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Certification of suitability of Monographs of the European Pharmacopoeia

Guideline on Requirements for Revision/Renewal of Certificates

(Revision of the Annex XI to Resolution AP-CSP (93) 5 as amended)

Strasbourg

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CERTIFICATE OF SUITABILITY
TO THE MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

**GUIDELINE ON REQUIREMENTS FOR REVISION/RENEWAL OF CERTIFICATES
(former Appendix XI to Resolution AP-CSP (99) 4)**

Date of implementation: 1 September 2004

The holder of a Certificate of suitability shall inform the EDQM of any change in the information included in the certification dossier by sending an application form and all necessary documents demonstrating that the conditions laid down in the present guideline are met.

Classification of changes

The changes have been classified in three categories (notification/minor/major) depending on the potential impact of the change on the quality of the final substance. These three categories are based on those (IA/IB/II) of the Commission Regulation (EC) No 1084/2003 concerning the examination of variations to the terms of marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State and the Commission Regulation (EC) No 1085/2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93.

Any change not classified as a notification or a minor change should be classified as a major change except in the following cases where a new application should be submitted:

- addition of a new route of synthesis and/or a new manufacturing site where the specifications of the final substance are different
- transfer to a new holder that is not the same legal entity as the current one, where the transfer does not occur because of a merger or because the company is sold, and where the manufacturer does not take out the Certificate of suitability in their own name.

The changes related to Ph. Eur. monograph revisions or any other regulatory requirements are treated separately and generally initiated by the EDQM.

Documentation to be provided

For any change the documentation consists in:

- a justification of the change
- the application form duly filled in and enclosing a comparative list of updated sections/pages of the dossier
- the specific documents described below for each change

Each time batch data are needed they should be in accordance with the specifications of the current Ph. Eur. monograph and when relevant with the additional requirements included in the Certificate of suitability. 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.

The changes are presented in four sections:

- Notifications (N)
- Minor revisions for Certificates of suitability for chemical purity and microbiological quality (R) and minor revisions for TSE Certificates of suitability (T)
- Major revisions
- Quinquennial renewals

NOTIFICATIONS

N1) Change in the name and/or address of the certificate holder or the manufacturer of the final substance

Conditions:

- the certificate holder/manufacturer shall remain the same legal entity (except where the company is sold or in case of a merger).

Documentation:

- a formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or the new address is mentioned
- all updated declarations (see application form)

N2) Change in the name and/or address of the manufacturing site

Conditions: the location of the manufacturing site shall remain the same.

Documentation:

- a formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or the new address is mentioned
- updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected

N3) Deletion of any manufacturing site

Conditions: none

Documentation: none apart from a justification of the deletion

N4) Deletion of a manufacturer of any intermediate/starting material

Conditions: none

Documentation □ none apart from a justification of the deletion

N5) Change in batch size of final substance or intermediate up to 10-fold compared to the original batch size

Conditions:

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

Documentation

- the batch numbers of the tested batches having the proposed batch size
- updated description of the process specifying the new batch size

N6) Change in batch size of final substance or intermediate: downscaling

Conditions:

- any changes to the manufacturing methods are only those necessitated by the downscaling, e.g. use of different-sized equipment
- test results of at least two batches complying with the approved specifications should be available for the proposed batch size
- the substance is not a biological substance or a sterile substance
- the change does not affect the reproducibility of the manufacturing process
- the change should not be the result of unexpected events arising during manufacture or because of stability concerns

Documentation

- the batch numbers of the tested batches having the proposed batch size
- updated description of the process specifying the new batch size

N7) Minor changes to a test procedure for the final substance or a starting material/intermediate/reagent used in the manufacturing process of the final substance

Conditions:

- 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); no new impurities are detected

- appropriate (re-)validation studies have been performed in accordance with relevant guidelines
- results of method validation show the new test procedure to be at least equivalent to the former procedure
- the final substance, starting material, intermediate or reagent is not a biological substance.

Documentation:

- updated description of the method

N8) Tightening of the specification limits for the final substance, a starting material/intermediate/reagent used in the manufacturing process of the final substance

Conditions:

- the change should not be the result of unexpected events arising during manufacture
- any change should be within the range of currently approved limits
- when the change regards the specifications of the final substance it must comply with the tightened specifications throughout its period of use

Documentation

- comparative table of current and proposed specifications

N9) Change in the code product/reference number and/or in the brand name of the final substance or any material used in the synthesis of the substance

Conditions:

- the change does not regard the quality of the final substance or the concerned material

Documentation:

- current and proposed code product / reference number / brand name

N10) Amendment to stability data further to a commitment at the time of granting of the Certificate of suitability

Conditions:

- no out-of-specification results should have been observed during the stability study

Documentation:

- table of updated results

N11) Removal of the re-test period from the Certificate of suitability

Conditions:

- the change should not be the result of unexpected events arising during manufacture or because of stability concerns

Documentation: none apart from the justification of the removal

N12) For a Certificate for TSE risk, deletion of a source country or change in source of a material used in the preparation of the final substance from a TSE risk material to a vegetable or synthetic material

Conditions:

- no change in the manufacturing process

Documentation

- if applicable a declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin

MINOR CHANGES FOR CERTIFICATES FOR CHEMICAL PURITY AND MICROBIOLOGICAL QUALITY

R1) Minor change in the manufacturing process of the substance

Conditions:

- no change in qualitative and quantitative impurity profile (including related substances, residual solvents, residual catalysts) or in physico-chemical properties
- the substance is not a biological substance
- the change does not regard the sterilisation step(s) if any
- the synthetic route remains the same, i.e. intermediates remain the same. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.

Documentation:

- direct comparison of the present process and the proposed process
- batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the present and proposed process
- demonstration that the change has no impact on the quality of the substance

R2) Change in batch size of the substance or an intermediate more than 10-fold compared to the original batch size

Conditions:

- any changes to the manufacturing methods are only those necessitated by scale-up, e.g. use of different-sized equipment
- the substance is not a biological substance or a sterile substance
- the change does not affect the reproducibility of the manufacturing process

Documentation

- updated description of the process specifying the new batch size
- batch analysis data (in comparative tabular format) on a minimum of two production batches manufactured according to both the current and the proposed sizes. Batch data on the next two full production batches should be available upon request and reported by the certificate holder if outside specification (with proposed action).
- a commitment to provide updated stability study results demonstrating the compliance of the batches of the up-scaled size with the approved specifications when a re-test period is mentioned on the Certificate of suitability

R3) Specification of the final substance/intermediate/reagent used in the synthesis of the final substance: addition of a new test parameter or changes to or replacement of a test procedure

Conditions:

- any change should not be the result of unexpected events arising during manufacture
- any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
- any new test procedure should have been appropriately (re-)validated in accordance with relevant guidelines results of method validation and should have been shown to be at least equivalent to the former procedure
- the final substance is not a biological substance
- the change does not affect tests for sterility or bacterial endotoxins
- test results of at least two batches of the final substance manufactured using the concerned starting material/intermediate and complying with its approved specifications should be available

Documentation:

- comparative table of current and proposed specifications
- details of any new analytical method and validation results showing that the current method and the proposed method are at least equivalent
- batch analysis data on two production batches of the final substance for all tests in the new specifications
- a commitment to provide updated stability study results demonstrating the compliance with the changed specifications when a re-test period is mentioned on the Certificate of suitability

R4) Change in the manufacturer or addition of a new manufacturer of a starting material or intermediate used in the manufacturing process of the final substance

Conditions:

- the specifications and the route of synthesis (including solvents used) of the concerned material are identical to those already approved
- the final substance, starting material or intermediate is not a biological substance
- when the change regards the manufacturer of a key intermediate test results of at least two batches of the concerned key intermediate and complying with its approved specifications should be available

Documentation

- a declaration from the holder of the Certificate of suitability that the specifications of the final substance are the same as those already approved
- a declaration from the holder of the Certificate of suitability that the synthetic route, the specifications and the quality control procedures of the starting material or intermediate are the same as those already approved
- batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the current and the proposed sources of the starting material or intermediate

R5) For a “double” Certificate of suitability (for chemical purity and microbiological quality and for TSE risk), change in source of a material used in the preparation of the final substance from a TSE risk material to a vegetable or synthetic material

Conditions:

- no change in the manufacturing process
- the specifications of the final substance remain the same
- the final substance is not a biological substance

Documentation

- updated specifications of the new source of the material
- batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the current and proposed source of the material or intermediate
- a declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin

R6) Change in the manufacturing site or addition of a new manufacturing site for the final substance

Conditions:

- the quality control specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved
- the final substance is not a biological substance or a sterile substance

Documentation

- a declaration from the holder of the Certificate of suitability that the synthetic route, quality control procedures and specifications of the final substance are the same as those already approved
- batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the final substance from the current and the proposed sites
- updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected

R7) Change in the re-test period of the final substance and/or the storage conditions for the final substance when a re-test period is already mentioned on the Certificate of suitability or request to include a re-test period on the Certificate of suitability

Conditions:

- stability studies have been done in accordance with relevant guidelines
- the change should not be the result of unexpected events arising during manufacture or because of stability concerns
- the final substance is not a biological substance.

Documentation:

- results or updated results of the stability studies for at least two pilot or production scale batches

MINOR CHANGES FOR TSE CERTIFICATES

T1) Change in the manufacturing site

Conditions:

- no change in the manufacturing process and in the materials and in the origin of the material used in the process
- no other TSE risk material is processed in the new manufacturing site

Documentation

- a declaration from the holder of the Certificate of suitability that the manufacturing process is strictly identical to that already approved
- a declaration from the manufacturer that no other TSE risk material is processed in the new manufacturing site
- updated declarations of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected
- information on the quality assurance system (including traceability) applied in the new manufacturing site

T2) Minor change in the manufacturing process (including process parameters) or in the specifications of the final substance

Conditions:

- the change has no impact on the TSE risk
- the TSE Certificate of suitability does not cover the chemical purity and the microbiological quality

Documentation

- updated description of the process
- a declaration from the manufacturer that the change has no impact on the TSE risk

T3) Change in the quality assurance system applied in the manufacturing site

Conditions:

- the new quality assurance system is at least equivalent to the former one
- no change in the manufacturing process (including process parameters) or in the specifications of the final substance

Documentation

- updated information on the quality assurance system (including traceability)
- updated declaration of manufacture in accordance with the dossier and according to GMP rules and of willingness to be inspected

MAJOR CHANGES

For a certificate for chemical purity and microbiological quality

Documentation

- batch analysis data of at least three batches (minimum pilot scale)

- fully updated information related to the change(s) and any consequential changes including updated stability data if applicable

For a certificate for TSE risk

Documentation

- fully updated information related to the change(s) and any consequential changes

Note: a transfer of the ownership of the Certificate of suitability (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) is feasible in exceptional cases with the below conditions:

- the current Certificate of suitability is held by another company than the manufacturer (e.g. a broker or trader)
- the manufacturer takes out the Certificate of suitability in their own name

In such a case the request is a major change and the documentation to be provided is similar to that for the Notification N1 (Change in the name and/or address of the certificate holder or the manufacturer of the final substance). The documentation to be provided should be completed by a letter signed by both parties, i.e. the former holder and the manufacturer, agreeing that the ownership of the Certificate of suitability is passed on to the manufacturer from the date of the request.

QUINQUENNIAL RENEWAL

When there is no change to the certification dossier the Certificate of suitability remains valid for five years from the date of first issuing. Six months prior to expiry date and regardless of any revisions treated in the meantime, the holder of a Certificate of suitability shall ask for the quinquennial renewal of the Certificate of suitability by providing an update of the certification dossier. If no change has occurred since the issuing of the last revision of the Certificate of suitability, at the very least a statement should be provided that no changes that may affect the quality, safety or efficacy of the substance have been made and certificates of analysis from at least two recent production batches should be provided. Furthermore, a completed application form including the relevant updated declarations as well as samples of the substance (for Certificates of suitability for chemical purity and microbiological quality only) should be submitted.