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

PQRI/USP Workshop, USP Meeting center
9-10 November 2016

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Elemental impurities in the Ph. Eur.
A (r)evolution

No guideline for safety limits

2008
EMA guideline on specification limits for residues of metal catalysts or metal reagents

2013
ICH Q3D development and implementation

2018

Non specific « heavy metals » test
Limit at 10 or 20 ppm Lead

Flexibility Method 2.4.20

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EMA timelines

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Should comply with Guideline from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Marketing authorisation for new product (containing new active substance)</td>
<td>June 2016</td>
</tr>
<tr>
<td>New Marketing authorisation for product containing an established active substance</td>
<td>June 2016</td>
</tr>
<tr>
<td>Marketed products including new mutual recognition applications of already approved products</td>
<td>December 2017</td>
</tr>
</tbody>
</table>


Ph. Eur aligned to the extent possible with these implementation dates
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.
Content and structure of the Ph. Eur.

Provide basic and very general information that are valid for all texts. Help to understand aspects of wording, structure and requirements of the Ph. Eur.

- **General methods**: general recommendations for analytical procedures.
- **General texts**: informative texts, guidelines (e.g. microbiology, chemometrics)
  Become mandatory when cited in monograph

- **Dosage forms**: applied during licensing
- **Group of products**: defined by production method, risk factors or intended use.
  Summarises mandatory quality aspects common to a given group.
Implementation in general text 5.20 (1/2)

- Replacement of the EMA guideline on metal catalysts and metal reagents by the principles of the ICH Q3D guideline
- No verbatim reproduction to avoid introducing a “Ph. Eur. Copy” of the guideline. The enforceable text is the version as published by the ICH.
- Modules for implementation available from ICH website
- Foreseen publication: Ph. Eur. Suppl. 9.3 [impl. date 01/2018]
Implementation in general text 5.20 (2/2)

- Only the introduction and the scope of ICH Q3D are reproduced and supplemented with information specific to Q3D in the Ph. Eur.

- Extracts of the draft proposal for chapter 5.20:

  [...] The European Pharmacopoeia (Ph. Eur.) applies this guideline via the general monograph Pharmaceutical preparations (2619) to medicinal products except products for veterinary use, unlicensed preparations and products excluded from the scope of the guideline [...] 

  [...] The guideline does not require limits to be tightened based on process capability, provided that the elemental impurities in medicinal products do not exceed the PDEs. The PDEs established in the guideline are considered to be protective of public health for all patient populations. In some cases, lower levels of elemental impurities may be warranted when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the medicinal product or one of its ingredients (e.g., element catalysed degradation of a substance for pharmaceutical use).[...] 

Pending adoption, for Ph Eur suppl. 9.3 [impl. date 01/2018]
Implementation in general method

General method 2.4.20 *Determination of elemental impurities:*

1. Editorial revision to align the wording with the ICH Q3D guideline
   Publication foreseen in Ph. Eur. Suppl. 9.3 (no public consultation)
   "metal catalyst and metal reagent residues" to "elemental impurities"

2. International harmonisation (coordinating pharmacopoeia: USP)
   Work ongoing with high priority within the PDG.
   *(public consultation hoped in 2017)*

Other general methods: e.g. Heavy metals (2.4.8), Arsenic (2.4.2)
Not foreseen to delete yet (eg needed for products for veterinary use)
Proposed implementation in general monographs 1/2

- Substances for pharmaceutical use (2034):
  - Elements intentionally added are controlled during production.

  *The identity of the elemental impurities derived from intentionally added catalysts and reagents is known and strategies for controlling them should be established by using the principles of risk management.*

- Clarification for the deletion of specifications for substances

  *Elemental impurities. Permitted daily exposures for elemental impurities (e.g. as included in the ICH Q3D guideline, the principles of which are reproduced in general chapter 5.20 Elemental impurities) apply to the medicinal product. Individual monographs on substances for pharmaceutical use therefore do not contain specifications for elemental impurities unless otherwise prescribed.*

Pending adoption, for Ph Eur suppl. 9.3 [impl. date 01/2018]
Proposed implementation in general monographs 2/2

- Pharmaceutical Preparations (2619):
  - Addition of a cross reference to general text 5.20 (principles of ICH Q3D) to render the text legally binding for medicinal products in scope of Q3D.
  - Clarification for medicinal products outside of the scope of ICH Q3D guideline EIs at least considered in risk management strategy.

**Elemental impurities.** The provisions of general chapter 5.20 Elemental impurities apply to medicinal products except products for veterinary use, unlicensed preparations and other products excluded from the scope of 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 suitable analytical procedures according to general chapter 2.4.20 Determination of elemental impurities.

Pending adoption, for Ph Eur suppl. 9.3 [impl. date 01/2018]
Outcome of public consultation

Public consultation ended on 31st August 2016

Products out of scope of ICH Q3D GL:

Concern that additional requirements would be introduced

→ Control = comprehensive approach using risk management

→ No intent to extend the scope of ICH Q3D GL

→ Q3D sets human toxicological limits (PDE)

NEVERTHELESS: EIs are an important quality attribute of substances and products; just as any other type of impurity

In the absence of specifications for EIs → Should be covered by a risk management strategy in line also with good manufacturing practices
Implementation in individual monographs – HM tests

• Suppression of heavy metals tests (2.4.8) from individual monographs (except those for vet. use only). Published in the 9th Edition.

• Total number of texts: 754 monographs (43%) ➔ combined with a new edition for practical reasons

• No anticipated entry into force expected for already marketed products: from a regulatory point of view manufacturers are expected to comply with ICH Q3D by December 2017.

• 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."

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Other monographs

• No test for elemental impurities in individual finished products monographs

• Water, purified (0008) : was in public consultation (Pharmeuropa 28.3)

*Elemental impurities.* If purified water in bulk does not meet the requirement for conductivity prescribed for Water for injections (0169) in bulk, a risk assessment according to general chapter 5.20. [...] is carried out, taking into consideration the role of water in the manufacturing process, in particular when water is used in a process but is no longer present in the final product.

• Materials/containers : discussion ongoing in Group of experts
Implementation in individual monographs - specific metal tests

• Discussions started in 2015: assessment by groups of experts of tests on EIs (ICH Q3D classes 1, 2a, 2b and 3)  
⇒ recommendation to delete unless otherwise justified

**Problem**

• Historical 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
FERROUS FUMARATE

**Ferrosi fumaras**

\[ \text{C}_4\text{H}_2\text{FeO}_4 \quad M \text{, 169.9} \]

**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** (2.4.19): 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.

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**Example monograph**

**Cadmium:** maximum 10 ppm.

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

**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.

**Mercury:** maximum 1 ppm.

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

**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.

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**Nickel:** maximum 200 ppm.

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

**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 D*).

**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.

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In the test section:

9 tests
Example monograph

FERROUS FUMARATE

C₉H₆FeO₄  
M, 169.9

[141-01-5]

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 D).
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.
Specific metal tests 1/2

In Ph. Eur. approx. 300 monographs describe more than 450 individual metal tests:

- EI’s without a PDE ("other elements", e.g. Fe, Ca, Al): Tests remain
- EI’s having a PDE: No systematic deletion from individual monographs → a more differentiated approach needed to be envisaged

- Residues from elements intentionally added
- not intentionally added but potentially present
- potentially introduced from manufacturing equipment
- potentially leached from container closure system

Delete and treat globally

Substances of natural origin

→ GMP

→ CCS compatibility studies
Specific metal tests 2/2

Possible steps:
- Delete tests in APIs
- Delete for some classes of elements (e.g. class 2B), unless justified
- **Keep other individual tests** in monographs on substances where EIs were not intentionally added (substances of natural origin e.g. mined excipients)
- Obtain batch data and revise these tests/ or add new ones based on batch data
  - Decision to be taken at November COM meeting

**Concern on the support and commitment to effectively revise/ maintain these tests in monographs.**

⚠️ **Need for more experts in groups on inorganic substances**

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Call for experts

• All groups to be re-appointed in November 2016

• **New**: nomination process opened up to experts from non Ph. Eur. member states and from non-Observers

• The final decision to appoint a member to a Group of experts or working party is taken by the Ph. Eur. Commission
Acknowledgments

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Dr T Gosdschan present chair of the EPC
Thank you for your attention!

HEAVY METALS DON’T ROCK