

Certification of Substances Department

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Certification of suitability to the Monographs of the European Pharmacopoeia

Implementation of policy on elemental impurities in the Certification Procedure

Implementation date	01/06/21
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Revision history of the document

Revision N°	date	Reason
Initial version		Implementation of Q3D to the certification procedure
R1	September 2018	Update based on experience gained.
R2	May 2021 (adoption date)	Change of title. Implementation of risk based assessment of elemental impurities in veterinary products and clarification of the presentation of the RMS.

1. Background

The ICH Q3D guideline on elemental impurities has been effective in the European Union since June 2016 for new marketing authorisation applications and since December 2017 for authorised medicinal products. In addition, the European Pharmacopoeia general monograph Pharmaceutical preparations (2619) requires manufacturers of products outside the scope of general chapter 5.20 Elemental impurities to control the levels of elemental impurities in products using the principles of risk management. These principles have been implemented as of 1 January 2021 for veterinary medicinal products submitted in the European Union.

ICH Q3D on elemental impurities covers 24 elements (classified under the following classes 1, 2A, 2B and 3) and defines permitted daily exposure (PDE) in drug products. It is not limited to reagents and catalysts in drug substances or excipients, but also considers all contributions from manufacture including equipment, water and container-closure system.

The ICH Q3D guideline emphasises the need to develop a risk-based control strategy to limit elemental impurities, which is summarised in an appropriate “Risk Management Summary” document. A similar approach is now expected to be developed for veterinary medicinal products

This document is intended to serve as guidance on how to manage elemental impurities in the procedure for “Certification of Suitability to the monographs of the European Pharmacopoeia” (CEP), and is revised based on experience gained by EDQM since the last revision of the policy.

2. Scope

This document describes the policy for the control of elemental impurities in substances covered by a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP). It is applicable to new, renewed and revised CEPs where control of elemental impurities is impacted, including applications for substances for veterinary use only (which were previously excluded from the scope). Any applicant should submit a risk assessment, taking into consideration the elements and principles described in ICH Q3D, and propose suitable controls for elemental impurities using the principles of risk management as part of their CEP applications.

The reference documents taken into consideration when elaborating this policy are:

- ICH guideline Q3D on elemental impurities (EMA/CHMP/ICH/353369/2013) and associated ICH training modules.
- Elemental Impurities in marketed products. Recommendations for implementation (EMA/CHMP/ QWP/109127/2015).
- Implementation strategy of ICH Q3D guideline (EMA/CHMP/QWP/115498/2017).
- Implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products EMA/CVMP/QWP/631010/2017.
- Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products EMA/CVMP/QWP/153641/2018.
- European Pharmacopoeia General Monograph 2619: Pharmaceutical Preparations.

3. Implementation of the policy

The applicant is given two possible options in a CEP dossier:

- Provide a Risk Management Summary (**RMS**) for elemental impurities which may be present in the manufacturing process of the final substance.
- Do not provide a Risk Management Summary (**RMS**).

The EDQM encourages applicants to provide a RMS. Submitting a RMS in a CEP application provides significant benefit as it will facilitate the risk assessment for the medicinal product.

3.1 Risk Management Summary provided

Applicants should clearly identify this option in their application.

A Risk Management Summary report should be provided in module 3 of the dossier (preferably in CTD section 3.2.S.3.2 “Impurities”), which should detail the rationale used to conduct the study, include a justification of the control strategy implemented following the risk assessment, which should be completed with a Table, as described in Annex 1 of this document (which is intended to be annexed to the CEP when granted).

It should be noted that where insufficient data is given for this option, the application will be considered as if no RMS is provided.

3.1.1 Requirements for CEP Applications

As well as considering the principles outlined in ICH Q3D, the following points should also be taken into account when taking the RMS approach for a CEP application.

How to build the RMS

- The RMS should consider all potential sources of contamination; including elemental impurities intentionally introduced into the process after the introduction of the starting material(s), contributions from materials (such as contaminants in starting materials, reagents, water), equipment, and packaging.

The route of administration considered in the risk assessment should be indicated, which forms the basis of the risk management discussion. Reference to unrealistic routes of administration will not be accepted.

- The RMS should consider the elemental impurities mentioned in ICH Q3D (as per the table 5.1 “*Elements to be considered in the Risk Assessment*”)
 - Class 1 and 2A elements, as well as all elements intentionally added in the manufacture whatever their classification should be systematically discussed.
 - If relevant, and depending on the route of administration considered, Class 3 elements should be discussed.

- Justification as to why specific elemental impurities were included in the scope of the RMS is considered useful information and should be included.

How to define the control strategy

- The control strategy should focus on the absence or presence of elemental impurities in the final substance, relying on the process capabilities and on the control of elemental impurities (using preferably option 1, or alternatively option 2a of the ICH Q3D guideline, when justified).
- Absence of an elemental impurity can be concluded when it is shown with convincing evidence that it is purged to a level which is consistently below 30% of the calculated concentration limit based on the indicated route of administration and based on the option 1 daily intake (as per table A.2.2 of the ICH Q3D guideline), in a minimum of 3 consecutive commercial batches or a minimum of 6 consecutive pilot batches of the final substance. Other approaches concluding on the absence of an elemental impurity may be considered if scientifically justified (e.g. using option 2a of the ICH Q3D guideline). The summary table submitted by the applicant (and appended to the CEP) should specify on which basis absence of elemental impurities has been determined.
- When applicable, a justified specification for elemental impurities in the final substance should be introduced. For any elemental impurity intentionally introduced into the last synthetic step of the process, a specification in the final substance is expected (as this is associated with an elevated risk for impurities being carried forward), unless it is consistently and convincingly demonstrated that the process is capable to purge the impurity from the final substance to a level which is below 30% of the calculated concentration limit. The limits applied for the control of elemental impurities in the final substance should reflect the process capabilities, and the PDE of ICH Q3D may be used as reference.
- Screening results of several batches for elemental impurities may support but do not replace a RMS as described above. This might be done in a similar manner as is illustrated in appendix 4 of the ICH Q3D guideline.
- For the analytical methods used:
 - **For screening purposes:** The analytical methodology used should be mentioned along with minimum validation information such as sensitivity of the method (LOD/LOQ).
 - **Control included in the specification of the final substance:** A detailed description of the analytical method used should be provided which is suitable to be annexed to the CEP. The analytical method should be validated in accordance with the requirements of ICH Q2.

RMS table

A table summarising the conclusions of the RMS should be provided in the dossier (example given in Annex 1 of this document).

This table is intended to carry necessary information about the level of contamination of the substance source, in order to build the risk assessment for elemental impurities via the component approach in the finished medicinal product.

3.1.2 Information reported on Certificates of Suitability

When a RMS is provided, this is mentioned on the CEP when granted, with the corresponding table appended.

Any specification proposed by the applicant is mentioned on the CEP when relevant, together with the corresponding analytical method.

Note: Information mentioned on the CEP is intended to feed the risk assessment for elemental impurities in the context of the marketing authorisation application for the medicinal product in which the substance covered by the CEP is introduced.

3.2 No Risk Management Summary provided

3.2.1 Requirements for CEP Applications

If no risk assessment has been performed, the following points should be addressed in the CEP application:

- Any elemental impurities (whatever the Class) intentionally introduced in the manufacture of the final substance after the introduction of the starting material(s) should be declared and data showing their level in the final substance should be provided.
- For any elemental impurity intentionally introduced into the last synthetic step of the process, a specification in the final substance is expected (as this is associated with an elevated risk for impurities being carried forward), unless it is consistently and convincingly demonstrated that the process is capable to purge the impurity from the final substance to a level which is below 30% of the appropriate concentration limit (preferably based on option 1 of table A.2.2 of the ICH Q3D guideline, or alternatively and if justified, based on option 2a
- The limits applied for the control of elemental impurities in the final substance should reflect the process capabilities, and the PDE of ICH Q3D may be used as reference.
- The method used to control elemental impurities in the final substance should be described in detail (in a format to be annexed to the CEP) and validation data according to ICH Q2 should be submitted.

3.2.2 Information reported on Certificates of Suitability

All elemental impurities intentionally added after the introduction of the starting material(s) are listed on the CEP, regardless of the levels found in the final substance. Alternatively, if no elemental impurities are intentionally added, this is mentioned on the CEP.

The CEP does not contain any information regarding the absence of elemental impurities in the final substance.

The specification proposed by the applicant is mentioned on the CEP as relevant, together with the corresponding analytical method.

Note: Information mentioned on the CEP is intended to feed the risk assessment for elemental impurities in the context of the marketing authorisation application for the medicinal product in which the substance covered by the CEP is introduced.

4. Existing CEPs and requirements for revisions

The following points should be considered by holders of existing CEPs.

4.1 Clarification Regarding Tests for Specific Metals in a Substance Monograph

For individual monographs which contain specific tests for elemental impurities, it is expected that these tests are part of the specification, unless otherwise justified (and approved by EDQM).

4.2 Triggers to initiate a revision of CEP applications concerning elemental impurities

4.2.1 Introduction of a RMS without other changes

CEP holders are given the possibility to introduce a RMS as part of a revision application (when there are no changes to the process or to the control strategy for the substance), by submitting a request for revision classified as “minor by default”. This request for revision may be submitted at any time during the lifecycle of the dossier, except during an on-going procedure.

4.2.2 Changes to the manufacturing process

Changes to the manufacturing process should be classified according to the EDQM “Guideline on Requirements for Revision/renewal of Certificates of Suitability to the European Pharmacopoeia Monographs (PA/PH/CEP (04) 2)”. If the changes have an impact on elemental impurities, CEP holders are given the possibility to submit a RMS.

If an RMS has already been introduced in the CEP application, the validity of the RMS should be verified and discussed and if needed an update should be provided. Only significant changes in elemental impurity levels, leading to a different conclusion should be reported.

If no RMS is provided or present in the application, sufficient information should be submitted as described above (section 3.2).

4.2.3 Changes to the control strategy for the substance (changes to analytical methods or specification, without changes to the manufacturing process)

Such changes should be classified according to the EDQM “Guideline on Requirements for Revision/renewal of Certificates of Suitability to the European Pharmacopoeia Monographs (PA/PH/CEP (04) 2)” and may include:

- Changes to limits for elemental impurities in the final substance: addition/deletion/tightening/widening
- Changes to the method(s) used to control elemental impurities in the final substance.

If a RMS has already been introduced in the CEP application, the validity of the RMS should be verified and discussed and if needed an update should be provided. Only significant changes in elemental impurity levels, leading to a different conclusion should be reported.

4.3 Renewal

The renewal application presents a good opportunity for CEP holders to submit a RMS in their application.

During assessment of the request for renewal, the EDQM reviews systematically the control of elemental impurities against the policy described in this document.

When granted, renewed CEPs are in line with the policy described in sections 3.1 or 3.2 of this document.

CEPs which have already been renewed will be updated only if CEP holders have made changes impacting elemental impurities.

Annex 1: template of RMS table

Example of Risk Management Summary to be prepared:

Route of administration considered in the risk assessment:				
Element	Class	Intentionally added?	Considered in risk management?	Conclusion
Cd	1	*	Yes	**
Pb	1	*	Yes	**
As	1	*	Yes	**
Hg	1	*	Yes	**
Co	2A	*	Yes	**
V	2A	*	Yes	**
Ni	2A	*	Yes	**
Tl	2B	*	*	**
Au	2B	*	*	**
Pd	2B	*	*	**
Ir	2B	*	*	**
Os	2B	*	*	**
Rh	2B	*	*	**
Ru	2B	*	*	**
Se	2B	*	*	**
Ag	2B	*	*	**
Pt	2B	*	*	**
Li	3	*	*	**
Sb	3	*	*	**
Ba	3	*	*	**
Mo	3	*	*	**
Cu	3	*	*	**
Sn	3	*	*	**
Cr	3	*	*	**

* Yes / No

** The control strategy followed should be clear and mentioned on the RMS:

- “Absent” should be defined (e.g. “less than 30% of ICH Q3D option 1 limit”)
- or “NMT limit in ppm” calculated based on option 1 (or alternatively and if justified, based on option 2a)
- or “No risk identified”

N.B.: It is recommended not to include individual batch results in the table. CEP holders should ensure that the substance complies with the maximum level indicated.