European Pharmacopoeia activities on Elemental Impurities
an update

EDQM Webinar
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Amela Saracevic and Ulrich Rose
European Pharmacopoeia Department
EDQM
Elemental impurities
Content of the presentation

- Implementation of Q3D in Ph. Eur.
- Changes in individual and general monographs
- Harmonisation of general chapter 2.4.20
- Second phase for revision of excipient monographs

Control of impurities in Ph. Eur.

- Organic impurities
- Inorganic impurities
- Volatile impurities, Water and residual solvents
- Special groups, e. g. DNA-reactive imps, inorganics subjected to Q3D
**ICH Q3D Guideline**

- For new medicinal products, including new drug products with existing drug substances
- Including Biologicals and Biotech products
- Excluding: Herbals, radiopharmaceuticals, vaccines, blood
- *Not excluded:* « crude products of animal and plant origin »
- Natural abundance taken in account
- No risk assessment needed for low toxicity metals (e.g. Fe, Ca, Mg, K, Na)

**EMA guideline vs. ICH Q3D**

- EMA guideline covered only metal catalysts or metal reagent residues (*Guideline on the specification limits for residues of metal catalysts or metal reagents*)
- Elements limited only in EMA guideline: Fe, Mn, Zn
- Higher limits in EMA guideline for:
  - Ni and V for oral and parenteral products
- For other stated metals EMA guideline limit ≤ Q3D
- EMA guideline: few limits for inhalation route (Pt, Ni and Cr)
After adoption: What has happened in Europe?

- **CHMP:** (Committee for Medicinal Products for Human Use):
  - Full implementation of Q3D in Europe
- **CVMP:** (Committee for Medicinal Products for Veterinary Use):
  Decided not to apply the guideline for « APIs for veterinary use only » --->
  Consequence: No change in current policy, APIs still to be controlled by the test given in the individual monograph

Ph. Eur. General chapter 2.4.8 « Heavy Metals » will remain

Summary of current situation in Ph. Eur.

Ph. Eur. monographs for APIs and excipients describe the classical « heavy metals » test (precipitate with sulfide) **revised**
*(except those for vet. use only)*

General chapter 2.4.8 « Heavy Metals » describing methods A to H (digestion methods) **remains**

Some monographs describe specific tests, e. g. for arsenic, mercury, lead and others, sometimes using chemical methods, sometimes instrumental techniques (AAS, AES…)
Commission has decided to implement a more individual solution
Implementation Strategy: General texts (1)

• Many points to consider:

• Revision of general text 5.20 on « Metal Catalyst or Metal Reagent Residues »: « Elemental Impurities »
  ➢ Replacement of the previous EMA guideline by the principles of the ICH Q3D guideline
  • Publication: suppl. 9.3, January 2018

Implementation Strategy: General texts (2)

• Only parts of the introduction and the scope of ICH Q3D are reproduced together with information specific to Q3D in the Ph. Eur.

• Extracts of the revised version of chapter 5.20:
  • 5.20: Elemental Impurities

  [...] The European Pharmacopoeia (Ph. Eur.) applies this guideline to medicinal products with the exception of products for veterinary use, unlicensed preparations and products excluded from the scope of the guideline [...]
  • [...]

  [...] 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).[...]

Published in Ph Eur as of suppl. 9.3 (impl. date 01/2018)
Implementation Strategy: General monographs (1)

General monographs 2034 and 2619

- **2034: Substances for pharmaceutical use:**
  Modifications in « Production » and « Test » section

- **2619: Pharmaceutical preparations:**
  Addition of a cross-reference to the revised chapter 5.20.

  ICH Q3D becomes legally binding for products in scope

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Implementation Strategy: General monographs (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.

Published in Ph Eur as of suppl. 9.3 (impl. date 01/2018)
Implementation Strategy: General monographs (3)

• 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 (e.g. veterinary products) ➔ EIs at least considered in risk management strategy

Elemental impurities. General chapter 5.20 Elemental impurities applies 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.

Implementation Strategy: Individual monographs - APIs

➢ For human use (and human or veterinary use):
Reference to classical heavy metals test (chapter 2.4.8) has been deleted from individual monographs

754 revised monographs were adopted at the 153rd session of the Commission in November 2015 and are published since the 9th edition

➢ For monographs « veterinary use only »:
  • Reference to 2.4.8 remained in these monographs until further notice
  • Chapter 2.4.8 therefore remained unchanged
UPDATE: For veterinary medicinal products (VMP)

• As seen in General monograph 2619: "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."

• CVMP has published timelines for the submission of elemental impurities RMS (risk management summary) of VMPs


• All VMP (incl. those with existing active substances) are expected to comply by January 2023 the latest (phased application)

➤ remaining HM tests in “veterinary use only” monographs will be proposed for deletion

Implementation Strategy: General chapter 2.4.20 (1)

General Chapter 2.4.20 : Previous title « Determination of Metal Catalysts or Metal Reagent Residues »

➤ A minor revision has been adopted to align wording (New title « Determination of Elemental impurities ») with Q3D, further modifications may be necessary ➔ Suppl. 9.3 (1st of January 2018)

➤ Chapter has been added on the work program of the Pharmacopoeial Discussion Group PDG (G 07).

➤ Published for comments in the fora in winter 2019/20 (Pharmeuropa 31.4)
2.4.20 : « Elemental Impurities »

• Currently: « As a reference procedure is not provided for each metal, matrix and concentration, the choice of procedure according to Figures..., including sample preparation, detection technique and instrument parameters, is the responsibility of the user »

• Techniques proposed: AAS, AES, XRFS, ICP-AES, ICP-MS and others -> Can all be used provided that « a suitable sample preparation and/or measurement method must be developed and validated. » unless there is a specific description in the monograph. Validation parameters are provided.

2.4.20 : Draft harmonised chapter:

ELEMENTAL IMPURITIES - PROCEDURES

INTRODUCTION
This chapter describes two analytical procedures (Procedures 1 and 2) and validation criteria for the evaluation of the levels of elemental impurities. The chapter permits the use of any procedure that meets the validation criteria specified in this chapter.

➢ The two procedures are ICP-AES (OES) and ICP-MS
➢ Both procedures are given as examples and no cross validation of alternative procedures is required
Implementation Strategy: Specific metal tests (1)

A number of specific monographs describe individual metal tests:

- **EIs not in scope** of Q3D ("other elements", e. g. Fe, Ca, Al):
  - Tests remain in the Ph. Eur.
- **EIs in scope:**
  - **No systematic deletion** from individual monographs
  - *a more differentiated approach is applied*

Implementation Strategy: Specific metal tests (2)

**Particular case:** Substances of natural origin, e. g. mined excipients:

- May contain elemental impurities which have not been intentionally added
- Purification and elimination of EIs difficult or impossible
Implementation Strategy: Specific metal tests (3)

Particular case: Substances of natural origin, e.g. mined excipients:
- Deletion of tests from monographs might pose problems for quality of unlicensed medicines (not subjected to Q3D)
- Quality of excipients used for the production of medicines which are out of scope of Q3D, e.g. vaccines
- Deletion would leave almost « empty » monographs
- There may be other « special cases » where tests will remain for quality reasons

Implementation Strategy: Specific metal tests (4)

Particular case: Substances of natural origin, e.g. mined excipients, but not limited to these

First phase: deletion of tests for metals that have been intentionally added (reagents, catalysts) → Completed

Second phase: Verification of batch data, possible revision of monographs, may lead to deletions and additions of tests
Example monograph (1)

**FERROUS FUMARATE**

*tributinum*

**DEFINITION**

Iron(II) fumarate.

**COA/EDQM**

[105/01-11]

**TESTS**

Solution A: Dissolve 2 g in a mixture of 15 ml of 0.01 mol/L hydrochloric acid and 30 ml of distilled water. Cool to room temperature, filter if necessary, allow to cool, then concentrate to dryness in a water bath.

Solution B: 1 g of ferrous fumarate in 100 ml of distilled water.

Reference solution: Prepare a reference solution using the standard solution of iron (10 mg/L). If necessary, dilute with water.

**In the test section:**

9 tests

- Atomic absorption spectrometry (2.2.2, Method F).
- Test solution, Solution A.
- Reference solution.
- Prepare the reference solution using the standard solution of iron (10 mg/L) and diluting with a final 1% solution of ferric nitrate nitrate and 0.1% solution of sodium hydroxide.
- Source: hollow cathode lamp.
- Wavelength: 233 nm.
- Automatic device: an arc-spray lamp.
- Zinc: maximum 0.00004.
- Atomic absorption spectrometry (2.2.2, Method F).
- Test solution, Solution A.
- Reference solution: Prepare the reference solution using the standard solution of iron (10 mg/L) and diluting with a 1% solution of ferric nitrate nitrate and 0.1% solution of sodium hydroxide.
- Source: hollow cathode lamp.
- Wavelength: 233 nm.

Example monograph (2)

**FERROUS FUMARATE**

*tributinum*

**DEFINITION**

Iron(II) fumarate.

**COA/EDQM**

[105/01-11]

**TESTS**

Solution A: Dissolve 2 g in a mixture of 15 ml of 0.01 mol/L hydrochloric acid and 30 ml of distilled water. Cool to room temperature, filter if necessary, allow to cool, then concentrate to dryness in a water bath.

Solution B: 1 g of ferrous fumarate in 100 ml of distilled water.

Reference solution: Prepare a reference solution using the standard solution of iron (10 mg/L) and diluting with a 1% solution of ferric nitrate nitrate and 0.1% solution of sodium hydroxide.

**In the test section:**

If all EIs linked with ICH Q3D are deleted:

4 tests left

Would a « Ph. Eur compliant » ferrous fumarate still be meaningful?
Final revision of ferrous fumarate monograph

- Updated limits for arsenic, lead, nickel, limit for chromium kept
- Cobalt and vanadium added
- Cadmium and mercury deleted

Elemental impurities. Any method that fulfills the requirements of general chapter 2.4.20. Determination of elemental impurities may be used.

<table>
<thead>
<tr>
<th>Element</th>
<th>Maximum content (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>1.5</td>
</tr>
<tr>
<td>Chromium</td>
<td>200</td>
</tr>
<tr>
<td>Cobalt</td>
<td>20</td>
</tr>
<tr>
<td>Lead</td>
<td>2</td>
</tr>
<tr>
<td>Nickel</td>
<td>50</td>
</tr>
<tr>
<td>Vanadium</td>
<td>40</td>
</tr>
</tbody>
</table>

Example monograph (3): Calcium phosphate

Calcium phosphate

**Calcium phosphate**

**Tribasic phosphates**

Calcium phosphate, 

**Approved name:**

Calcium phosphate, 

**Class:** 

Tricalcium phosphate, 

**CAS:** 1331-82-8

**Functional character:**

Calcium phosphate is a dibasic phosphate and is one of the main minerals in the structure of bones and teeth. It is used as an antacid and as a source of calcium. It is also used in the production of other chemicals, such as phosphoric acid and phosphates. It is also used in the production of other chemicals, such as phosphoric acid and phosphates.

**Preparation:**

Calcium phosphate is prepared by heating calcium carbonate with phosphorus pentoxide. This produces calcium phosphate, which is then purified by reaction with water.

**Assay:**

The assay of calcium phosphate is determined by titration with standardized hydrochloric acid. The end point is indicated by the addition of a few drops of phenolphthalein.

**Test:**

The test for calcium phosphate is performed by the addition of a dilute solution of hydrochloric acid. The solution should be clear and colorless. If the test is positive, a white precipitate of calcium phosphate will form.

**Store:**

Calcium phosphate should be stored in a cool, dry place.

**References:**

Example monograph (4): Calcium phosphate

CAIUM PHOSPHATE

Tricalcium phosphates


calculations

Not intrinsically crystalline in water. A suspension in distilled water precipitates a precipitate of calcium hydroxide.

Elemental assays

A: Dissolve 1 g of the substance in 10 ml of water. Add 1 ml of hydrochloric acid, 1 ml of 0.1 M silver nitrate, and 1 ml of 1% sodium hydroxide solution. Add 1 ml of 0.1 M silver nitrate, and 1 ml of 1% sodium hydroxide solution. If a white precipitate forms, dissolve it in 10 ml of water, and add 1 ml of 0.1 M silver nitrate, 1 ml of 1% sodium hydroxide solution. A white precipitate forms.

Example monograph (5): Calcium phosphate

DRAFT

Elemental Impurities: Any method that fulfills the requirements of general chapter 2.4.20.

Determination of elemental impurities may be used.

<table>
<thead>
<tr>
<th>Element</th>
<th>Maximum content (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>2</td>
</tr>
<tr>
<td>Lead</td>
<td>1</td>
</tr>
</tbody>
</table>

Arsenic (24.2.19): Method A: maximum 4 ppm, determined in 5 ml of solution C.

Iron (24.9.): maximum 400 ppm.

Dilute 0.5 ml of solution E to 10 ml with water.
Example monograph (6): Calcium phosphate

Advantages of this policy:
- Contribute to the protection of public health including unlicensed medicines
- Monographs reflect current quality on the market
- In line with Q3D
- High flexibility ensured for manufacturers: manufacturer may choose any method provided that the validation requirements given in general chapter 2.4.20 are fulfilled

Conclusions
- ICH Q3D is implemented in Ph. Eur.
- General monographs 2034 and 2619 revised to refer to this GL: thus it became legally binding in member states of the Ph. Eur. Convention
- General chapter 5.20 revised
- "Classical" heavy metal tests (2.4.8) have been deleted from individual monographs, except those only "for veterinary use"
- High flexibility when using chapter 2.4.20
- All individual monographs reviewed:
  - Specific tests for elements "intentionally added" deleted from individual monographs
  - Specific tests in selected monographs may be kept based on careful case-by-case decision of the group of experts concerned
Thank you for your attention

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