

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)



Implementation of Q3D and the Certification procedure

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- June 2016: new marketing authorization
- December 2017: authorised medicinal products
- Gives permitted daily exposure (PDE) in drug products.
- 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.
- Emphasises developing a risk-based control strategy to limit elemental impurities which is summarised in an appropriate “Risk Management Summary” document.

Different approaches for Risk Management

Drug Product Approach

The manufacturer analyses batches of the drug product for the presence of any elemental impurities as support of risk assessment management and to justify a control strategy.

Component Approach (encouraged since more transparent)

The contribution of elemental impurities from each component is identified, evaluated and summarized. The combined contribution of an element is compared with the PDE in the risk assessment and if necessary handled in the subsequent risk management and the establishment of a control strategy.

Implementation of ICH Q3D in the Certification Procedure

Serve the Component Approach as per Q3D: provide necessary information to MAH for their risk assessment on the Drug Product;

Useful for substances manufacturers and MAH and keep the benefits of the centralised assessment

Implementation of ICH Q3D in the Certification Procedure

Two 2 possible options for the CEP Applicant

1. Risk Management Summary (RMS) is submitted for elemental impurities which may be present in the manufacturing process of the final substance. (encouraged by EDQM)
 2. No Risk Management Summary (RMS) is presented.
- Submitting a RMS in a CEP application provides significant benefit as it facilitates the risk assessment for the medicinal product.
 - The approach taken is independent of the use or non-use of EI in the manufacturing process.
 - The approach followed should be clarified.

A Risk Management Summary should contain...

- The reasons why certain impurities are considered and the justification of the control strategy
- Information on elements intentionally added, as part of description of the manufacturing process
- A table summarising the conclusions of the Risk Management Summary should be provided in the dossier
- Level of contamination of the substance (batch data), in order to implement the ICH Q3D component approach in the medicinal product

How to build a Risk Management Summary

- All potential sources of contamination should be considered
- All elemental impurities mentioned in ICH Q3D should be considered (as per table 5.1)
- The intended route of administration/use should be indicated
- Screening results of several batches for elemental impurities may support but do not replace a Risk Management Summary .
- The analytical method used should be mentioned (with specificity, LOD, LOQ).

Risk Management Summary

Annex 1: template of RMS table

Example of Risk Management Summary to be prepared:

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	*	*	**
Mn	3	*	*	**
Cu	3	*	*	**
Sn	3	*	*	**
Cr	3	*	*	**

* Yes / No

** The following statements may be used as explained under 3.1:

- "Absent" with its meaning definition (e.g. "less than 30% of ICH Q3D option 1 limit", or "less than X ppm").
- or "≤ X ppm".
- or "No risk identified"

- The intended route of administration substance should be indicated = 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 24 elemental impurities mentioned in ICH Q3D
- The summary table submitted by the applicant (and appended to the CEP) should specify on which basis absence of elemental impurities has been determined (option 1 or option 2a).

No risk assessment performed for EI

The dossier should contain...

- any elements intentionally added (whatever the class) should be declared, as part of description of the manufacturing process
- For elements intentionally added in the synthesis (the last synthetic step is critical), data showing levels in the final substance and controls applied, if any.

Control strategy - for both options

Elements intentionally introduced prior to the last step:

- Specification in the final substance if proposed by the applicant → mentioned on CEP (test appended, irrespective of presence/absence of the elemental impurities);
- In case no specification proposed by applicant → no test appended to the CEP

Note: The final conclusion on compliance with ICH Q3D should be done within the context of the marketing authorisation application.

Control strategy - for both options

Elements intentionally introduced in last synthetic step:

- A limit in the specification for final substance is normally expected unless levels significantly below 30% of ICH Q3D option 1 limit
- Suitable description of the analytical method used with full validation data (ICH Q2)

Note 1: The final conclusion on compliance with ICH Q3D should be done within the context of the marketing authorisation application

Note 2 : Other approaches concluding on the absence of an elemental impurity may be used (e.g. when the daily dose of a drug substance is low). The summary table submitted by the applicant (and appended to the CEP) should specify on which basis absence of elemental impurities has been determined.

Information reported on Certificates of Suitability

- **When a Risk Management Summary is provided** this is mentioned on the CEP when granted, with the corresponding table appended.
- **When no Risk Management Summary is provided**, 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.

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.

- **In both cases** the specification proposed by the applicant is mentioned on the CEP together with the corresponding analytical method.

Impact of introduction of Q3D in PhEur

- GM 2034: **Elemental impurities** : *“Individual monographs on substances for pharmaceutical use therefore do not contain specifications for elemental impurities unless otherwise prescribed”.*
- Individual monographs have been revised to delete the test for heavy metals and for specific elemental impurities

Impact of introduction of Q3D in PhEur

Example Diacerin monograph: deletion of the test for chromium

Chromium is not used in the last step of the synthesis and not found at significant level

Yes

Yes

< 0.5 ppm

Not necessary to add a test for chromium on the CEP

Annex 1: template of RMS table

Example of Risk Management Summary to be prepared:

Intended route of administration / Use of the substance:				
Element	Class	Intentionally added?	Considered in risk management?	Conclusion
Ca	1	*	Yes	**
Ph	1	*	Yes	**
As	1	*	Yes	**
Hg	1	*	Yes	**
Co	2A	*	Yes	**
V	2A	*	Yes	**
Ni	2A	*	Yes	**
Tl	2B	*	*	**
Au	2B	*	*	**
Pd	2B	*	*	**
P	2B	*	*	**
Os	2B	*	*	**
Rh	2B	*	*	**
Ru	2B	*	*	**
Se	2B	*	*	**
Ag	2B	*	*	**
Pt	2B	*	*	**
Li	3	*	*	**
Sb	3	*	*	**
Ba	3	*	*	**
Mn	3	*	*	**
Cu	3	*	*	**
Sn	3	*	*	**
Ct	3	*	*	**

* Yes / No

** The following statements may be used as explained under 3.1:
 - "Absent" with its meaning definition (e.g. "less than 30% of ICH Q3D option 1 limit");
 - "less than X ppm";
 - "or < X ppm";
 - or "No risk identified"

Impact of introduction of Q3D in PhEur

Example Diacerin monograph: deletion of the test for chromium

Chromium is used in the last step of the synthesis and found at significant level

Yes

Yes

< 6 ppm

Test for chromium on the CEP

Annex 1: template of RMS table

Example of Risk Management Summary to be prepared:

Intended route of administration / Use of the substance:				
Element	Class	Intentionally added?	Considered in risk management?	Conclusion
Ca	1	*	Yes	**
Ph	1	*	Yes	**
As	1	*	Yes	**
Hg	1	*	Yes	**
Co	2A	*	Yes	**
V	2A	*	Yes	**
Ni	2A	*	Yes	**
Tl	2B	*	*	**
Au	2B	*	*	**
Pd	2B	*	*	**
P	2B	*	*	**
Os	2B	*	*	**
Rh	2B	*	*	**
Ru	2B	*	*	**
Se	2B	*	*	**
Ag	2B	*	*	**
Pt	2B	*	*	**
Li	3	*	*	**
Sb	3	*	*	**
Ba	3	*	*	**
Mn	3	*	*	**
Cu	3	*	*	**
Sn	3	*	*	**
Ct	3	*	*	**

* Yes / No

** The following statements may be used as explained under 3.1:
 - "Absent" with its meaning definition (e.g. "less than 30% of ICH Q3D option 1 limit");
 - "less than X ppm";
 - "or < X ppm";
 - or "No risk identified"

Impact of introduction of Q3D in PhEur

- Example Diacerin monograph: deletion of the test for chromium
Chromium is not used in the synthesis

On the CEP, **statement to be deleted** "The test for chromium described in the monograph is not necessary since this compound is not used in the synthesis".

No other elemental impurity is added and the following statement is mentioned: *No elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance.*

Other elemental impurities are added: RMS mentions that chromium is not intentionally added and that other elemental impurities are added (+ limit on CEP if necessary).

Thank you for your attention



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