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Certification of suitability to Monographs of the European Pharmacopoeia

TOP TEN DEFICIENCIES
New Applications for Certificates of Suitability
(2011)

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Top ten deficiencies found after first assessment of new applications in 2011

This document is a summary of the main questions resulting from the first assessment of new applications for Certificates of Suitability (CEP) for chemical purity. It is based on the content of a sample of 90 deficiency letters sent to applicants during the first months of 2011.
From the data obtained, the average number of questions for each application is 7, with the actual number of questions ranging from 0 to 14. During the period of reference, 2 CEPs were granted after the first evaluation (out of 90 dossiers treated).

The Top 10 most frequent questions are listed below with recommendations regarding EDQM requirements added. By including these recommendations - together with the requirements described in the EDQM Guideline "Content of the dossier for chemical purity" PA/PH/CEP (04) 1 (current version) which is available on our website - applicants can improve the quality of their dossiers with a view to facilitating and speeding up the granting of their CEP.

TOP 1 (3.2.S.2.3): Absence of discussion on the carry-over of impurities/by-products from key materials in the process:
The impurities (related substances, solvents, catalysts) of the key materials of the process (starting materials, intermediates) should be described; their carry-over as well as the formation of by-products in the final substance should be discussed. In some cases, a scientific discussion demonstrating/justifying the absence of impurities may replace analytical testing and batch results. The European guidelines on residual solvents, genotoxic impurities and residues of metal catalysts should be used to support this discussion, as well as the Q &A published on EMA web-site dated July 2010 related to *Harmonisation of Policies on Setting Specifications for Potentially Genotoxic Impurities, Heavy metal Catalysts Residues and Class 1 Solvents Residues*.

TOP 2 (3.2.S.2.2) / (3.2.S.2.3): Proposed starting material not accepted:
More and more frequently, applicants propose short synthesis, with complex products proposed as starting materials in the application. This is generally not acceptable and the complex material is considered by the assessors as an intermediate in the synthesis.
Applicants are reminded that the approved starting material is the starting point for GMP and variations, and must be representative of the overall synthetic process and not just a late intermediate resulting in a shortened synthesis. The proposed starting material should be justified. Proposing a complex molecule as starting material may lead to a request for redefinition of the starting material further back in the synthesis.

The policy for definition of Starting Materials for APIs applied at EDQM is the following:
— The proposed starting materials should generally not have a structure that is very close to that of the final substance in relative size and complexity (but will depend on the number of steps to the final active substance).

- Multiple synthesis steps should separate the starting material(s) and the active substance. A synthesis step is a step in the synthesis where covalent bonds are formed or broken. A process consisting of only 1-2 steps is generally not sufficient to ensure full control of the quality of the final substance. Fewer steps may be acceptable in some cases, for example for simple molecules, or when the proposed starting material is the subject of a CEP.
- The full description of the process should cover all the synthetic steps critical for safety (impurities) and/or efficacy; such as steps in which a genotoxic substance is used or formed, step contributing to the overall stereochemistry of the active substance or steps such as biocatalytic transformations.
- Commercial availability is an insufficient justification to accept a starting material. Starting materials produced by custom synthesis and those available commercially are not accepted unless supported by additional criteria as described above.
- It is the combination of the number of chemical synthetic transformation steps carried out under GMP and the control strategy applied to these steps, which provides assurance of quality of the active substance.
- The name and address of manufacturers of starting materials should be stated in the dossier.
- In order to justify the specifications of the starting material information on the manufacture of the starting material should be provided. This should include a flow diagram outlining enough steps of the synthesis and information on the solvents, reagents and catalysts used during its synthesis.
- Any declaration on GMP and/or on willingness to be inspected presented by starting material manufacturers will in effect have no influence on which substance will be accepted as an appropriate starting point for the part of the synthesis since GMP cannot be imposed for the manufacture of a starting material.
- An appropriate control strategy should be proposed to ensure the robustness and consistency of the manufacturing process.

When the assessors do not accept the proposed Starting Material(s) and a redefinition is asked for, suppliers of the proposed materials will thus become suppliers of intermediates and consequently the relevant declarations (compliance with GMP and willingness to be inspected) from these suppliers must be provided. This implies also that related updated CTD sections are provided to reflect the finally approved route of synthesis (from the redefined starting material to the final substance).

TOP 2 (3.2.S.3.2): Genotoxic impurities:

Compliance with the *CHMP Guideline on the Limits of Genotoxic Impurities, EMEA/CHMP/QWP/251344/2006* must be demonstrated for substances obtained by a manufacturing process not yet approved in Europe. A specific discussion as part of the overall discussion on impurities should be provided with regard to impurities with potential genotoxicity.

The Q&A (H) published on EMA website dated July 2010 related to *Harmonisation of Policies on Setting Specifications for Potentially Genotoxic Impurities, Heavy metal Catalysts Residues and Class 1 Solvents Residues* should also be taken into account when setting specifications for potentially genotoxic impurities. Limits for these impurities should be set either in a suitable intermediate or in the final substance.

TOP 4 (3.2.S.4.4): Absence of comparison of the quality of the final substance obtained with starting materials from different suppliers:

A substance may be manufactured using starting materials from different suppliers, which should be specified in the CEP application. Where more than one supplier of starting materials(s) is used, a demonstration should be provided that the quality of the final substance is equivalent whatever the source of starting material involved in the synthesis; batch analysis results from the substance manufactured from the different suppliers should be submitted to confirm that the impurity profile is identical.

TOP 5 (3.2.S.2.3): Incomplete specifications for the declared starting materials:

The specifications of the declared starting materials are often not sufficient and fail to include suitable limits for relevant impurities/solvents/catalysts.

Information on the synthesis of the starting materials (flow diagram) should be provided to support the description of the impurity profile and the proposed specification. The specification should preferably include suitable limits for related substances (specified/unspecified, individual and total), reagents, solvents and catalysts as needed.

TOP 6 (3.2.S.2.3): Absence of discussion for Class 1 solvent as contaminant of another solvent:

Some solvents (e.g. acetone, toluene, ethanol, methanol, isopropanol, xylene, hexane and petroleum ether) may be contaminated with Class 1 solvents (e.g. benzene). Therefore, when these solvents are used in the manufacturing process of the final substance, and in particular in the purification steps, potential residues of their contaminant in an intermediate or in the final substance should be addressed.

According to the European "*Note for Guidance on Specifications for Class 1 and Class 2 residual solvents in active substances, annex to the CPMP/ICH/283/95 Impurities: Guideline for Residual Solvents & CVMP/VICH/502/99 Guideline on Impurities: Residual Solvents"*, 3 options may be used that support the absence of routine testing of the contaminant in the final substance.

Compliance with this guideline should be demonstrated in the justification of the quality of the solvents used in the Impurities section of the application. Where one of the 3 options is met and demonstrated in the application, a routine test for the Class I solvent in a suitable intermediate or in the final active substance is not required.

TOP 6 (3.2.S.2.3): Incomplete specifications for reagents/solvents:

Specifications of all materials used during the synthesis should be given, and suitable purity tests should be introduced. Particular attention should be paid to the quality of solvents used during the final purification steps (including water); these materials should have adequate purity. The quality of water used during the manufacture of APIs should comply with the Note for Guidance on *Quality of water for pharmaceutical use CPMP/QWP/158/01 Revision.*

If applicable a suitable and reasonable mass balance should be observed between purity and impurities limits in the specification for the materials.

TOP 8 (3.2.S.2.4): Specifications for key intermediate(s):

The specifications for the key intermediates are not detailed enough. A discussion on the potential impurities likely to arise from the process and their limits is expected. The need to take into account the impurities controlled in an intermediate in the discussion on the suitability of the monograph should not be forgotten.
When the proposed starting materials are not accepted by the assessors they should be re-defined as intermediates in the synthesis. As a result appropriate specifications are expected for this intermediate.

TOP 9 (3.2.S.4.3): Absence of cross validation between PhEur and in-house method for the control of related substances:
Alternative methods may be used by the applicant, provided they have been shown to give equivalent results to those obtained with the ones of the monograph. Such methods should be described and their validation data given in the dossier. Where alternative methods are used they should be cross validated with reference to the Ph. Eur monograph's method(s) and typical chromatograms should be provided. These methods will not be appended to the CEP if those of the monograph are considered appropriate to control the quality of the substance. To do so, results of testing the same batches with both methods, showing compliance with specifications should be provided.

TOP 10 (3.2.S.4.3): Suitability of the monograph to control the impurity profile of the final substance:
The suitability (or unsuitability) of the Ph.Eur. monograph to detect and limit all related substances present in the final substance should be demonstrated, even if a suitable in-house method is used for their control. This discussion should also address how potential/actual impurities from the described route of synthesis are controlled. If the monograph method is not suitable to detect impurities, an additional method should be proposed for such impurities unless it can be demonstrated that they are absent.

TOP 10 (3.2.S.2.2): Absence of information related to the maximal batch size for the approved process:
The maximum batch size for which the manufacturer has acquired experience with the defined manufacturing method, and which should correspond to batches referred to in the dossier, should be stated. Where the substance has yet to be produced in commercial quantities (eg. only pilot scale batches manufactured) the CEP can be granted provided scale-up is reported to the EDQM via an appropriate notification. For a sterile product, an application for a variable and/or alternative batch size should be justified.
