

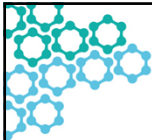


How to build a good CEP application - ICH Q3D

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The place of the Certification Procedure in the global regulatory environment
Prague, 19 September 2017

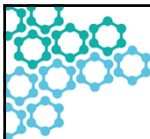


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Overview

- Q3D – a Finished Product Risk Management Approach
- Recap on approach to Q3D in the Certification Procedure
 - Transparency on CEPs regarding Elemental Impurities
- *Useful links to trainings / guidance documents*



EU Marketing Authorisation Applications

ICH Q3D compliance is required for all new applications (since June 2016)

- Appropriate Risk Management approach required
 - Consider all possible sources
 - Communication between suppliers and manufacturers
 - Demonstrate pragmatic and scientific approach
 - Screening/data alone without risk assessment is not sufficient
 - Not a one-time exercise: revisit if changes are made to the product
- Documentation requirements
 - On site PQS: detailed review should be maintained
 - Dossier 3.2.P.5.5: summary of the review required

For current products, compliance will be required from Dec 2017



Latest Significant changes to the European Pharmacopoeia due to ICH Q3D*

Supplement 9.3: in effect from January 2018

- General Chapter 5.20 "Metal Catalyst or metal reagent residues" => "Elemental Impurities"
- General monograph Substances for pharmaceutical use 2034
- General monograph Pharmaceutical Preparations 2619
 - NB: Chapter 5.20 will be legally binding for pharmaceutical preparations (within scope)
- See [EDQM training Webinar On Elemental impurities \(May 2017\)](#), information on approach, other monograph changes, those still under review e.g. water

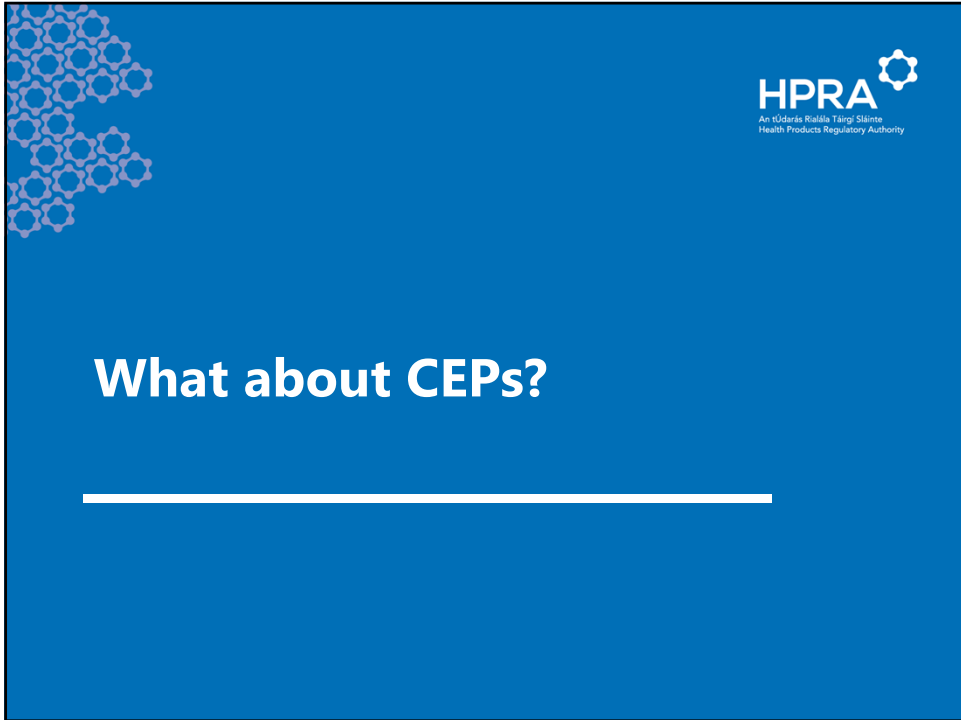
*Adapted from EDQM Training Webinar on Elemental Impurities May 2017



What is needed in the MA dossier?

- Ensure summary appropriately and accurately reflects the process and product
 - Is the product solid or liquid? Will it be reconstituted?
 - Does the chosen maximum daily dose match the SPC?
 - Are stated limits for EI in excipients included in 3.2.P.4?
- Justify the choice of approach taken
- Limits not in line with ICH Q3D may need toxicological justification
- Overall: 3.2.P.5.5 should not contain detailed information, but sufficient summary to provide assurance the appropriate approach is taken

See end of presentation for useful information and training links

A white slide with a decorative pattern of green and blue hexagons in the top-left corner. The HPR logo is in the top-right corner, consisting of the letters 'HPRA' in black, a gear icon, and the text 'An tÚdarás Riailia Tairgí Sláinte' and 'Health Products Regulatory Authority' below it. The title 'Policy Paper: Implementation of ICH Q3D in the Certification procedure' is in green text. Below the title is a bulleted list of four items. At the bottom left is the date '25/09/2017' and at the bottom right is the number '8'.

Policy Paper: Implementation of ICH Q3D in the Certification procedure

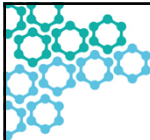
- PA/PH/CEP (16) 23 published August 2016
- In force from all CEPs granted since 01/09/2016
 - Not for Out-of-scope materials e.g. vet only, herbals etc
- Based on EMA Policy document on EMA implementation strategy of ICH Q3D
- How to address EIs for the CEP application and how this will be communicated on the CEP for CEP users

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Approach being taken for CEPs

- See [EDQM training Webinar On Elemental impurities \(May 2017\)](#) for detailed information.
- Two possibilities for applicants:
 - Provide a Risk Management Summary (RMS)
 - Preferred by EDQM and (presumably) CEP users
 - Fewer questions during MA application
 - No Risk Management approach is carried out
 - Could lead to significant work during FP EI review



Scenario 1: RMS provided*

It should be apparent that the component approach is followed.

- The route of administration should be indicated.
 - oral, parenteral or inhalation
 - ICH Q3D option 1 (10 g drug product/d) should be used.
- A RMS should be provided:
 - + Why are impurities considered?
 - + Justification of control strategy
 - - Screening alone is not a RMS



Scenario 1: RMS provided*

Which EI should be included in the screening?

Impurities which might reach the control threshold.
This could be for example EI:

- introduced close to the final substance,
- originated from multiple sources,
- with low PDE and/or
- introduced as contaminants of raw materials at highly variable levels,
- present in packaging material for non-solid APIs/excipients (leaching study).

*Slide from EDQM Training Webinar on Elemental Impurities May 2017



Scenario 1: RMS provided*

•Possible way to present RMS:

Source	used in step X of 4	known/likely EI	Risk assessment	Risk of carry-over	Action
Catalyst	4	Pd	Homogeneous catalyst (Ph ₃ P) ₂ Pd used in last step.	Red	Specification in final substance.
Process aids	4	Pb, Cu	Activated charcoal used in last step. Pot. impurities limited in raw material specification.	Green	No further action required.
Reagents	1-4	Cd, Pb, As, Hg, Ni, Se, Sb, Cu, Cr	HCl, NaOH, H ₂ SO ₄ . Based on data on raw materials and the used quantities limited carry-over is expected.	Yellow	Verify risk assessment for class 1 EI by screening.
Solvents	1-4	Ni	Cyclohexane used in last step. Purified by distillation. For other solvents no catalyst is used.	Green	No further action required.
Water	4	Cd, Pb, As, Hg, Ni, Sb, Cu	Purified water is used.	Green	No further action required.
Equipment	1-4	Ni, Mo, Cr	Glass-lined steel and steel 1.4435 is used. Harsh conditions (pH < 5.0) and high mechanical forces during particle size reduction.	Yellow	Perform screening for these EI to check carry-over.
Container closure system	-	Sb	Used as catalyst in PET synthesis. Low concentration of EI in packaging material. Solid substance and thus limited interaction.	Green	No further action required.

(does not replace the summary table for the CEP)

*Slide from EDQM Training Webinar on Elemental Impurities May 2017



Scenario 2: no RMS provided*

All intentionally introduced EI should be declared (catalysts, reagents).

–Those introduced after the introduction of the Starting Material

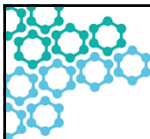
2. Particulars for Intentionally Added Element(s)

Any element intentionally added during the manufacturing must be included in the description of the drug substance manufacturing process in the marketing authorization dossier, an ASMF or a CEP application, as well as its fate and the need for any controls (for instance the use of a metal catalyst in the last step of the synthesis). This obligation of description is independent of whether the substance is made in-house, relies on an ASMF or on a CEP.

Implementation strategy of ICH Q3D guideline
EMA/CHMP/QWP/115498/2017

•Carry-over data should be provided.

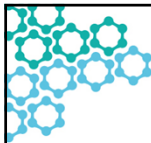
*Adapted from EDQM Training Webinar on Elemental Impurities May 2017



Analytical methods for Elemental impurities in CEP assessment*

- For screening: Analytical methodology (ICP-MS/AES / AAS; no method description) + specificity and sensitivity
- For control in the final specification:
 - Specific methods should be used
 - Detailed description and full validation

*Adapted from EDQM Training Webinar on Elemental Impurities May 2017



What will be presented on the CEP?*

Depends on the approach taken!

- RMS provided:

A risk management summary for elemental impurities has been provided. (Annex 2)

- RMS not provided:

The following elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance: Palladium

Or

No elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance.

(Considers EIs intentionally added after the introduction of the Starting Material)

*Adapted from EDQM Training Webinar on Elemental Impurities May 2017



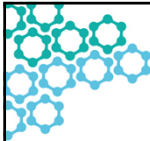
Will limits be presented on the CEP?*

- Regardless of approach: the limit for an EI may also be presented on the CEP if applicable

- Test for elemental impurities by ICP-MS Palladium	not more than 10 ppm	(Annex 3)
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- Examples where limits will be stated on the CEP:
 - EI used in the last synthetic step and present >30% of the ICH option 1 limit, a limit will be required in the specification
 - EI intentionally added, and applicant chooses to have a limit in the specification (even if levels <30% ICH option 1 limit)
- Chosen limits are generally accepted during CEP review, if relevant to the batch data
 - not considered if "safe" for the Finished Product use => may be examined at MA application if necessary
 - Limit may be questioned if could otherwise affect API quality (e.g. degradation)

*Adapted from EDQM Training Webinar on Elemental Impurities May 2017

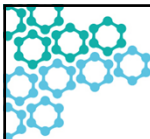


RMS annexed to the CEP* (1)

If a RMS is approach is taken, the outcome will be annexed to the CEP:

Intended route of administration / Use of the substance: parenteral				
Element	Class	Intentionally added?	Considered in risk management?	Conclusion
Cd	1	no	Yes	absent
Pb	1	no	Yes	absent
As	1	no	Yes	absent
Hg	1	no	Yes	absent
Co	2A	no	Yes	absent
V	2A	no	Yes	absent
Ni	2A	YES	Yes	< 2 ppm
	2B	no	no	absent
			no	absent
			no	absent

*Adapted from EDQM Training Webinar on Elemental Impurities May 2017



RMS annexed to the CEP* (2)

- The applicant is to provide the summary table, which should be fully correct
- The route of administration considered should be mentioned (does not restrict use of CEP)
- An appropriate < x ppm level should be stated if an EI is not considered absent
 - Specific batch results should not be included

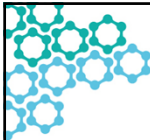
*Adapted from EDQM Training Webinar on Elemental Impurities May 2017



Some Specific Situations*

- Usual Max Daily Dose of API > 10g
 - No conclusion of absence possible => levels will be reported on the CEP
- Other routes of administration
 - Can choose Oral/Parenteral approach for CEP => suitability will be considered in MAA
- Use of a CEP to describe a material used in the application of another CEP
 - If EI to be mentioned on the first CEP, it will also be mentioned on the second CEP

*Summarised from EDQM Training Webinar on Elemental Impurities May 2017



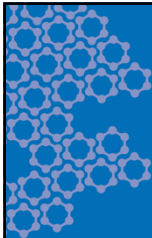
Conclusion

- ICH Q3D currently applies to new MAAs
- Deadline for all authorised products to comply is approaching!
- Use of a Risk Management Summary in CEP procedure will aid all involved in MAA
- The Q3D policy in place for the CEP procedure is publicly available and may be reviewed as needed




Acknowledgements

- Lennart Seidler, Annick Dégardin, Ciarán Feeney, Céline Thouvenel, Bruno Spieldenner (EDQM)
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- Cristian Sampaolesi (EDQM) and Nick Lee (HPRA)




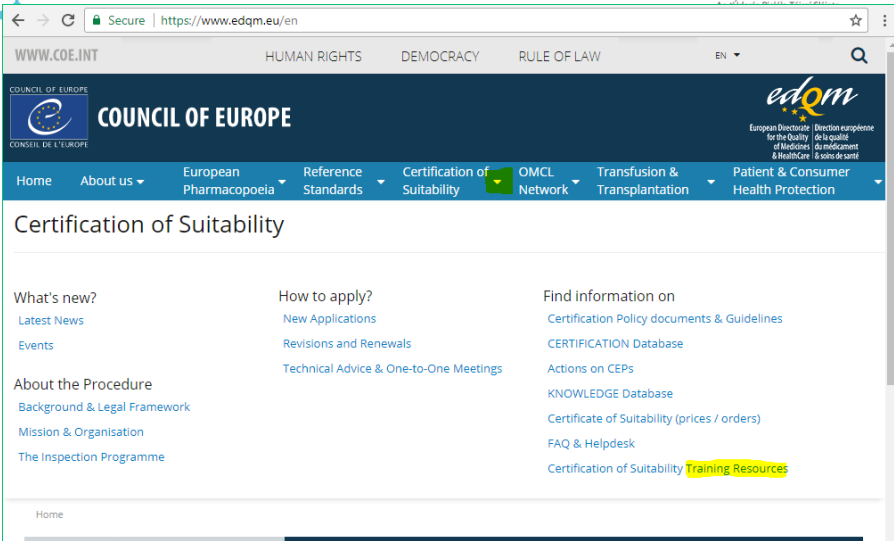
Thank you for your attention



References/useful links

- ICH Q3D Guideline:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf
- ICH Q3D audio presentation and ICH Q3D Implementation training package:
<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>
- EMA implementation strategy:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500222768.pdf
- EU workshop on ICH Q3D from a quality perspective April 2016:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/03/event_detail_001265.jsp&mid=WC0b01ac058004d5c3#
- Latest press release on update on the ph. Eur. Policy on elemental impurities January 2017
https://www.edqm.eu/sites/default/files/press_release_pheur_policy_on_elemental_impurities_update_january_2017.pdf
- EDQM Implementation of ICH Q3D in the certification procedure:
https://www.edqm.eu/sites/default/files/implementation_of_ich_q3d_in_the_certification_procedure_august_2016.pdf
- **EDQM Webinar on Elemental Impurities 16 May 2017**
<https://www.edqm.eu/en/certification-suitability-training-resources>

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The screenshot shows the EDQM website interface. The browser address bar displays 'https://www.edqm.eu/en'. The navigation menu includes 'Home', 'About us', 'European Pharmacopoeia', 'Reference Standards', 'Certification of Suitability', 'OMCL Network', 'Transfusion & Transplantation', and 'Patient & Consumer Health Protection'. The 'Certification of Suitability' section is active, displaying a grid of links:

- What's new?**
 - Latest News
 - Events
- How to apply?**
 - New Applications
 - Revisions and Renewals
 - Technical Advice & One-to-One Meetings
- Find information on**
 - Certification Policy documents & Guidelines
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 - KNOWLEDGE Database
 - Certificate of Suitability (prices / orders)
 - FAQ & Helpdesk
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