a CEP TSE	**Conditions**	**Specific documentation**	**Type of change**
a) A newly introduced CEP used to describe a source material used in the synthesis of the compound covered by TSE CEP	**1**	**1**	**IN**
b) A revised version of a CEP already referenced to describe a source material used in the synthesis of the compound covered by TSE CEP	**1**	**1**	**IN**

Conditions
1. The CEP for the source material must have been granted and be valid.
Documentation
1. Copy of the current CEP for the source material with the box of access completed appropriately.

5. RENEWAL

The Certificate of suitability is valid for five years from the date when the original certificate was granted. Regardless of any revisions treated in the meantime, the holder of a Certificate of suitability shall ask for its renewal six months prior to expiry date by providing an update of the Certification dossier.

5. Renewal of the certificate of suitability	Conditions	Specific documentation	Type of change
a) No change has been made since the last CEP was granted or last revision approved	**1**	**1, 2, 3**	**Renewal**
b) Changes are included in the request for renewal	**1**	**2, 3, 4, 5, 6**	**Renewal**

Conditions
1. No major changes to the content of the CEP application are introduced.
Documentation
1. A statement that no changes that may affect the quality, safety or efficacy of the final substance have been made.
2. Certificates of analysis from at least two recent production batches.
3. Updated declarations as annexes to the application form.
4. An updated dossier in CTD format and/or updated sections affected by the changes.
5. List of changes introduced in the format of a comparative table (i.e. approved text vs proposed text).
6. Relevant data supporting each change as described in this guideline.

6. TRANSFER OF HOLDERSHIP

A transfer of the holdership of a CEP (i.e. change in the name of the certificate holder that is not the same legal entity and where the change does not occur following a sale or a merger) when the conditions of 4.I.1 Change in the name and/or address of the certificate holder are not respected is possible via a specific procedure.

Documentation:

- the application form with the new details of the holder and updated declarations as annex to the application form.
- a letter signed by both parties, i.e. the current and proposed holders, agreeing that the holdership of the CEP is passed on to the new holder from the date of the request.