DIRECTION EUROPÉENNE DE LA QUALITÉ
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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

Public consultation	December 2025

Revision history of the document

Revision N°	Date	Reason
Previous version 7R	September 2018	
8R	October 2025	Changes made consequential to the adoption of the EU Variations guideline, the EU regulation on veterinary medicinal products and also to changes within the Certification procedure (e.g. need for separate CEP in some cases)

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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. 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 and also Regulation (EU) 2019/6 and Regulation EU 2021/17 on veterinary medicinal products and repealing Directive 2001/82/EC but differ occasionally due to specific CEP needs and leading sometimes to a different approach.

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

CEP holders are encouraged to submit all annual notifications together once a year, but which may also be submitted accompanied by other types of changes.
Where a group of changes consists of different types of revisions, the group must be submitted and handled according to the "highest" revision type included in the group.

CEP holders are reminded that in case of submission of only notifications, but which includes changes not classifiable as a notification, will be rejected and the changes will then need to be resubmitted using the correct classification (with associated documentation and fee).

The possibility to change format of the CEP is also specifically addressed, following implementation of the CEP 2.0.

This guideline should be read in conjunction with PA/PH/CEP (24) 51 "Stepwise process to get a CEP/having a change approved".

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.

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 circumstances 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 it is a qualified contract manufacturer

- Change to the manufacturing process resulting in
    - Sterile grade of a non-sterile active substance
    - Addition or replacement of raw materials 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
    - Different hydrates
    - Introduction of a new substantially different route of synthesis (even when the impurity profile of the final substance is equivalent). 'Substantially different' would include e.g. a different synthetic strategy (different synthetic intermediates), the use

of different type of reagent suggesting reaction mechanisms are changed and hence new reaction by-products are expected to be formed and when there is a reasonable expectation of their carry-over to the final substance, or the introduction of new technology (e.g. 'flow chemistry' or 'continuous manufacturing process technology')

- A change in the impurity profile of the final substance (for example resulting from a change in the materials used in the purification steps or the elemental impurities classified in ICH Q3D susceptible to be present are different).

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.

For substances for veterinary use only, as indicated in the title of the Ph. Eur. monograph a separate classification is applicable for some changes. See section 7.

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

Editorial changes should not be submitted as separate revisions but may be reported at the same time as other changes. 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.

3. DOCUMENTATION TO BE PROVIDED:

For any revision the documentation should consist of the CTD modules 1, 2 (for a major revision) and 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.
- SPOR OMS data for any new site (including for manufacturers of intermediates). These data should be available **before** applying for any request for revision where this information is needed.

For module 2 (only for major revisions)

- A revised document taking into account the changes made, addressing their impact and updating the relevant data of the dossier.

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 (e.g. 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.

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

Changes for Substances for veterinary use only

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 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	AN
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 manufacturing site of a starting material used in the manufacturing process of the final substance	**Conditions**	**Specific documentation**	**Type of change**
a) Addition or replacement of a manufacturing site of a starting material used in the manufacture of the final substance or reagent required to be mentioned in the dossier	**1, 2, 3**	**1, 2, 3, 4**	**AN**
b) Addition or replacement of a new herbal substance manufacturing site using the same or different plant production (i.e. cultivated or wild collection) and including change in geographical source		**1, 4, 5**	**MIN**
c) Addition or replacement of a manufacturing site of a biological starting material used in the manufacture of a biological final substance which may have a significant impact on the quality, safety or efficacy of the final substance		**1, 3, 4**	**MAJ**
d) Addition or replacement of a storage site of the Master Cell Bank and/or Working Cell Banks	**4**	**3**	**AN**
e) Addition or replacement of a batch control/testing site of a starting material used in the manufacturing of a biological final substance, applying physicochemical and/or microbiological analytical procedure	**5, 6**	**3**	**AN**
f) Addition or replacement of a batch control/testing site of a starting material used in the manufacturing of a biological final substance applying a biological/immunological/immunochemical analytical procedure			**MIN**

Conditions

1.	The specifications and the route of synthesis (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. For herbal substances, the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal substance are the same as those already approved.
2.	The final substance is not a biological substance or a sterile substance.
3.	Where material of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with Ph Eur general monograph *Products with risk of transmitting agents of animal spongiform encephalopathies (1483)* unless reference to the general monograph is already mentioned on the current CEP.
4.	The storage conditions are identical to those already approved.

5.	Method transfer from the old to the new site has been successfully completed.
6.	The analytical procedure is not a biological/immunological/immunochemical procedure.
Documentation	
1.	A declaration from the Certificate holder that the specifications of the starting material 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. If relevant, a TSE certificate of suitability for any new source of material 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) [or 3 batches (unless otherwise justified) for biologicals] of the final substance from the approved and proposed manufacturers/sites.
5.	A detailed comparison regarding specifications and critical quality attributes of the herbal substance. A GACP declaration from the new supplier.

4.II.1.2 Change in the manufacturing site of an intermediate used in the manufacturing process of the final substance (including where relevant quality control testing sites)		**Conditions**	**Specific documentation**	**Type of change**
a)	Addition or replacement of a manufacturing site of an intermediate	**1, 2, 3, 4**	**1, 2, 3, 4, 5**	**IN**
b)	Addition or replacement of a manufacturing site of an intermediate used in the manufacture of a chemical or biological final substance but where different manufacturing conditions are used, which may have a potential to change important quality characteristics of the final substance, such as qualitative and/or quantitative impurity profile or a different route of synthesis which is not substantially different	**4**	**1, 3, 4, 5**	**MAJ**
c)	Addition or replacement of a quality control testing site for an intermediate	**2, 5**	**3**	**AN**
d)	Addition or replacement of a batch control/testing site of an intermediate used in the manufacturing of a biological final substance, applying physicochemical and/or microbiological analytical procedure	**5, 6**		**AN**
e)	Addition or replacement of a batch control/testing site of an intermediate used in the manufacturing of a biological final substance, applying a biological/immunological/immunochemical analytical procedure			**MIN**
Conditions				
1.	The specifications and the route of synthesis (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. For herbal substances, the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal substance are the same as those already approved.
2.	The final substance is not a biological substance or a sterile substance.
3.	Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or where material concerned with compliance with the general monograph *Products with risk of transmitting Animal Spongiform Encephalopathies (1483)* unless reference to the general monograph is already mentioned on the current CEP.
4.	The specifications of the final substance are unchanged and/or the elemental impurities classified in ICH Q3D susceptible to be present are unchanged. The addition of an alternative process into a file where the synthetic route which is substantially different and even when the impurity profile of the final substance is equivalent, is not acceptable and a separate application is needed.
5.	Method transfer from the current to the new site has been successfully completed.
6.	The analytical procedure is not a biological/immunological/immunochemical procedure.
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) [or 3 batches (unless otherwise justified) for biologicals] 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.

4.II.1.3 Change in manufacturing site of the final substance (including where relevant quality control testing sites) that belongs to the same group as already approved		**Conditions**	**Specific documentation**	**Type of change**
a)	Addition or replacement of a manufacturing site of a final substance which is part of the same company or group as the currently approved manufacturer	**1, 2, 3**	**1, 2, 3, 4**	**IN**
b)	Addition or replacement of a manufacturing site of the final substance which is part of the same company or group as the currently approved manufacturer but where different manufacturing conditions are used, which may have a potential to change important quality characteristics of the final substance, such as qualitative and/or quantitative impurity profile or a different route of synthesis which is not substantially different	**4**		**MAJ**

c)	Addition or replacement of a herbal drug preparation manufacturing site using the same or different plant production (i.e. cultivated or wild collection), which is part of the same company or group as the currently approved manufacturer	**4**	**1, 2, 5**	**MIN**
d)	Addition or replacement of a manufacturing site of a biological final substance which is part of the same company or group as the currently approved manufacturer	**4**	**1, 3, 4, 6**	**MAJ**
e)	Addition or replacement of a quality control testing site for the substance	**2, 5**	**1**	**AN**
f)	Addition or replacement of a sterilisation site for the final substance using a standard Ph. Eur. listed method of sterilisation	**1**	**1, 4, 6, 7**	**MIN**
g)	Introduction of a new (additional) site of micronisation	**1, 2, 6, 7**	**1, 2, 3, 4**	**IN**

Conditions

1.	The specifications and the route of synthesis (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. For herbal substances, the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal substance are the same as those already approved. The substance should already be sterile grade material.
2.	The final substance is not a biological substance or a sterile substance.
3.	Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with general monograph *Products with risk of transmitting Animal Spongiform Encephalopathies (1483)* unless reference to the general monograph is already mentioned on the current CEP.
4.	The specifications of the final substance are unchanged and/or the elemental impurities classified in ICH Q3D susceptible to be present are unchanged. If this condition is not met a separate application is needed.
5.	Method transfer from the current to the new site has been successfully completed.
6.	The particle size specification of the final substance and the corresponding analytical method remain the same and are already included on the CEP.
7.	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.	A declaration from the certificate holder that the starting material (specifications and analytical procedures) and the synthetic route, quality control procedures and specifications of the final substance and of the intermediate used in the manufacturing process of the final substance are the same as those already approved. For herbal substances, a declaration that the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal substance are the same as those already approved. 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.	A detailed comparison regarding specifications and critical quality attributes (e.g. for extracts: reference to the herbal starting material (incl. scientific binominal name and plant part), physical state, extraction solvent (nature and concentration), drug extract ratio (DER) and manufacturing process (including a stepwise comparison of all manufacturing steps in tabular format). .
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.
7.	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).

4.II.1.4 Change in the manufacturing process of an intermediate, the final substance, or starting materials for a biological final substance		**Conditions**	**Specific documentation**	**Type of change**
a)	Minor changes in the manufacturing process	**1, 2, 3, 4**	**1, 2, 3**	**AN**
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	**1, 3, 4**	**1, 2, 3, 4, 5**	**MIN**
c)	Major change in the manufacturing process likely to change the qualitative and/or quantitative impurity profile of the final substancealso including the introduction of a ‘telescoped process’ (where multiple chemical transformations are run without isolation of intermediates)	**1, 3**		**MAJ**
d)	For a sterile grade material change in the manufacturing process concerning the sterilisation step(s),			**MIN**
e)	Change in the geographical source of a herbal starting material and/or production of a herbal substance		**1, 2, 6, 7**	**MIN**
f)	Deletion of a manufacturing process	**5, 6**	**2**	**AN**
	Conditions			
1.	The specifications of the final substance or intermediates are unchanged. There is no adverse change in qualitative and quantitative impurity profile of the final substance.			

2.	For non-biological intermediates and final substance: 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. For herbal drug preparation, the geographical source, production of the herbal substance and the manufacturing route remain the same. For biological final substance/starting material/intermediate: the manufacturing steps remain the same and there are no changes to the manufacturing parameters (critical and non-critical PPs and IPCs) or to the specifications of the starting materials, intermediates, or final substance.
3.	The change does not result from unexpected events arising during manufacture and is not as a result of a safety or quality issue.
4.	The manufacturing process is not 'substantially different' from the approved one, or the specifications of the final substance are unchanged and/or no different elemental impurities classified in ICH Q3D are now potentially present and which changes the statement included on the certificate or in the RMS. If this condition is not met a separate CEP application is needed.
5.	The deletion should not be due to critical deficiencies concerning manufacturing.
6.	There should at least remain one manufacturing process, as previously approved.
Documentation	
1.	Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) of the final substance or intermediate as appropriate, manufactured according to the approved and proposed process.
2.	A direct comparison of the approved and the proposed process.
3.	A declaration from the Certificate holder that the specifications of the final substance are the same as those already approved.
4.	Specifications of the proposed source of the material.
5.	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).
6.	For herbal starting material supplier, a GACP declaration from the new supplier.
7.	A declaration from the CEP holder that an evaluation has been performed which should include a detailed comparison regarding quality determining process characteristics (e.g. for extracts: extraction time, temperature, pressure).

4.II.1.5 Change in batch size (including batch size ranges) of final substance or intermediate		**Conditions**	**Specific documentation**	**Type of change**
a)	An increase compared to the original approved batch size	**1, 2, 3, 4**	**1, 2**	**AN**
b)	Downscaling of the approved batch size	**1, 2, 3, 4, 5**	**1, 2**	**AN**
c)	The scale for a biological final substance/intermediate is increased / decreased without process change (e.g. duplication of line)		**1, 2**	**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.	The substance is not a biological substance or a sterile substance.
3.	The change does not affect the reproducibility of the manufacturing process.
4.	The specifications of the final substance/intermediates remain the same and the control strategy for impurities has been reviewed and remains appropriate.
5.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
Documentation	
1.	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.
2.	Batch analysis data (in a comparative tabulated format) on a minimum of two production batches of the final substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch analysis data of 3 batches (unless otherwise justified) for biological final substance, should be available for the proposed batch size.

4.II.1.6 Change to in-process controls applied during the manufacture of the final substance, intermediate of the final substance or starting materials for biological final substance		**Conditions**	**Specific documentation**	**Type of change**
a)	Minor change of in-process control limits	**1, 2, 3**	**1**	**AN**
b)	Addition of a new in-process control and limits with its corresponding analytical procedure	**1, 4**	**1, 2**	**AN**
c)	Deletion of a non-significant or obsolete in-process control	**1, 5, 6**	**3**	**AN**
d)	Widening of the approved in-process limits, which may have a significant effect on the overall quality of the final substance			**MAJ**
e)	Deletion of in-process test which may have a significant effect on the overall quality of the final substance			**MAJ**
f)	Change of an analytical procedure for an in-process control	**1, 3, 7, 8**	**1, 2**	**AN**
g)	Changes to a test procedure (including replacement or addition) for a biological substance or changes to a biological method		**1, 2**	**MIN**
h)	Replacement of an in-process control with its corresponding analytical procedure		**1, 2, 5**	**MIN**
Conditions				
1.	The change does not result from unexpected events arising during manufacture, and/or is not as a result of a safety or quality issue (e.g. new unqualified impurity detected, or a change in total impurity limits).			

2.	Any change should be within the range of currently approved limits.
3.	The analytical 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 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 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.
6.	The change is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).
7.	The new analytical procedure is not a biological/immunological/immunochemical procedure.
8.	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 starting materials/reagents/intermediates/final substance

4.II.2.1 Change in the specification attribute and/or acceptance criteria of a final substance, starting material/reagent/intermediate used in the manufacturing process of the final substance		**Conditions**	**Specific documentation**	**Type of change**
a)	Change within the specification acceptance criteria	**1, 2, 3**	**1**	**IN**
b)	Addition of a new specification attribute with its corresponding analytical procedure and acceptance criteria	**1, 4, 5, 6**	**1, 2, 3, 4**	**IN**
c)	Deletion of a non-significant or an obsolete specification attribute	**1, 7, 8**	**1, 5**	**AN**

d)	Deletion of a specification parameter which may have a significant effect on the overall quality of the final substance			**MAJ**
e)	Change outside of the specification acceptance criteria for the final substance			**MAJ**
f)	Change outside of the specification acceptance criteria for starting material/reagent/intermediate which may have a significant effect on the overall quality of the final substance			**MAJ**
g)	Change outside of the specification acceptance criteria for starting material/reagent/intermediate			**MIN**
h)	Addition of a specification parameter dealing with a new grade to be included on the certificate (e.g. a micronised material)		**1, 2, 3, 6, 7**	**MIN**
i)	Change of the analytical marker or widening of the acceptance criteria of the analytical marker (other extracts) for a herbal substance.			**MIN**
j)	Change in the testing of specification attribute of the substance, from routine to skip/periodic testing and vice versa		**8**	**MIN**
k)	Replacement of a specification attribute with its corresponding analytical procedure			**MIN**

Conditions

1.	The change does not result from unexpected events arising during manufacture and is not as a result of a safety or quality issue (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.	For any material the change does not concern a genotoxic impurity (including nitrosamines). If it involves the final substance, other than for residual solvents which must be in line with ICH limits, any new impurity control should be in line with the Ph. Eur.
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The route of synthesis of the final substance remains unchanged.
7.	The change is not related to a revision of the control strategy with an intention to minimize testing of parameters and attributes (critical or non-critical).
8.	The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is not used in the manufacture of the final substance), any critical physical characteristics e.g. particle size, bulk or tapped density, polymorphism, identity test, water content

Documentation

1.	Comparative table of current and proposed specifications.
2.	Details of any new analytical method and validation data, where relevant.
3.	Batch analysis data on two production batches [3 production batches (unless otherwise

	justified) for biologicals]) of the relevant substance for all specification attributes
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 is non-significant or that the specification attribute is obsolete. guidance.
6.	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).
7.	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.
8.	Justification from the Certificate holder for the change in the testing of specification attribute. A change from routine testing to skip/periodic testing is warranted when the manufacturing process is under control and supported by sufficient amount of historical data compliant with the specification or as foreseen by relevant guidelines. A change from skip/periodic testing to routine testing should be supported by analytical data demonstrating failure to meet the approved acceptance criteria for the skip tested specification.

4.II.2.2 Change to analytical procedure for the final substance or starting material/reagent/intermediate used in the manufacturing process of the final substance		**Conditions**	**Specific documentation**	**Type of change**
a)	Minor changes to a analytical procedure for a starting material/reagent/intermediate or the final substance.	**1, 2, 3**	**1, 2**	**AN**
b)	Minor changes to an analytical procedure description appended to a CEP	**1, 2, 3**	**3**	**IN**
c)	Other change to an analytical procedure (including replacement or addition) for the final substance		**1, 2, 3**	**MIN**
d)	Other change to an analytical procedure (including replacement or addition) for a starting material/reagent/intermediate	**1, 2, 4, 5**		**MIN**
e)	Deletion of an analytical procedure for the final substance, if an alternative procedure is already authorised	**6**		**AN**
f)	Introduction, replacement or change to a biological/immunological/immunochemical analytical procedure for starting material /reagent /intermediate, used in the manufacturing process of a final substance		**1, 2, 3**	**MIN**
g)	Introduction, replacement or substantial change to a biological/immunological/immunochemical analytical procedure for a final substance and which is not foreseen in the Ph Eur monograph.			**MAJ**
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.	Any new analytical procedure 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 include standard pharmacopoeial microbiological methods).
6.	An alternative analytical procedure is already approved for the specification attribute.
Documentation	
1.	Description of the analytical method and revised specifications.
2.	Comparative validation results, or if justified comparative analysis results showing that the current analytical procedure and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure unless the new analytical procedure is added as an alternative procedure to a current one.
3.	When relevant updated description of the method in a format to be appended to the certificate of suitability.

4.II.2.3 Change to an in-house reference standard/preparation for a biological active substance	**Conditions**	**Specific documentation**	**Type of change**
a) Replacement of an in-house reference standard/preparation not covered by an approved qualification protocol (1)			**MAJ**
b) Replacement of an in-house reference standard/preparation not covered by an approved qualification protocol, where comparability test results using current and proposed reference standard/preparation material are available		**1, 2**	**MIN**
c) Introduction of a qualification protocol for the preparation/replacement of an in-house reference standard or preparation (2)			**MAJ**
d) Substantial change to the qualification protocol for the preparation/replacement of an in-house reference standard or preparation which may have a significant impact on the quality, safety or efficacy of the active substance			**MAJ**
e) Other change to the qualification protocol for the prepartation/replacement of an in-house reference standard or preparation		**1**	**MIN**
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format),			

	including a description of the manufacturing and qualification of the new in-house reference standard.
2.	Comparative test results, showing that the current in-house reference standard and the proposed one are equivalent.
	(1) Note: Other changes to or with respect to an in-house reference standards /preparations, not covered by an approved protocol, should be classified in analogy to respective changes affecting the biological active substance/finished product. (2) Note: Upon approval of the variation for the qualification protocol, the introduction of a new reference standard for a biological active substance/finished product or the extension of its re-test period/storage period, according to the approved qualification protocol will be covered by the existing quality assurance system and hence, there will be no need to file a variation as long as all approved acceptance criteria are met.

4.II.2.4 Introduction or modification of a risk assessment or change in format of certificate	**Conditions**	**Specific documentation**	**Type of change**
a) Introduction or change of a RMS (Risk management summary) regarding elemental impurities		**1**	**MIN**
b) Introduction or change of a nitrosamine risk assessment		**2**	**MIN**
c) Switch to CEP 2.0		**3**	**MIN**
Documentation			
1. Risk management discussion and summary for elemental impurities.			
2. Risk-assessment from the Certificate holder in accordance with the relevant EU documents.			
3. Updated sections 3.2.S.4.1 and 4.2 in accordance with relevant guidance documents.			

4.II.3 Container closure system

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

4.II.3.2 Change in the specification attribute and/or acceptance criteria of the immediate packaging of the final substance		**Conditions**	**Specific documentation**	**Type of change**
a)	Change of specification acceptance criteria	**1, 2, 3**	**1**	**AN**
b)	Addition of a new specification attribute with its corresponding analytical procedure	**1, 4**	**1, 2, 3**	**AN**
c)	Deletion of a non-significant or obsolete specification attribute	**1, 5**	**1, 3**	**AN**
d)	Replacement of a specification attribute with its corresponding analytical procedure		**1, 2**	**MIN**
Conditions				
1.	The change does not result from unexpected events arising during manufacture of the packaging material or because of stability concerns during storage of the final substance, and is not as a result of a safety or quality issue.			
2.	Any change should be within the range of currently approved acceptance criteria.			

3.	The analytical procedure remains the same, or changes in the analytical procedure are minor.
4.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way. The analytical procedure remains the same, or changes in the analytical procedure are minor .
5.	The change is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).
Documentation	
1.	Comparative table of current and proposed specifications.
2.	Details of any new analytical procedure and validation data, where relevant.
3.	Justification of the new specification attribute and the acceptance criteria.

4.II.3.3 Change in analytical procedure for the immediate packaging of the substance	**Conditions**	**Specific documentation**	**Type of change**
a) Minor change to an approved analytical procedure criteria	**1, 2, 3**	**1**	**AN**
b) Other change to an analytical procedure (including replacement or addition)	**1, 3**	**1**	**AN**
c) Deletion of an analytical procedure if an alternative procedure is already approved	**4**	**1**	**AN**

Conditions	
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former procedure.
2.	The analytical procedure should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
3.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
4.	There is still an analytical procedure registered for the specification attribute. The analytical procedure remains the same, or changes in the analytical procedure are minor .
Documentation	
1.	Comparative validation results or if justified comparative analysis results showing that the current analytical procedure and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure.

4.II.3.4 **Change of a secondary packaging component of the final substance (including replacement, addition or deletion), when mentioned in the dossier**	**Conditions**	**Specific documentation**	**Type of change**
a) Composition	**1, 2, 3, 4**	**1**	**AN**
b) Specification	**1, 2, 3, 4**	**1**	**AN**

Conditions	

1.	The secondary packaging does not play a functional role on the stability of the final substance, or if it does, it is not less protective than the approved one.
2.	The changed packaging component must be adequate for the storage of the substance at the approved conditions
3.	The change should not be due to critical deficiencies of the former packaging component.
4.	The change is not a result of any unexpected events arising during manufacture or because of stability concerns during storage of the final substance.
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 when mentioned on the certificate	**Conditions**	**Specific documentation**	**Type of change**
a) Removal or reduction of an approved re-test period	**1**	**1, 2, 3**	**IN**
b) Addition of a re-test period for the final substance and/or change in the storage conditions for the final substance		**1, 2, 4**	**MIN**
c) Extension of the re-test period based on extrapolation or stability modelling not in accordance with relevant stability guidelines			**MAJ**
d) Extension of re-test period supported by real time data not in accordance with an approved stability protocol or an extension based on extrapolation of stability data in accordance with relevant stability guidelines	**1**	**1, 3**	**MIN**
e) Extension of a re-test period/storage period supported by real time data fully in line with the stability protocol	**2**	**1, 2**	**IN**
f) Change to more restrictive storage conditions	**1, 3**	**1, 2**	**AN**
g) Change to an approved stability protocol	**1, 4**	**1, 4**	**AN**

Conditions	
1.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
2.	Stability studies have been performed in accordance with a currently approved stability protocol. Real time data are submitted. All batches meet their pre-defined specification at all time points. No unexpected trends have been observed.
3.	The physical state of the substance has not changed.
4.	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	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format). This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on three pilot or production scale batches of the substance or intermediate in the approved packaging material.
2.	Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.
3.	Justification for the proposed changes and updated stability protocol. 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.	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.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	**Conditions**	**Specific documentation**	**Type of change**
a) New design space for one or more unit operations in the manufacturing process of the final substance including the resulting in-process controls and/or analytical procedures		**1, 2**	**MAJ**
b) New design space (method operable design range (MODR)) for an analytical procedure for a starting material/reagent/ intermediate or the final substance		**1, 2**	**MIN**
c) Changes to, or extension of, an approved design space for the final substance and/or an analytical procedure for a starting material/reagent/intermediate		**1, 2**	**MIN**
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.			

4.II.5.2 Introduction of a post approval change management protocol (PACMP) related to the final substance	**Conditions**	**Specific documentation**	**Type of change**
		1, 2	**MAJ**

Documentation
1. Detailed description for the proposed change.
2. Change management protocol related to the final substance.

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

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) Implementation of changes foreseen in a PACMP via AN notification	**1**	**1, 2**	**AN**
b) Implementation of changes foreseen in a PACMP via Type IN notification	**2**	**1, 2, 3**	**IN**
c) Implementation of changes foreseen in a PACMP via a minor change		**1, 2, 3**	**MIN**
Conditions			
1. The proposed change has been performed fully in line with the approved change management protocol which requires its notification within 12 months following implementation.			
2. The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.			

Documentation	
1.	Reference to the approved change management protocol.
2.	Declaration that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol (*).
3.	Results of the studies performed in accordance with the approved change management protocol.
	Note: (*) In case the acceptance criteria and/or other conditions in the protocol are not met, the change cannot be implemented as a revision of this category and should instead be submitted as variation of the applicable category without PACMP

4.II.5.6 Introduction of a product lifecyclemanagement document (PLCM) related to the final substance	**Conditions**	**Specific documentation**	**Type of change**
		1, 2	**MAJ**
Documentation			
1.	The content of the product lifecycle management document 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, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic understanding of how material attributes and process parameters impact the critical quality attributes of the substance has been achieved		
2.	The product lifecycle management document includes a description of the material attributes, quality attributes and process parameters (or analytical procedure parameters), their proposed limits and ranges, and future variation reporting categories, in a tabular format.		

4.II.5.7 Changes related to the final substance in line with an approved product lifecycle management document (PLCM)		**Conditions**	**Specific documentation**	**Type of change**
a)	Major change to the final substance in line with an approved PLCM		**1, 2**	**MAJ**
b)	Minor change to the final substance in line with an approved PLCM	**1**	**1, 2**	**AN**
c)	Minor change to the final substance in line with an approved PLCM	**2**	**1, 2**	**IN**
d)	Minor change to the final substance in line with an approved PLCM		**1, 2**	**MIN**
Conditions				
1.	The change has been foreseen in the product lifecycle management document as a Type IA variation requiring notification within 12 months following implementation			
2.	The change has been foreseen in the product lifecycle management document as a Type IA_{IN} variation requiring immediate notification following implementation			

Documentation
1. A summary and justification of the proposed change(s), clearly describing the present and proposed situation and supporting documentation.
2. An updated product lifecycle management document (PLCM) with relevant sections modified.

4.II.5.8 Changes to an approved an approved product lifecycle management document (PLCM) related to the final substance	**Conditions**	**Specific documentation**	**Type of change**
a) Major changes to an approved PLCM			**MAJ**
b) Minor changes to an approved PLCM		**1, 2**	**MIN**
Documentation			
1. A summary and justification of the proposed change(s), clearly describing the present and proposed situation and supporting documentation.			
2. An updated product lifecycle management document (PLCM) with relevant sections modified.			

4.III. CHANGES TO TSE CEPs

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 in the source of a TSE risk material, or introduction of a 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 company or 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 alkaline 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 new or updated CEP or deletion for a starting material orintermediate sed in the manufacturing process of the final substance		**Specific documentation**	**Type of change**
a) New CEP including replacement or addition	**1, 2, 3, 4**	**1, 2, 3**	**IN**
b) Updated CEP for a starting material	**1, 2, 3, 4**	**1, 2, 3**	**AN**
c) Updated CEP for an intermediate	**1, 2, 3, 4**	**1, 2, 3**	**IN**
d) A deletion of a CEP used to describe a material when multiple sources of material are used	**5**	**2**	**AN**
e) 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 manufacturing process of the starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required, or if it does, the update of the CEP/TSE Certificate is only due to administrative changes.	
4. The final substance specification for impurities is unchanged. This applies to organic impurities, residual solvents, mutagenic impurities (including nitrosamines) and elemental impurities. Tightening of impurity limits, changes to specifications for impurities according to the Ph. Eur. and/or residual solvents according to ICH Q3C, are excluded.	
5. At least one manufacturer for the same substance remains in the dossier.	
Documentation	
1.	Copy of the current CEP for the material with the box of access completed appropriately, or letter of access provided.
2.	For a starting material the details of the site of manufacture of the starting material should be provided in the section “3.2.S.2.3 Control of materials” of the dossier. For an intermediate 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.
3.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) 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, or letter of access provided.			

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. This applies for substances for human and veterinary only use.

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**	**Renewal**
b) Changes are included in the request for renewal	**1**	**2, 3, 4, 5**	**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. An updated dossier in CTD format and/or updated sections affected by the changes.			
4. List of changes introduced in the format of a comparative table (i.e. approved text vs proposed text).			
5. 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.

7. SUBSTANCES FOR VETERINARY USE ONLY

For substances for veterinary use only certain changes do not require assessment and should be submitted as either an annual notification (AN) or immediate notification (IN). They are classified s shown below. If corresponding conditions are not met or for any other change not listed below the classification for substances for human use applies.

	Conditions	Specific documentation	Type of change
7.I.1 Deletion of:			
a) a manufacturing site for a final substance, or intermediate, testing site, or supplier of a starting material for a final substance or a reagent (when mentioned in the dossier)	**1**		**AN**
b) a manufacturing process for the final substance including an intermediate used in the manufacture of the final substance when an alternative is already approved	**2**		**AN**
c) a non-significant in-process test during the manufacture of the final substance (e.g. deletion of an obsolete in-process test)	**3**	**1**	**AN**
d) a non-significant specification parameter (e.g. deletion of an obsolete parameter) of a final substance, a starting material, an intermediate or reagent used in the manufacturing process of the final substance	**3**	**1**	**AN**
e) an analytical procedure for the final substance or a starting material, reagent or intermediate of the final substance or for the immediate packaging of the final substance	**4**		**AN**
f) a non-significant specification parameter (e.g. deletion of an obsolete parameter) in the specification parameters or limits of the immediate packaging of the final substance	**5**	**1**	**AN**
g) an approved change management protocol related to the final substance	**6**		**AN**
h) details on testing frequency of a final substance or of packaging material for the immediate packaging of a final substance,			**AN**

when mentioned in the dossier			
7.I.2 Change in the manufacturer of a starting material, reagent or intermediate used in the manufacturing process of the final substance or change in the manufacturer of the final substance if part of the same group.			
a) change in a manufacturer (including relevant testing sites) that is part of the same group as the currently approved manufacturer	**7**	**2**	**IN**
b) changes to quality control testing arrangements for the final substance: replacement or addition of a site where batch control or testing of the final substance takes place	**8**		**AN**
c) Introduction of a new site of a micronisation when a grade is already mentioned on the certificate	**9**	**3**	**IN**
d) new storage site of Master Cell Bank or Working Cell Banks	**10**		**AN**
7.I.3 Reduction of re-test period or change to more restrictive storage conditions when mentioned on the certificate	**11**		**IN**
7.I.4 Change to an approved stability protocol when there is a retest period mentioned on the certificate	**12**	**4**	**AN**
7.I.5 Implementation of changes foreseen in an approved change management protocol (CMP)	**13**		**AN**
7.I.6 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance			
a) up to 10-fold increase compared to the originally approved batch size	**14**	**5**	**AN**
b) downscaling down to 10-fold	**15**	**5**	**AN**
c) more than 10-fold increase compared to the originally approved batch size	**16**	**5**	**AN**
7.I.7 Change to in-process tests or limits applied during the manufacture of the final substance			
a) tightening of in-process limits	**17**	**5**	**AN**
b) addition of a new in-process test and limits	**18**	**5**	**AN**
7.I.8 Change in the specification parameters or limits of the final substance, starting material, intermediate or reagent used in the manufacturing process of the final substance or of the immediate packaging of the active substance	**19**	**6**	**AN**

7.I.9 Tightening of specification limits of the final substance, starting material, intermediate or reagent used in the manufacturing process of the final substance	**20**	**6**	**AN**
7.I.10 Addition of a new specification parameter to the specification with its corresponding analytical procedure for an active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance	**21**	**6**	**IN**
7.I.11 Addition of a new specification parameter to the specification with its corresponding analytical procedure for the immediate packaging of the active substance	**22**	**6**	**AN**
7.I.12 Minor changes:			
a) to an approved analytical procedure for the final substance or a starting material, reagent or intermediate used in the manufacturing process of the final substance or to an approved analytical procedure for an in-process test for the final substance	**23**	**7**	**AN**
b) to an approved analytical procedure for the immediate packaging of the final substance	**24**	**7**	**AN**
c) in the manufacturing process of the final substance	**25**	**8**	**AN**
d) to an approved change management protocol of the final substance that does not change the strategy defined in the protocol	**26**		**AN**
e) to production equipment (when described in the dossier) including processes related to the equipment	**27**		**AN**
7.I.13 Changes to an analytical procedure (including replacement or addition):			
a) for a reagent used in the manufacturing process of the final substance but which does not have a significant effect on the overall quality of the final substance	**28**	**9**	**AN**
b) for the immediate packaging of the final substance			**AN**
c) Change in qualitative or quantitative composition of the immediate packaging for the final substance	**29**	**10**	**AN**
7.I.14 Submission of a CEP for a starting material used in the manufacturing process of the final substance			
a) Updated certificate	**30**		**AN**
b) New certificate	**31**		**AN**
7.I.15 Submission of a CEP for an intermediate			

used in the manufacturing process of the final substance			
c) A revised version of a CEP already referenced to describe a material, when the manufacturing sites mentioned on this CEP are unchanged	**31**		**AN**
d) A revised version of a CEP already referenced to describe a material, when the manufacturing sites mentioned on this CEP are changed	**32**		**IN**

Conditions
1. The deletion shall not be due to critical deficiencies concerning manufacturing. There shall be at least remain one manufacturing site, as previously approved, performing the same function as the one(s) concerned by the deletion.
2. The final substance, intermediates or in-process materials used in the manufacture of the final substance shall still conform to the approved specifications.
3. The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical in-process test and shall not have the potential to affect the identity, quality, purity, potency or physical characteristics of the final substance and of starting material, intermediate or reagent used in the manufacturing process of the final substance.
4. An alternative analytical procedure shall already be approved in the file and this analytical procedure has not been added through a variation procedure according to Article 61 of Regulation (EU) 2019/6.
5. The change shall not relate to a commitment or to an unexpected event during manufacture of the immediate packaging material and storage of the final substance. The change shall not concern a critical parameter or have the potential to affect the identity or quality of the immediate packaging.
6. The change shall not be the result of an unexpected event or an out of specification result during the implementation of the change(s) described in the protocol.
7. The change shall not be applicable to a sterile substance or a biological substance. For starting materials and reagents the specifications (including in-process controls, methods of analysis of all materials), shall be identical to those already approved. For intermediates and final substance the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis shall be identical to those already approved. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with general monograph *Products with risk of transmitting Animal Spongiform Encephalopathies (1483)* unless reference to the general monograph is already mentioned on the current CEP.
8. The change shall not be applicable to a sterile substance or a biological substance. Method transfer from the former to the new site shall have been successfully completed.
9. The change shall not be applicable to a sterile final substance or a biological substance. The change shall not provoke an adverse change in physico-chemical properties. The particle size specification for the final substance and the corresponding analytical procedures shall remain the same.
10. No change shall be made to the storage conditions, the retest period and the specifications.
11. The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.
12. The change shall not be the result of unexpected events arising during manufacture or because of stability concerns. The change shall not have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the final substance.
13. The change shall be in accordance with the approved CMP and the results of studies performed indicate that the predefined acceptance criteria specified in the protocol are met. The implementation of the change shall require no further supportive data to the CMP.

14.The change shall not be applicable to a sterile final substance. The final substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications
15. The change shall not be the result of unexpected events arising during manufacture or because of stability concerns
16. The change shall not be applicable to a sterile final substance. The intermediates, reagents, catalysts or solvents used in the process shall remain the same. The final substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications. The change shall not provoke an adverse change in qualitative and quantitative impurity profile, or in physico-chemical properties of the final substance.
17. The change shall be within the range of currently approved limits. The analytical procedure shall remain the same, or changes in the analytical procedure shall be minor.
18. Any new analytical method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological substance, except if this method is a standard pharmacopoeial microbiological method
19. The change shall not result from unexpected events arising during manufacture or storage (e.g. new unqualified impurity or change in total impurity). The change shall not be a consequence of any commitment from previous assessments to review specification limits) unless it has been previously assessed and agreed as part of a follow-up measure in a previous procedure under Regulation (EU) 2019/6.
20. The test procedure shall remain the same, or changes in the analytical procedure shall be minor. The change shall be within the range of currently approved limits.
21. The new analytical method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological substance, except if this method is a standard pharmacopoeial microbiological method. The change shall not concern a mutagenic impurity. If it involves the final active substance, other than for residual solvents which shall be in line with ICH/VICH limits, any new impurity control shall be in line with the Ph. Eur..
22. The new analytical method shall not concern a novel non-standard technique or a standard technique used in a novel way.
23. The analytical method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods). Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure. There shall be no changes of the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
24. Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method). Any new analytical method shall not concern a novel non-standard technique or a standard technique used in a novel way.
25. The change shall not provoke an adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. 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. The specifications of the final substance or intermediates are unchanged.
26. The intermediates, reagents, catalysts or solvents used in the process shall remain the same. The final substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications. There shall be no adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. The changes shall be within the range of currently approved limits.
27. The change shall not result in any changes or modifications of the production process or quality of the final substance
28. There shall be no changes to the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

29. Sterile, liquid or biologicalfinal substances shall be excluded. The new packaging material shall be at least equivalent to the approved material in respect of its relevant properties. Relevant stability studies have been started under VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the 3 months' stability data do not yet have to be available. These studies shall be finalised and the data shall be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).
30. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and substance specific requirements (e.g. particle size profiles, polymorphic form), if applicable. The manufacturing process of the starting material shall not include the use of material from human or animal origin, or if it does, any information in relation to material from human or animal origin shall remain unchanged.
31. The manufacturing process of the intermediate shall not include the use of material from human or animal origin.
Documentation
1. Comparative table of former and new in-process test.
2. TSE data as appropriate. Batch analysis data for at least two batches (minimum pilot scale).
3. Batch analysis data for at least two batches (minimum pilot scale).
4. Results of appropriate real time stability studies.
5. Test results of at least two batches in accordance with the specifications for the proposed batch size.
6. Comparative table of former and new in-process tests and limits.
7. Description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable). Comparative validation results, or if justified comparative analysis results showing that the current method and the proposed one are equivalent.
8. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) manufactured in accordance with the currently approved and proposed process.
9. Amendment of the relevant section(s) of the dossier and comparative validation data, as appropriate. In the absence of comparative validation data, if justified, comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure.
Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O2, CO2 moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or Union legislation on plastic materials and objects in contact with foodstuffs. Where appropriate, proof shall 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). Comparative table of former and new immediate packaging specifications, permeability data and interaction data, as appropriate.