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Certification of suitability to the Monographs of the European Pharmacopoeia

TOP TEN DEFICIENCIES
New Applications for Certificates of Suitability for chemical purity (2015-2016)

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This document is a summary of the ten most frequent questions raised after the initial evaluation of new applications for Certificates of suitability (CEP) for chemical purity. It is based on the content of a sample of 20 deficiency letters sent selected randomly during the second half of 2015 and beginning of 2016.

The top ten most frequent questions are listed below together with expectations and recommendations on how to address the specific deficiencies, with reference to applicable guidelines.

This document is intended to help applicants to improve the quality of their dossiers, in order to facilitate and speed up the granting of their CEPs. It should be taken into account while building up a dossier, in combination with the EDQM Guideline "Content of the Dossier for Chemical Purity and Microbiological Quality (PA/PH/CEP 04 1)" available on the EDQM website.

TOP 1 (S.3.2) Absence or deficient discussion on the risk of having potential mutagenic impurities in the final substance.

This is applicable to sources of substances which have not yet been introduced in medicinal products available on the European market.
Applicants are expected to provide a complete discussion on mutagenic impurities in their application for a CEP. It is necessary to refer to ICH M7 (in force since January 2016). Any addendum, available on the ICH website, may also be useful reading for product-specific recommended safety values (refer also to Note 5 of ICH M7).
It is expected that potential mutagenic impurities arising from the synthesis of the substance and its starting materials (if relevant and if not otherwise justified) or from degradation processes are listed and classified in the CEP dossier as per ICH M7. Impurities can be classified with respect to their mutagenic and carcinogenic potential in 5 different classes (refer to table 1 of ICH M7) and actions for control are proposed accordingly. Sometimes no mutagenicity data are available for impurities showing alerting structures and arising from synthetic processes (class 3 impurities as per ICH M7); these impurities should be controlled at or below an acceptable limit or mutagenicity assays should be conducted (refer to Note 2 of ICH M7) in order to understand if the impurity is non-mutagenic (hence class 5) or mutagenic (hence class 2). The outcome of bacterial mutagenicity assays can also be predicted by (Q)SAR methodologies (*in-silico* studies). According to ICH M7 two (Q)SAR methodologies that complement each other should be applied, one which is expert rule-based and a second one which is statistical-based. The principles set by the OECD should be followed.
In order to set an acceptable limit for (potential) mutagenic impurities in the substance it is necessary to divide the "acceptable intake" of the (potential) mutagenic impurity by the maximum daily dose of the substance. In order to identify the acceptable intake for a mutagenic impurity, the "less-than-lifetime" (LTL) concept may be used. Note 7 of ICH M7 is very helpful to identify this acceptable intake, and ICH M7 also gives guidance on how to identify acceptable total intakes for multiple impurities.

Once an acceptable limit is adequately identified, it is expected that a control strategy is developed according to the four proposals given by ICH M7 (from option 1 to option 4), according to the nature of those impurities and their probability to be present in the final substance. Batch data should be given in support (if deemed necessary) and the analytical methods used should be described. Purge studies may be developed in support to approaches based on option 3 and option 4. Purge studies should be well-developed and justified and all the physico-chemical parameters used (reactivity, solubility, volatility, ionisability, physical processes, etc) should be given with the studies and discussed.

TOP 2 (S.2.3) Absence or insufficient discussion on fate and carryover of related substances of starting materials (included) to the final substance.

The impurity profile of molecules identified as starting materials should be well characterised. This means that applicants need to know what kind of impurities can be found in starting materials, in particular with regard to related substances since usually these are molecules that can react according to the chemistry foreseen by the process, leading to impurities in intermediates and potentially in the final substance. Once the impurity profile of starting materials is sufficiently characterised a detailed discussion is expected not only with regard to carryover of impurities from starting materials to the final substance but also with regard to their fate: what happens to them once introduced in the process along with the starting material. Carryover of unreacted starting materials themselves should also be discussed. If deemed necessary, adequate evidence (e.g., analytical data, literature, information from process development or process validation, etc.) should be given in support.

TOP 3 (S.2.2, S.2.4) Lack of details and/or poor description of the manufacturing process of the substance from the introduction of starting materials (synthesis, narrative description, flow charts, recovery and reprocessing procedures). Incongruences noted between information given in section S.2.2 and section S.2.4.

The manufacturing process should be described in details including all used chemicals along with their quantities, all the operations conducted and all the corresponding operational conditions adopted (in terms of temperatures, pressures, times, etc.). The process needs to be well-described since this is the main source of information that allows assessors to take position on potential formation of impurities and on the potential ability of the process to remove impurities. In-process controls should be mentioned in section S.2.2 (as part of the description of the manufacturing process) and details should be given in section S.2.4 (in terms of acceptance criteria and analytical methods), including controls implemented on isolated intermediates. It is expected that no incongruences are noted while comparing information given in these two sections of the dossier.
The maximum batch size or the batch size range the process described in the dossier refers to should be given in section S.2.2. This information should be congruent with the size of batches described in section S.4.4.
These requirements apply equally to the manufacturing steps for outsourced intermediates, which should be fully described in the CEP applications.

TOP 4 (S.2.3) Non-acceptable starting materials, necessity to redefine them earlier in the process.

Starting materials are the starting points for GMP and variations/revisions and they should be representative of the overall synthetic process. Starting materials should be identified and selected according to the requirements set by ICH Q11 and any additional related available guidance. These are considered as mandatory readings before initiating the exercise of defining starting materials. The reasons why the proposed starting materials are considered as adequate and in line with applicable guidelines should be explained in details in the dossier, in section S.2.3.
If found not acceptable by the assessors, starting materials should be redefined back in the process and this may have major consequences on the manufacture and on the content of the dossier. Manufacturers initially proposed for those non-acceptable starting materials become manufacturers of intermediates (subject to EU GMP Part II and willingness to be inspected) and the dossier should be completely restructured accordingly, since the process from new starting materials to intermediates should be described in section S.2.2. Therefore applicants are expected to select carefully their starting materials.

TOP 5 (S.2.3) Non-adequate or poorly justified specifications in place to control the quality of starting materials.

The quality of molecules identified as starting materials should be sufficiently characterised and kept under control by adequately justified specifications. It is expected that specifications in place to control the quality of starting materials mirror their manufacturing processes. The specification of a starting material should include tests for identity and purity (e.g., controls on impurities), and acceptance criteria for assay, specified, unspecified and total impurities, residual solvents, reagents, mutagenic impurities etc as needed. Tests and acceptance criteria should be based on process knowledge and control strategy. The analytical methods used should be suitably validated and described in section S.2.3. The justification of the specification should include evaluation of the risks and the ability of the subsequent steps to purge impurities. Assurance should be given in the dossier that there are no risks of having uncontrolled impurities in the final substance potentially above acceptable limits. These are risks always kept in mind by assessors while evaluating applications in the context of the Certification Procedure.

TOP 6 (S.2.3) Non-adequate or missing specifications (and analytical methods) for reagents and solvents (recovered and recycled included) used to manufacture the substance from the introduction of starting materials.

It is expected that specifications, including analytical methods in place are described in section S.2.3 for all chemicals and reagents used to manufacture the substance from the introduction of starting materials. It is also expected that a purity test is included in the specification and that a reasonable mass balance is shown by the specification, unless otherwise justified. Specifications in place to test recycled materials before being reused should be given. Any relevant difference comparing to the corresponding specification for the fresh material should be highlighted and the potential impact these differences might have on the quality of the final substance should be discussed.

TOP 7 (S.3.2) Non-adequate or missing discussion on carryover of reagents and elemental impurities to the final substance.

A discussion (as part of the general discussion on the impurity profile of the substance in section S.3.2) on fate and carryover to the final substance of reagents is expected, as applicable. If elemental impurities are used or likely to be present, a discussion on their carryover is expected. For elemental impurities, the guidelines of reference are ICH Q3D and the related EDQM document PA/PH/CEP (16) 23 available on the EDQM website.

TOP 8 (S.2.4) Non-adequate or poorly justified specifications in place to control the quality of isolated intermediate.

Sometimes poorly justified specifications are proposed for isolated intermediates. It is expected that the impurity profile of isolated intermediates is sufficiently characterised and kept under control by adequate specifications. This piece of information (as part of the control strategy of the substance) is particularly important for intermediates which are isolated late in the process, for intermediates that show low purity, or when an impurity is tested in an intermediate instead of the final substance. Also in these cases acceptance criteria should be justified in relation to the fate and carryover of impurities (see top 9).

TOP 9 (S.3.2) Absence or insufficient discussion on fate and carryover of impurities from synthetic intermediates (included) to the final substance.

Isolated intermediates are most of the times contaminated by related substances that can react the same way as the intermediate to give intermediate-like and eventually final substance-like impurities. Hence a discussion based on evidence (e.g., analytical data, literature, information from process development or process validation, etc.) on fate and carryover of impurities present in intermediates is expected in the dossier. It is necessary to take into account impurities controlled in isolated intermediates in the section on impurities (S.3.2) and in the discussion on the suitability of the Ph.Eur monograph to control the quality of the substance. The risks of having uncontrolled impurities in the final substance potentially above acceptable limits should be addressed. Demonstration of absence in the final substance of the last synthetic intermediates is also expected.

TOP 10 (S.2.3) Non-adequate or missing information on the synthesis of starting materials and their manufacturers.

A brief description of the preparation of the starting materials (flow diagram of the process, including solvents and reagents used), along with name(s) and address(es) of their manufacturers (not their suppliers) is expected to be found in section S.2.3 of the dossier. This is to evaluate the suitability of the proposed starting material and its specification. In case more than one source of the same starting material is used, quality equivalence should be demonstrated by means of batch data collected on the final substance manufactured using all the possible sources of the same starting material.