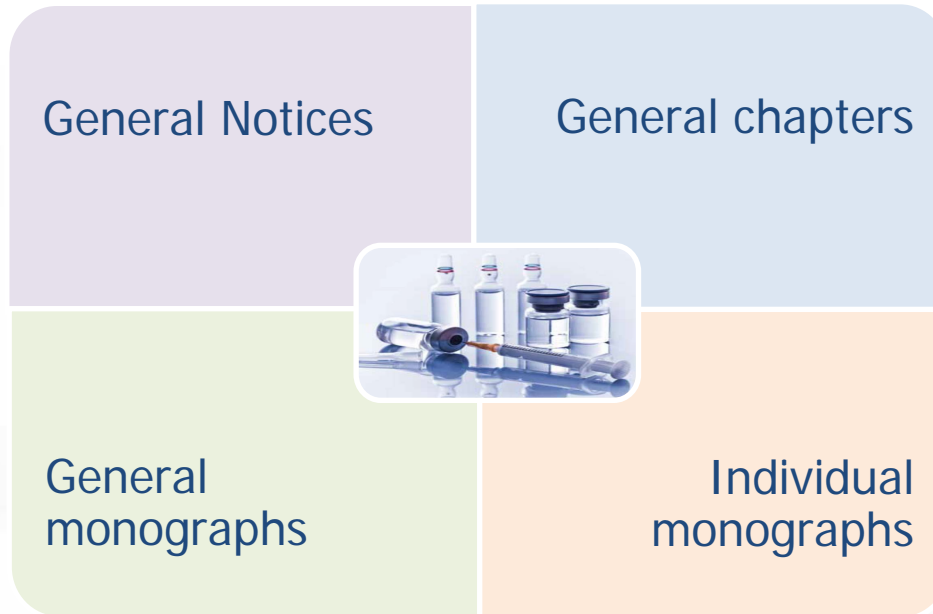


Implementation of the ICH Q3D guideline in the Ph. Eur.

EU workshop on ICH Q3D from a quality perspective, 6 April 2016

Bruno Spieldenner, European Pharmacopoeia department at EDQM

Content and structure of the Ph. Eur.



General notices



- Apply to **all** texts
- Provide basic information to the user and rules to understand texts, conventional expressions
- Address general issues

General chapters 1/2



1. General methods:

- Give general requirements for equipment and procedures
- Editorial convenience: avoid repetition in each monograph
- Provide standard procedures that can be used where there is no monograph

2. General texts:

- Informative texts
- Specific to certain topics (e.g. microbiology, chemometrics)
- In some cases, reproduces the principles of regulatory guidelines

General chapters 2/2

- Not mandatory “per se”
- When referred to in a monograph (general or individual), they become part of the standard
- Some chapters are only informative or provide examples → it is clearly indicated

General monographs 1/2



1. General monographs on dosage forms:

- Classified by pharmaceutical form/route of administration
- Applied during licensing (if applicable)

2. General monographs on classes of substances

- “Classes” defined by: production method, origin, risk factors (e.g. fermentation, TSE risk)
- Aspects that cannot be treated in each individual monograph such as residual solvents, bacterial endotoxins ...
- Quality aspects that are common to a class of products

General monographs 2/2

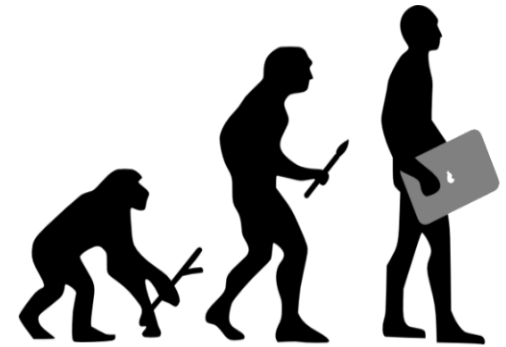
- Complementary to the individual monograph (unless otherwise indicated)
- General monographs are ALL mandatory and apply to ALL substances and preparations within the scope of the Definition section of the general monograph
- No cross-reference in individual monographs: Check in the Introduction & Definition which monograph applies!

Individual monographs



- Substance based
- Specific
- But... not stand-alone

Elemental impurities in the Ph. Eur.



- The Stone age : from genesis to 2008
 - use of non specific wet chemical test for « heavy metals »
 - limit to 10 or 20 ppm (with reference to lead)
- The Bronze age : from 2008 to 2013
 - EMA GL on the specification limits for residues of metal catalysts or metal reagents
- The Golden age ? : starting 2013
 - CHMP decision to delay the application of the EMA guideline to existing marketed products
 - discussions on the implementation of ICH Q3D guideline

Press releases on Ph. Eur. strategy

- [18th July 2014](#) : Ph. Eur. strategy regarding elemental impurities and implementation of ICH Q3D.
- [28th April 2015](#): Ph.Eur. policy on elemental impurities and timelines for revision of general and individual texts.
- [7th August 2015](#): clarification for products outside of the scope of ICH Q3D.

Timelines

Implementation plan within Ph.Eur. is aligned to the extent possible

Products should comply with the ICH/CHMP Guideline for Elemental Impurities under the following timeframe:

Product	Should comply with Guideline from:
New Marketing authorisation for new product (containing new active substance)	June 2016
New Marketing authorisation for product containing an established active substance	June 2016
Marketed products including new mutual recognition applications of already approved products	December 2017

Source: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/03/WC500184920.pdf

Implementation in general chapters

General text 5.20:

- Replacement of the EMA guideline on metal catalysts and metal reagents by the principles of the ICH Q3D guideline
- No public enquiry
- Foreseen publication: Ph. Eur. Suppl. 9.3 [impl. date 01/2018]

General method 2.4.20:

1. Revision to align wording with ICH Q3D guideline _ Foreseen publication: Ph. Eur. Suppl. 9.3
2. Remain committed to harmonisation (coordinating pharmacopoeia: USP) _ *publication date in Pharmeuropa not known yet*

Proposed changes in general monographs

- **Pharmaceutical Preparations (2619)** : Addition of a cross reference to general text 5.20
- **Substances for pharmaceutical use (2034)** : clarify how to handle substances used in drug products outside of the scope of ICH Q3D guideline

Publication schedule: **Pharmeuropa 28.2** (*April 2016*) for publication in Ph Eur suppl. 9.3 [*impl. date 01/2018*]

Proposed revision of general monograph 2619

PHARMACEUTICAL PREPARATIONS

Pharmaceutica

Elemental impurities. For pharmaceutical preparations within the scope of general chapter 5.20, the requirements for the control of elemental impurities are defined in general chapter 5.20.

For pharmaceutical preparations outside the scope of general chapter 5.20, manufacturers of these products remain responsible for controlling the levels of elemental impurities using the principles of risk management.

If appropriate, testing is performed using analytical procedures developed and validated according to general chapter 2.4.20.

General chapter 5.20 is not applicable to unlicensed pharmaceutical preparations.

Currently in public consultation

Proposed revision of general monograph 2034

SUBSTANCES FOR PHARMACEUTICAL USE

Corpora ad usum pharmaceuticum

Elemental impurities. According to general chapter 5.20 the limits for elemental impurities apply to the medicinal product; therefore, individual monographs on substances for pharmaceutical use do not contain a test for elemental impurities unless otherwise prescribed.

For medicinal products outside the scope of chapter 5.20, even in the absence of a test for elemental impurities in an individual monograph on a substance used for their production, the manufacturer is still responsible for controlling the levels of elemental impurities in their medicinal product, using the principles of risk management and applying validated analytical procedures, as appropriate.

Currently in public consultation

Implementation in individual monographs _ the HM tests

- ✓ Suppression of heavy metals tests (2.4.8) from individual monographs (except those for vet. use only) → adopted at the 153rd session of the European Pharmacopoeia Commission (Nov. 2015) for publication in the 9th Edition [impl. 01/2017].
- Total number of texts: 754 monographs (43%)
- Had to be aligned to a new edition for practical reasons
- See press release from April 2015:

"The absence of the heavy metals test from an individual monograph does not preclude substance manufacturers from controlling the levels of elemental impurities in their products. Control of heavy metals according to method 2.4.8 is still acceptable until ICH Q3D comes into force for a given finished product."

Implementation in individual monographs _ specific metal tests

- Discussions in 2015: assessment of tests on EI covered by ICH Q3D (class 1, 2a, 2b and 3) by groups of experts with a recommendation to delete unless otherwise justified

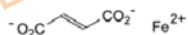
Problem:

- Reason for the presence of the test in the monograph
 - For substances of natural origin (e.g. mined excipients) where EI are potentially present but not intentionally added
- See example

Example monograph

FERROUS FUMARATE

Ferrosi fumaras



$C_4H_2FeO_4$
[141-01-5]

M_r 169.9

DEFINITION

Iron(II) (E)-butenedioate.

Content: 93.0 per cent to 101.0 per cent (dried substance).

TESTS

Solution S. Dissolve 2.0 g in a mixture of 10 mL of *lead-free hydrochloric acid R* and 80 mL of *water R*, heating slightly if necessary. Allow to cool, filter if necessary and dilute to 100 mL with *water R*.

Sulfates (2.4.13): maximum 0.2 per cent.

Heat 0.15 g with 8 mL of *dilute hydrochloric acid R* and 20 mL of *distilled water R*. Cool in iced water, filter and dilute to 30 mL with *distilled water R*.

Arsenic (2.4.2, *Method A*): maximum 5 ppm.

Mix 1.0 g with 15 mL of *water R* and 15 mL of *sulfuric acid R*. Warm to precipitate the fumaric acid completely. Cool and add 30 mL of *water R*. Filter. Wash the precipitate with *water R*. Dilute the combined filtrate and washings to 125 mL with *water R*. 25 mL of the solution complies with the test.

Ferric ion: maximum 2.0 per cent.

In a flask with a ground-glass stopper, dissolve 3.0 g in a mixture of 10 mL of *hydrochloric acid R* and 100 mL of *water R* by heating rapidly to boiling. Boil for 15 s. Cool rapidly, add 3 g of *potassium iodide R*, stopper the flask and allow to stand protected from light for 15 min. Add 2 mL of *starch solution R* as indicator. Titrate the liberated iodine with 0.1 M *sodium thiosulfate*. Carry out a blank test. The difference between the volumes used in the 2 titrations corresponds to the amount of iodine liberated by ferric ion.

1 mL of 0.1 M *sodium thiosulfate* is equivalent to 5.585 mg of ferric ion.

Cadmium: maximum 10 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Solution S.

Reference solutions. Prepare the reference solutions using *cadmium standard solution (0.1 per cent Cd) R* and diluting with a 10 per cent V/V solution of *lead-free hydrochloric acid R*.

Source: cadmium hollow-cathode lamp.

Wavelength: 228.8 nm.

Atomisation device: air-acetylene flame.

Lead: maximum 20 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Solution S.

Reference solutions. Prepare the reference solutions using *lead standard solution (10 ppm Pb) R* and diluting with a 10 per cent V/V solution of *lead-free hydrochloric acid R*.

Source: lead hollow-cathode lamp.

Wavelength: 283.3 nm.

Atomisation device: air-acetylene flame.

Mercury: maximum 1 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Solution S.

Reference solutions. Prepare the reference solutions using *mercury standard solution (10 ppm Hg) R* and diluting with a 25 per cent V/V solution of *lead-free hydrochloric acid R*.

Source: mercury hollow-cathode lamp.

Wavelength: 253.7 nm.

Following the recommendations of the manufacturer, introduce 5 mL of solution S or 5 mL of the reference solutions into the reaction vessel of the cold-vapour mercury assay accessory, add 10 mL of *water R* and 1 mL of *stannous chloride solution R1*.

Nickel: maximum 200 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Solution S.

Reference solutions. Prepare the reference solutions using *nickel standard solution (10 ppm Ni) R* and diluting with a 10 per cent V/V solution of *lead-free hydrochloric acid R*.

Source: nickel hollow-cathode lamp.

Wavelength: 232 nm.

Atomisation device: air-acetylene flame.

Zinc: maximum 500 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Solution S diluted to 10 volumes.

Reference solutions. Prepare the reference solutions using *zinc standard solution (10 ppm Zn) R* and diluting with a 1 per cent V/V solution of *lead-free hydrochloric acid R*.

Source: zinc hollow-cathode lamp.

Wavelength: 213.9 nm.

Atomisation device: air-acetylene flame.

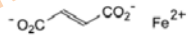
Loss on drying (2.2.32): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

In the test section :
9 tests

Example monograph

FERROUS FUMARATE

Ferrosi fumaras



$C_4H_2FeO_4$
[141-01-5]

M_r 169.9

DEFINITION

Iron(II) (E)-butenedioate.

Content: 93.0 per cent to 101.0 per cent (dried substance).

TESTS

Solution S. Dissolve 2.0 g in a mixture of 10 mL of *lead-free hydrochloric acid R* and 80 mL of *water R*, heating slightly if necessary. Allow to cool, filter if necessary and dilute to 100 mL with *water R*.

Sulfates (2.4.13): maximum 0.2 per cent.

Heat 0.15 g with 8 mL of *dilute hydrochloric acid R* and 20 mL of *distilled water R*. Cool in iced water, filter and dilute to 30 mL with *distilled water R*.

Ferric ion: maximum 2.0 per cent.

In a flask with a ground-glass stopper, dissolve 3.0 g in a mixture of 10 mL of *hydrochloric acid R* and 100 mL of *water R* by heating rapidly to boiling. Boil for 15 s. Cool rapidly, add 3 g of *potassium iodide R*, stopper the flask and allow to stand protected from light for 15 min. Add 2 mL of *starch solution R* as indicator. Titrate the liberated iodine with 0.1 M *sodium thiosulfate*. Carry out a blank test. The difference between the volumes used in the 2 titrations corresponds to the amount of iodine liberated by ferric ion.

1 mL of 0.1 M *sodium thiosulfate* is equivalent to 5.585 mg of ferric ion.

Zinc: maximum 500 ppm.

Atomic absorption spectrometry (2.2.23, *Method I*).

Test solution. Solution S diluted to 10 volumes.

Reference solutions. Prepare the reference solutions using *zinc standard solution (10 ppm Zn) R* and diluting with a 1 per cent V/V solution of *lead-free hydrochloric acid R*.

Source: zinc hollow-cathode lamp.

Wavelength: 213.9 nm.

Atomisation device: air-acetylene flame.

Loss on drying (2.2.32): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

If all EIs linked with ICH Q3D are deleted:
4 tests left

Would a « Ph. Eur compliant »
ferrous fumarate still be meaningful
?

Strategy for specific metal tests

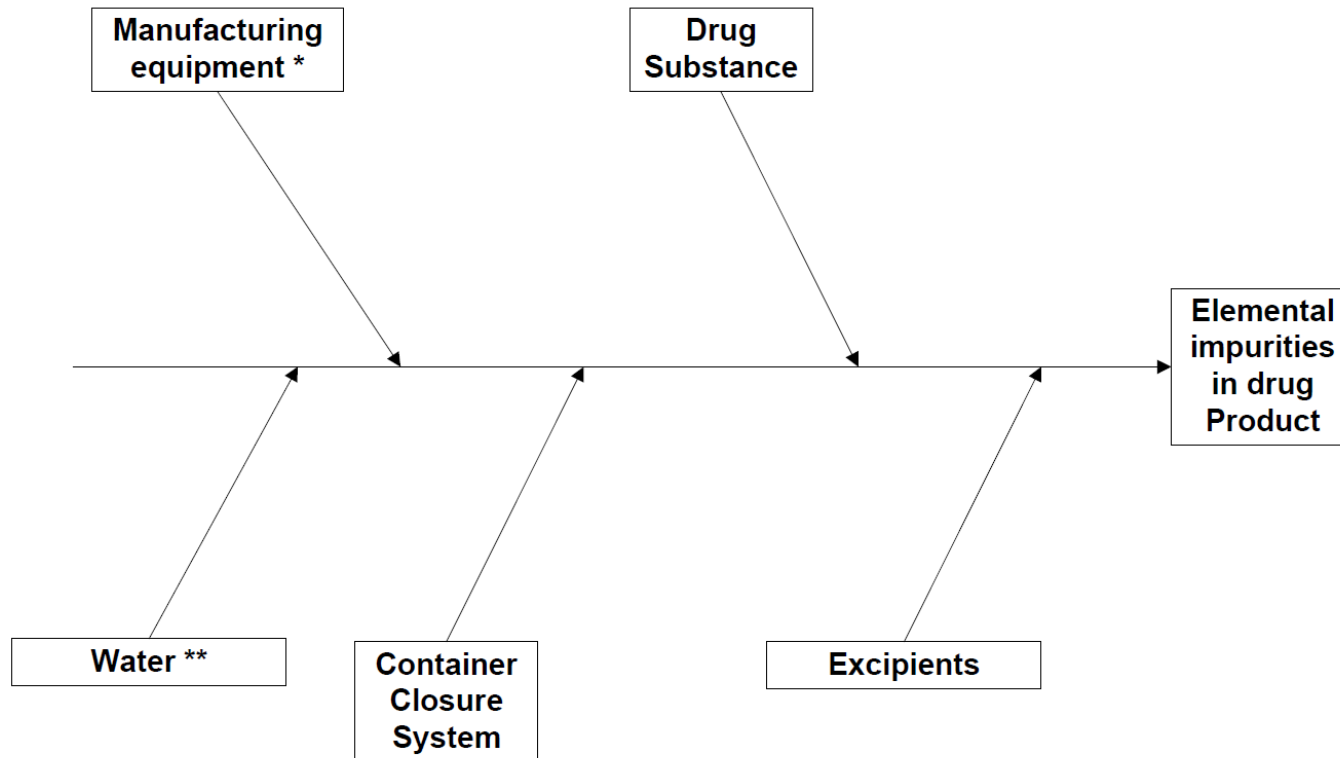
Difficult to have one approach for all types of substances and all classes of EI

In order to have a harmonised strategy, need for

- A differentiated approach depending on EI considered and their possible sources
- A stepwise approach

Depending on the source...

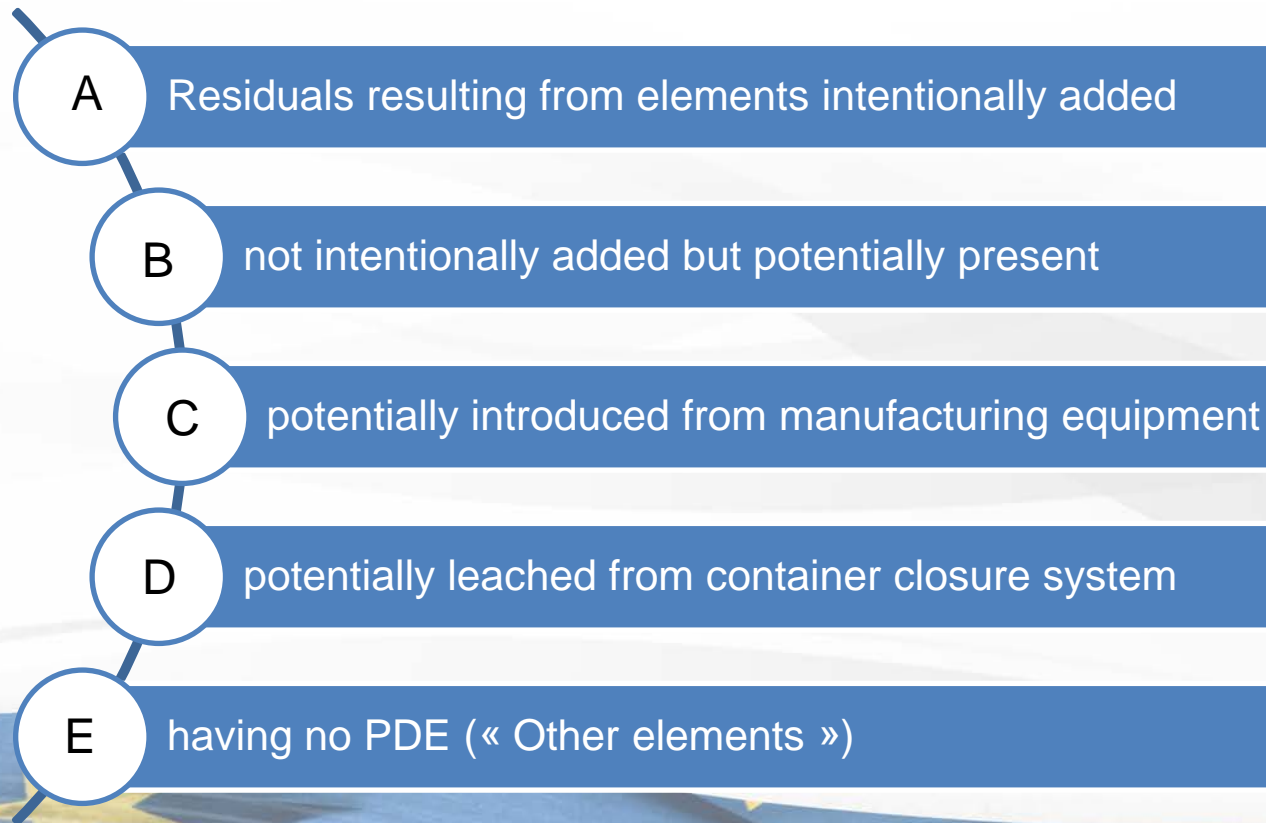
EI categories defined based on potential sources as identified in ICH Q3D (§5.2)



Source:
ICH Q3D

...a differentiated approach

EI categories defined based on potential sources as identified in ICH Q3D (§5.2)



Proposed approach for specific EI tests

ELEMENTAL IMPURITIES	PROPOSED APPROACH
resulting from elements intentionally added	Delete the individual tests. In case of doubt the test would be kept.

- Example: metal catalyst
- Potential elemental impurity is specific of the production pathway
- Information may represent manufacturing secret
- No change control

Proposed approach for specific EI tests

ELEMENTAL IMPURITIES	PROPOSED APPROACH
resulting from elements intentionally added	Delete the individual tests. In case of doubt the test would be kept. Add a sentence in the production section of general monograph 2034 on substance for pharmaceutical use

- ➔ Very difficult to follow evolutions from the Ph. Eur.'s perspective
- ➔ Proposal to add the following § in production section of general monograph 2034, will be published in Pharmeuropa 28.2 (April 2016):

Potential elemental impurities derived from intentionally added catalysts and reagents are considered in a risk assessment (e.g. according to Table 5.20.-1⁽¹⁾ in general chapter 5.20). The identity of the potential elemental impurities is known and techniques for controlling them are available.

(1) This table, which corresponds to Table 5.1 of ICH Q3D, will appear in the future version of chapter 5.20.

Proposed approach for specific EI tests

ELEMENTAL IMPURITIES	PROPOSED APPROACH
resulting from elements intentionally added	Delete the individual tests. In case of doubt the test would be kept. Add a sentence in the production section of general monograph 2034 on substance for pharmaceutical use
not intentionally added and are potentially present	<ol style="list-style-type: none"> Delete only tests on EI that are confirmed as being superfluous (rationale for omitting could be found). Class 2B elemental impurities should be deleted unless otherwise justified. Collect batch data and revise monograph if needed. Tests on EI of classes 1, 2A and 3 should be considered if necessary.

- Tests should remain mandatory
- Example: elements naturally present in mined excipients
- Batch data needed
- No test for Class 2B as EI unlikely to be naturally present (unless otherwise justified)

Table 5.1: Elements to be Considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Source:
ICH Q3D

Proposed approach for specific EI tests

ELEMENTAL IMPURITIES	PROPOSED APPROACH
resulting from elements intentionally added	Delete the individual tests. In case of doubt the test would be kept. Add a sentence in the production section of general monograph 2034 on substance for pharmaceutical use
not intentionally added and are potentially present	<ol style="list-style-type: none"> 1. Delete only tests on EI that are confirmed as being superfluous (rationale for omitting could be found). Class 2B elemental impurities should be considered. 2. Collect batch data and revise monograph if needed. EI tests for classes 1, 2A and 3 should be considered if necessary.
potentially introduced from manufacturing equipment.	Out of scope → GMP

Proposed approach for specific EI tests

ELEMENTAL IMPURITIES	PROPOSED APPROACH
resulting from elements intentionally added	Delete the individual tests. In case of doubt the test would be kept. Add a sentence in the production section of general monograph 2034 on substance for pharmaceutical use
not intentionally added and are potentially present	<ol style="list-style-type: none"> Delete only tests on EI that are confirmed as being superfluous (rationale for omitting could be found). Class 2B elemental impurities should be considered. Collect batch data and revise monograph if needed. EI tests for classes 1, 2A and 3 should be considered if necessary.
potentially introduced from manufacturing equipment.	Out of scope → GMP
potentially leached from container closure systems.	Out of scope → CCS compatibility studies

Proposed approach for specific EI tests

ELEMENTAL IMPURITIES	PROPOSED APPROACH
resulting from elements intentionally added	Delete the individual tests. In case of doubt the test would be kept. Add a sentence in the production section of general monograph 2034 on substance for pharmaceutical use
not intentionally added and are potentially present	<ol style="list-style-type: none"> 1. Delete only tests on EI that are confirmed as being superfluous (rationale for omitting could be found). Class 2B elemental impurities should be considered. 2. Collect batch data and revise monograph if needed. EI tests for classes 1, 2A and 3 should be considered if necessary.
potentially introduced from manufacturing equipment.	Out of scope → GMP
potentially leached from container closure systems.	Out of scope. → CCS compatibility studies
without PDEs, "Other elements" in ICH Q3D	Keep test

Next steps



PH. EUR.: TACKLING FUTURE CHALLENGES OF QUALITY OF MEDICINES TOGETHER

- International Conference organised by the EDQM, on the occasion of the publication of the 9th Edition of the Ph. Eur.
- **27-28 September 2016**, Tallinn, Estonia
- Plenary sessions and 4 parallel workshops
 - 1-day workshop on setting pharmacopoeial standards for **biotherapeutic products**
 - ½-day on **new technologies***
 - ½-day on control of **elemental impurities** *
 - ½-day on excipients, other pharmaceutical components and **international harmonisation***

** To be repeated to allow participation in two themes*

=> Don't wait ... register now!!

Acknowledgments

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Ms B. Jacquél

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Group 9 (inorganics)

Dr JL Robert, chair of the EPC

Members of the PCM working
party

Thank you for your attention!



HEAVY METALS DON'T ROCK

