

Certification of Substances Division

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Certification of suitability to Monographs of the European Pharmacopoeia

TOP TEN DEFICIENCIES

New Applications for Certificates of Suitability

(End 2009)

Top ten deficiencies found during first assessment of new applications from October to December 2009

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 108 deficiency letters sent to the applicants on applications treated from October to December 2009.

From the data obtained, the average number of questions for each application is 10 with the actual number of questions ranging from 2 to 20. During this period of reference, no CEP was granted after the first evaluation.

The Top 10 questions are listed below with additional 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.2.2) / (3.2.S.2.3): Redefinition of starting material:

More and more frequently, applicants propose a one-step synthesis, starting from a complex material in the application. This is generally not acceptable and the complex material is considered as a late, often purchased, 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 must be justified. This proposal and justification will be assessed and can lead to a request for redefinition of the starting material.

As a consequence, external suppliers may thus become suppliers of intermediates and consequently the relevant declarations (compliance with GMP and willingness to be inspected) from these suppliers must be provided.

TOP 2 (3.2.S.2.3): Absence of discussion on the carry-over of impurities/by-products from key materials:

The impurities (related substances, solvents, catalysts) of the key materials (starting materials, intermediates) should be described and their carry-over 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.

TOP 3 (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, 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 are listed that support the absence of routine testing of the contaminant.

Compliance with this guideline should be demonstrated in the justification of the quality of raw materials used or in the Impurities section. Where one of these 3 options is met and demonstrated as such 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 4 (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. The guideline is not applied retrospectively to authorised products unless there is recent data demonstrating the genotoxicity of a specific compound relevant to the application. For substances which fall within the scope of the guideline, a specific discussion as part of the overall discussion on impurities should be provided with regard to impurities with potential genotoxicity.

TOP 5 (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 application. Where more than one supplier of the starting materials(s) is used, demonstration should be provided that the quality of the final substance is equivalent whatever the source of starting material; batch analysis results from the substance manufactured from the different suppliers should be provided to confirm that the impurity profile is identical (same impurities/solvents/catalysts).

TOP 6 (3.2.S.2.3): Incomplete specifications for the declared starting materials

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

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

TOP 7 (3.2.S.4.3): Suitability of the monograph to control the impurity profile of the final substance

The suitability (or unsuitability!) of the European Pharmacopoeia 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, an additional method should be proposed for such impurities unless it can be demonstrated that these impurities routinely are absent.

Alternative methods may be used by the applicant, provided they have been shown to be equivalent to the ones of the monograph. Such methods should be described and their validation data given in the dossier. Such alternative methods will not be appended to the CEP if those of the monograph are considered appropriate to control the quality of the substance.

To demonstrate the equivalence between the monograph and in-house methods, cross validation data must be provided (eg. results of testing the same batches with both methods, showing compliance with specifications).

TOP 8 (3.2.S.6): Specification for container closure system

A brief description of and the specifications for the container closure system (primary & secondary packaging) should be included in the application.

For primary plastic packaging material, a declaration that the requirements of the CHMP guideline on plastic immediate packaging materials (CPMP/QWP/4359/03 – EMEA/CVMP/205/04) are met, should be provided. Any equivalent declaration is also accepted.

TOP 9 (3.2.S.3.2): Compliance with the requirements of the Ph. Eur General Monograph 2034: limit for unspecified impurities

The general monograph (GM) 2034 *Substances for Pharmaceutical Use* overrules the limit for unspecified impurities described in the specific monograph when they are different. In such a case, a suitable limit for unspecified impurities should be set and if appropriate, an additional validated method should be developed to control these impurities. When the specific monograph does not limit total impurities a limit should be proposed.

Where the specific monograph is out of the scope of the GM 2034, the principles described e.g. setting appropriate limit for unspecified impurities and for total impurities should be applied.

TOP 10 (3.2.S.2.3): Solvent recovery:

Information related to solvent recovery should be included in the description of the manufacturing process. The steps where solvents are recovered and the recovered solvents used should be highlighted. Section 3.2.S.2.3, Control of Materials, should be completed by a comparative table of specification for fresh and recovered solvents, and any differences between the specifications should be justified.