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Certification of suitability to the Monographs of the European Pharmacopoeia

TOP TEN DEFICIENCIES in New Applications for Certificates of Suitability for chemical purity

This document is a summary of the top ten deficiencies identified after the initial evaluation of new applications for Certificates of Suitability (CEP) for chemical purity. It is based on the content of a random sample of 30 deficiency letters selected from the year 2023.

During this period the failure of applicants to satisfactorily address some of the deficiencies described below in their application resulted in an increase in the number of questions raised during requests for additional information by EDQM along with their complexity. Consequently, the timeline for granting of the certificate of suitability was increased.

This document is intended to help applicants avoid such issues. Expanded details on specific points from each deficiency are provided to inform the users but should always be considered in conjunction with the EDQM guideline “Content of the Dossier for Chemical Purity and Microbiological Quality of Substances for Pharmaceutical Use” which outlines the specific requirements for the submission of CEP applications.

TOP 1: 3.2.S.2.2

Lack of details and/or poor description of the manufacturing process of the substance from the introduction of starting materials (This includes discrepancies noted between the information given in sections S.2.3 and S.2.4). (12% of all questions)

Specific points:

For synthetic and semi synthetic substances, it is expected that a synthetic flow diagram be provided. All synthetic intermediates should be presented, and if non-isolated, they should be presented within square brackets.

When reviewing the route of synthesis, assessors check that the information in S.2.2, S.2.3, and S.2.4 is consistent. Applicants should ensure that all raw materials used (including recovered materials) are addressed both in section S.2.2 and S.2.3 and that no reagents are included in error.

The quantities of all raw materials used, and the batch size should be detailed at each stage of the manufacturing process.

If blending of intermediates or the final substance is performed, the process description should make it clear that it is performed in accordance with ICH Q7 and that batches are fully tested prior to blending.

TOP 2: 3.2.S.2.4 and TOP 4: 3.2.S.2.3

Non-adequate or poorly justified specifications proposed to control the quality of isolated intermediates (11% of all questions) **and starting materials** (7% of all questions)**.**

Specific points:

It is expected that the specifications for starting materials and isolated intermediates include appropriate acceptance criteria for specified, unspecified, and total impurities. Acceptance criteria should be justified based on fate and the carryover of the impurity/ies (this may sometimes necessitate spiking studies). Any potential risk to the quality of the final substance should be discussed.

It is expected by assessors that any major and recurrent impurities;

a) Will be identified and/or characterised.
b) Will be specified individually at justified acceptance criteria based on fate and carryover discussions.

If the proposed acceptance criteria for unspecified impurities are wider than those proposed for specified impurities, this should be well justified.

Discrepancies in mass balance (sum of assay and total impurities) should be addressed. Where rationales for a discrepancy exist, these should be explained.

TOP 3: 3.2.S.3.2

Absence or deficient discussion on the risk of having potential mutagenic impurities in the final substance. (7.5% of all questions)

Specific points:

CEP applicants are expected to provide a specific discussion in their dossier regarding potential mutagenic impurities based on their understanding of the manufacturing process for the substance. This should include those:

a) introduced during the manufacturing process (e.g., reagents, starting materials, etc.)
b) arising from the synthesis of the final substance
c) formed as a result of degradation.

Such impurities should be listed and classified (class 1 to class 5) in the dossier in accordance with ICH M7. For mutagenic impurities, a suitable control strategy in accordance with the principles of ICH M7 should be proposed.

The Threshold of Toxicological Concern (TTC) for an impurity should be determined in accordance with ICH M7. For the calculation of the TTC, the Maximum Daily Dose (MDD) of the drug substance should be based on the Human Medicine European Public Assessment Report (EPAR), Summary of Product Characteristics (SmPCs), or agreed literature such as Martindale, while the appropriate acceptable intake should be based on an appropriate duration of use as described in ICH M7.

ICH M7 option 3 controls for mutagenic impurities should be justified with suitable spiking and/or carryover studies.

ICH M7 option 4 controls should be supported by a demonstration that, based on understanding of the process and impact on residual impurity levels (including fate and purge knowledge), the level of the impurity in the drug substance will always be below the acceptable limit. Option 4 controls may additionally need to be supported by analytical data (e.g., spiking and/or carryover studies).

TOP 5: 3.2.S.2.3

Absence or inadequate acceptance criteria (and/or analytical methods) for raw materials (incl. recovered materials) used in the manufacture of the final substance, from the introduction of starting materials. (7.1% of all questions)

Specific points:

Applicants should ensure that suitable specifications are provided for all raw materials used in the manufacturing process for the final substance.

Specifications of raw materials used late in the manufacturing process should not contain wide acceptance criterion without any suitable justification being provided. The impact of the use of these materials (incl. recovered materials) on the impurity profile of the final substance should be addressed.

In case material of fish origin or a peptone is used in the manufacturing process, the EDQM requirements should be met.

TOP 6: 3.2.S.2.2

The reprocessing and recovery of raw materials are inadequately addressed. (6.1% of all questions)

Specific points:

Reprocessing: In accordance with the EU "Guideline on the Chemistry of Active Substances" in Section 3.2.S.2.2 CEP applicants are expected to provide a detailed narrative description of any reprocessing step and to define the triggers for this reprocessing. Statements such as "Reprocessing is a repetition of the approved step X" are not considered appropriate replacements.

Recovery: In Section 3.2.S.2.2 CEP applicants are expected to suitably identify the point in the manufacturing process from where materials are recovered, to describe in detail how they are recovered, and to clearly identify where they are reintroduced in the process.

TOP 7: 3.2.S.3.2

Absent or deficient risk assessment related to Nitrosamines. (4**%** of all questions)

Specific points:

New CEP applications (chemical, semi-synthetic, products of fermentation, or herbals) are expected to include a comprehensive risk assessment for the presence of nitrosamines based on the principles outlined in the ICH Q9 and ICH M7 guidelines, as well as the current EMA Q&A document on nitrosamines (incl. its Appendix 1). The risk assessment should address not only risks from the manufacturing process but also those from the introduction of materials used in the manufacturing process (starting materials, reagents, solvents – fresh and recovered, etc.) as well as degradation. Any risk concerning the formation and carryover of nitrosamines should be suitably addressed, taking into account the above-mentioned EMA Q&A document.

TOP 8: 3.2.S.3.2

Failure to adequately address the origin, fate, and carryover of related substances into the final substance. (4**%** of all questions)

Specific points

A discussion based on Ph. Eur. impurities alone is generally not considered as sufficient, and the discussion on related substances should address the formation, carryover and fate of other impurities (e.g., starting materials, intermediates, process related impurities, and degradants).

The suitability of the Ph. Eur monograph to control impurities, not present in the transparency list of the monograph (i.e., additional in house impurities), for which a control in the final substance is proposed or required (e.g., found above the reporting threshold), should be addressed.

In the context of the related substances discussion it is expected that statements such as “not detected” or “less than limit of quantification” be supported by the provision of the LOD / LOQ for the associated method**.**

TOP 9: 3.2.S.3.2

Deficient discussion on residual solvents. (4**%** of all questions)

Specific points:

In the context of the discussion on residual solvents, it is expected that statements such as “not detected” or “less than limit of quantification” be supported by provision of the LOD / LOQ for the associated method**.**

The origin of impurities that are formed as by-products of the manufacturing process, but which are also common solvents (e.g. acetic acid, ethanol), should be clarified.

Where relevant, CEP applicants are expected to discuss the potential presence of Class 1 solvents (e.g. Benzene / Carbon tetrachloride /1,2-Dichloroethane / 1,1-Dichloroethene / 1,1,1-Trichloroethane) as contaminants of other solvents and to demonstrate compliance with the requirements of ICH Q3c Annex 1.

TOP 10: 3.2.S.2.3

Failure to suitably identify starting materials. (3.5**%** of all questions)

Specific points:

Starting materials should be identified and selected according to the requirements outlined in ICH Q11 and the associated Q&A document. The reasons why the proposed starting materials are considered acceptable and in line with applicable guidelines should be explained in detail in the dossier, in Section S.2.3.

Identification of a substance that contributes a significant structural component to the final substance as a reagent is not acceptable. In accordance with ICH Q11 such substances should be identified as starting materials.

In addition to the information provided above, applicants are encouraged to ensure they stay up to date on news about the CEP procedure, relevant trainings, and on the work of EDQM in general (including the elaboration and revision of Ph.Eur monographs) by consulting the EDQM website www.edqm.eu.

Applicants are also reminded that from the EDQM website they may also access tools to assist them in the preparation of their application for a CEP, including policies and guidelines, FAQ, the EDQM Helpdesk, and the possibility to request a technical advice meeting with the Certification department of the EDQM.