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Certification of Suitability to Monographs of the European Pharmacopoeia

Guidance on applications for «sister files»

Implementation	January 2019

I. Purpose

This guideline provides information on the scope and applicability of the sister files procedure within the Certification scheme.

II. Scope

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

An applicant who has been granted a certificate of suitability (CEP) may wish to apply for a second CEP for the same substance, either because it is not possible to apply for a revision of the CEP or because the applicant wishes to have separate CEPs for different conditions of preparation or qualities (for example, to cover an alternative manufacturing process, manufacturing site or an alternative grade).
This new application can be submitted as a "sister file", provided that the conditions listed in this guideline are fulfilled.

Assessment of this type of dossier focuses on the differences declared compared to the approved reference CEP dossier (hereafter termed as the 'CEP dossier referred to').

- Sterile and TSE CEPs are outside the scope of this procedure and are treated according to the standard rules for new applications. As a consequence, double certificates (covering chemical and TSE aspects) are also excluded from the procedure, except when the differences are only related to the chemical part.

III. Conditions

The application for a sister file requires the following conditions to be fulfilled:

- The substance is the same (complies with the same monograph, including its definition section) as that covered by the CEP dossier referred to and is obtained by the same means.

- The CEP dossier referred to has already been approved by the EDQM and the corresponding CEP **has been granted and is valid.** Moreover, the CEP dossier referred to cannot itself have been approved through the procedure for sister files.

- The holder is the same (or belongs to the same group) for both applications.

- Normally the manufacturer should be the same (or belong to the same group). In case the manufacturer of the final substance is not the same (or does not belong to the same group) for both applications, the manufacturing process, in-process controls and impurity profile of the final substance are the same as approved in the CEP dossier referred to.

- A sister file can only include concepts of Quality-by-Design or process analytical technology (PAT) if they have already been approved in the CEP dossier referred to.

The final decision on whether an application can be accepted under the sister file procedure will be made by the EDQM on receipt of the application. In case of rejection of a sister file application the applicant will be informed and the request will be transformed into a new dossier application and handled accordingly.

IV. Typical applications

The sister file procedure is typically applicable in the following cases for differences from the CEP dossier referred to (the general conditions described above have to be met, in particular the fact that the manufacturer should be the same or belong to the same group):

- The solvents used in the final purification steps have been changed; this leads to different specifications of the final substance since the solvents used in the final steps are mentioned on the CEP.
- A new solvent is introduced in the synthetic process that cannot be demonstrated as absent from the final substance. This changes the specification of the final substance.
- A different polymorphic form of the same substance is produced according to an alternative process (provided that the relevant monograph is not restricted to one single polymorph). Such forms can be obtained by modifying the crystallisation process for instance.
- The applicant wishes to have separate CEPs to cover alternative grades of the substance being produced (such as micronized), or to cover an alternative manufacturing site.
- The use of an alternative manufacturing route of synthesis which is 'substantially different' from the original route. 'Substantially different' would include a different synthetic strategy including e.g. different starting materials, different intermediates, the introduction of new technology or the use of different catalysts using different elemental impurities. 'Substantially different' could also include a change in reagent. However, even when a new route of synthesis is intended to replace the current route, companies are strongly encouraged to submit a separate CEP application via the sister file procedure to facilitate the lifecycle management and traceability of supply for customers and authorities.
- The addition of a new site of manufacture of the final substance and which does not belong to the current manufacturer (or same group) and when the impurity profile remains unchanged. When the manufacturer is not the same as the current manufacturer (not part of the same group) **and** a 'substantially different' manufacturing process is retained a new application should be made.

This list of examples is not exhaustive. CEP holders are encouraged to contact the EDQM prior to submission for clarification if necessary.

V. Required documentation

The documentation to be submitted for a sister file should include:

Module 1:

1) The EDQM application form for sister files, duly completed.

2) A cover letter. The request for a sister file should clearly appear on the cover letter along with the number of the CEP dossier referred to, a short overview of differences between the new and original applications and the sub-title to be included on the CEP.
   - The sub-title should allow the new application to be differentiated from the CEP dossier referred to. For instance, it can represent the physical characteristic of the substance (polymorphic form II, etc.) or an alternative process (process 2, site X, code number, etc.).
   - The comparative table included in the application form is a **key document for the acceptability of a sister file**. The submission may be blocked if this table is missing or incomplete.

   - The comparative table should include all sections of the dossier and it needs to be **detailed** regarding the content of each section. N.B. In cases when a substantially different route of synthesis is retained and which renders useless any detailed comparison, a simple comparison of the synthetic flow-diagrams is sufficient.
     Therefore, a statement such as "updates have been made" is not sufficient. If they have been changed, the process descriptions and flow-charts of both processes must be compared side by side and in an appropriate manner. This also means that changes to the specifications of the starting materials, intermediates, the final substance or the raw materials have to be reported and detailed in the table, as well as changes to any analytical method for the final substance or changes in manufacturers of starting materials, intermediates, etc.
   - If the content of a section or sub-section is the same as that in the original application (editorial changes excluded), this must be **stated** in the table.

If undeclared differences compared to the original application are detected during assessment, the sister file procedure will be stopped and the dossier will go through the standard rules for new applications.

Module 2:

3) A Quality Overall Summary.

Module 3:

4) Full technical documentation according to the current procedures, as for a standard new CEP application. The dossier should be complete and parts of the dossier cannot be substituted by a reference to the original application.

See also www.edqm.eu for more information on the necessary content of the dossier and for technical documents related to the format of submissions.

VI. Compliance to guidelines or policies

Although it refers to an existing CEP, a sister file is considered an independent application. A sister file is assessed for the declared differences between it and the original application but it will also be assessed against current guidelines and if successful a new CEP will be issued.

Quality guidelines and EDQM policies may have evolved since the original CEP was granted and this may have an impact on the content of the sister file as well as on the new CEP when granted, compared to the original one.
No matter what information was submitted in the original application, the sister file dossier must conform where applicable to current guidelines/policies, such as ICH Q11 'Development and manufacture of drug substances (chemical entities and biotechnological/biological entities)', ICH M7 'Assessment and control of DNA reactive (Mutagenic) impurities in Pharmaceuticals to limit potential carcinogenic risk' and the guidance given in the EDQM Policy document 'Implementation of ICH Q3D in the Certification Procedure'.

VII. Technical content of the dossier (Module 3)

During preparation of the documentation, the following considerations should be taken into account, as these items have been identified by assessors as prompting frequent requests for additional information:

- It should be ensured that the CEP dossier referred to is complete and the latest accepted version.
The sister file dossier should contain all relevant data as in the original application and this includes, as relevant, any data requested as additional information for the original application. For instance, when the absence of specific impurities or a solvent/catalyst/reagent has been demonstrated in the original file, those data should also appear in the sister file if the solvent/catalyst/reagent is still used. Depending on the case, this may comprise a discussion, results of analyses (updated, as needed), method description(s) and validation data.

- Complete information concerning manufacturers of starting materials should be included in the dossier such as name and address, as well as a short outline of the process or a flow-chart (as relevant). It is important to note that the introduction of new suppliers should be highlighted and batch analysis results of the substance manufactured using the different suppliers should be given in the sister file.

- Any differences in the specifications of the starting/raw materials/intermediates should be highlighted. If changes are made to significant parameters, this should be justified; for instance, if the limits for impurities have been widened for a starting material or an intermediate.

- Stability data:
  In case a retest period is requested, stability data to support a request for a re-test period should be submitted in line with the EMA guideline on stability testing of existing active substances and related finished products (CPMP/QWP/122/02). If the request for retest period is supported by stability data obtained on the substance covered by the CEP dossier referred to, then the requirements of the EMA guideline on Stability data for applications for variations (EMA/CHMP/CVMP/QWP/441071) should also be taken into account and the complete set of data should be included in the sister file.

VIII. Lifecycle of the dossier

Once the CEP is granted for the sister file, two CEPs will exist for the same substance and same manufacturer, both of which will have independent lifecycles. Both dossiers will have to be updated individually according to the policies in place at EDQM. Changes likely to affect both CEPs may be submitted where applicable as a grouped submission. Changes that affect only one CEP should be submitted only for the application concerned.

Since the granted CEPs are independent, one of the CEPs may be withdrawn with no impact on the other one.

IX. Timetable and fees

Please consult the EDQM Policy Document 'Management of Application for new Certificates of Suitability and Requests for Revision or Renewal of Certificates of Suitability' (PA/PH/CEP (13) 110, 2R) for information on the management of sister file applications including the timetable.

The fee for a sister file is the same as for a standard new CEP application.

To get more information about this procedure or for questions about its applicability to specific cases, please send your questions through the Helpdesk on the EDQM website: www.edqm.eu.