

Certification of Substances Division

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Certification of suitability to the Monographs of the European Pharmacopoeia

Implementation of ICH Q3D in the Certification Procedure

Addresses	Role	Date
TAB	For adoption	July 2016
TAB	Adopted by correspondence	August 2016

1. Background

The ICH Q3D guideline on elemental impurities is effective in the European Union from June 2016 for new marketing authorisation applications and from December 2017 for authorised medicinal products.

This document is intended to serve as guidance on how to implement ICH Q3D in the procedure for “Certification of Suitability to the monographs of the European Pharmacopoeia” (CEP).

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

The ICH Q3D guideline emphasises developing a risk-based control strategy to limit elemental impurities which is summarised in an appropriate “Risk Management Summary” document.

2. Scope

This document describes the policy for elemental impurities in substances covered by a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP).

This document covers pharmaceutical substances introduced in medicinal products within the scope of ICH Q3D. For products outside the scope of Q3D, the applicant should control adequately the levels of elemental impurities in their substance.

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 – Draft (EMA/404489/2016)

This policy is applicable to new, renewed and revised CEPs granted from **the 1st September 2016** (provided the applicant/holder has made reference to ICH Q3D principles in their application).

3. Implementation of the policy

The applicant is given 2 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, in the form of a Table, as described in Annex 1 of this document (preferably in CTD section 3.2.S.3.2 “Impurities”). This summary should detail the rationale used to conduct the study, and include a justification of the control strategy implemented following the risk assessment.

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, contributions from raw materials (such as water), equipment, and packaging.

The intended route of administration / use of the substance should be indicated, which forms the basis of the risk management discussion. Reference to unrealistic routes of administration or uses not pertaining to the known use of the substance will not be accepted.

- The RMS should consider all elemental impurities mentioned in ICH Q3D (as per the table 5.1 “*Elements to be considered in the Risk Assessment*”). Meaning that:
 - 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 of the use of the substance, 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.
- 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 commercial batches or a minimum of 6 pilot batches of the final substance.

- 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.
- Screening results of several batches for elemental impurities alone cannot be considered as a risk management approach, but may support a RMS as described above. This might be done in a similar manner as is illustrated in appendix 4 of the guideline ICH Q3D.
- For the analytical methods used:
 - **For screening purposes:** The analytical methodology used should be mentioned along with minimum validation information such as indication of the specificity and 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.

3.1.2: Information reported on Certificates of Suitability

When a RMS is provided, this will be mentioned on the CEP.

A table summarising the conclusions of the RMS will be appended to the CEP as per the 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 implement the ICH Q3D component approach in the finished medicinal product.

Any relevant specification, as proposed by the applicant, will be mentioned on the CEP together with the corresponding analytical method.

Note: The EDQM assessors will not make a final conclusion on compliance with ICH Q3D, as this should be done within 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, then 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 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 (based on option 1 of table A.2.2 of the ICH Q3D guideline).
- 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 intentionally added elemental impurities will be listed on the CEP, regardless of the levels found in the final substance. Alternatively if no elemental impurities are intentionally added in the process, this will be mentioned on the CEP.

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

Limits for elemental impurities in the final substance, as implemented by the CEP holder will be included on the CEP.

Note: The EDQM assessors will not make a final conclusion on compliance with ICH Q3D, as this should be done within 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

No systematic revision of existing CEPs is foreseen from the publication of this document, except for those mentioned in section 4.3.

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

4.1: Clarification Regarding the Test for Heavy Metals as per Ph. Eur. General Chapter 2.4.8

From Ph. Eur. Edition 9.0 onwards (implementation date January 2017), the test for heavy metals as per General Chapter 2.4.8 is removed from monographs for substances which are within the scope of ICH Q3D.

The process is the same as for implementation of revised monographs of the Ph. Eur. in marketing authorisation applications, it is therefore expected that the substance specification is aligned with the revised Ph. Eur. monograph for the substance within six months of its publication.

Holders of existing CEPs will not be individually contacted by EDQM, and likewise no request for revision should be submitted. However, in exceptional cases where the manufacturing process includes a risk of elemental impurities being present in the substance and the removal of the heavy metals test from the specification means there is no control of this risk, then appropriate actions should be taken and the dossier updated.

4.2: 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).

4.3: Clarification Regarding CEPs Containing a Limit for a Metal Residue Based on the Option 2a Calculation as per Ph. Eur. General Chapter 5.20

For existing CEPs which contain a limit for a metal residue based on the option 2a calculation of the General Chapter 5.20 described in the 8th edition of Ph. Eur., or of the EMA guideline EMEA/CHMP/SWP/4446/2000, the holders of these CEPs will be informed individually by EDQM, and a revision of the relevant CEPs will be automatically initiated by January 2017.

4.4: Triggers to initiate a revision of CEP applications concerning elemental impurities

4.4.1 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.

4.4.2. 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 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.

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

4.4.3. 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.

4.5: 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 will systematically review the control of elemental impurities against the policy described in this document.

When granted, renewed CEPs will be 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

Example of Risk Management Summary

This table has to be completed by the applicant.

Intended route of administration / Use of the substance:				
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 following statements may be used: **“Absent”** (meaning less than 30% of ICH Q3D option 1 limit, as defined under 3.1.1) / **“maximum level : < X ppm”**

It is not necessary to include individual batch results in the above table. CEP holders should ensure that the substance complies with the maximum level indicated.