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

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European Pharmacopoeia activities on Elemental Impurities
an update

EDQM Webinar
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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

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

  https://www.ema.europa.eu/en/implementation-risk-assessment-requirements-control-elemental-impurities-veterinary-medicinal

- 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)*

Implementation Strategy: General chapter 2.4.20 (2)

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.

Implementation Strategy: General chapter 2.4.20 (3)

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

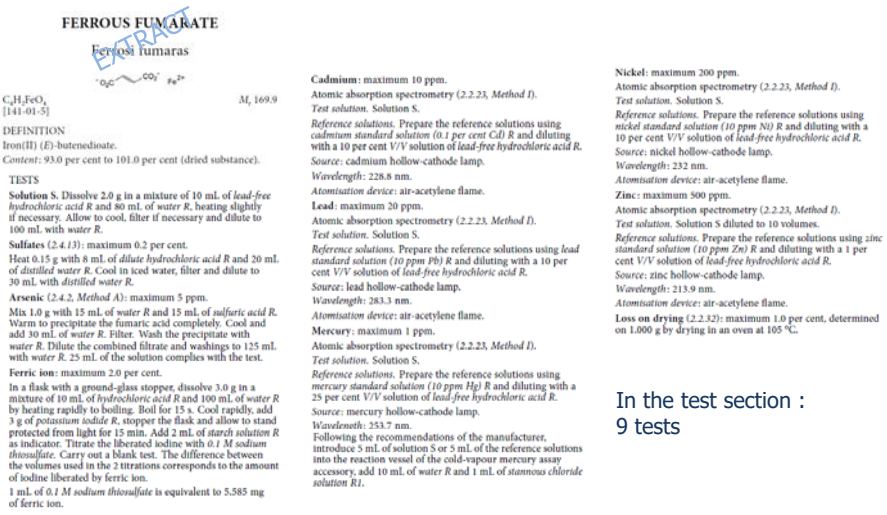
Implementation Strategy: Specific metal tests (4)

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

Ferrosi fumaras

EXTRACT

$C_4H_2FeO_4$ [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.

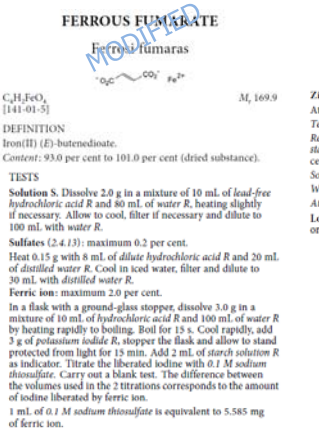
Wavelength: 213.9 nm.

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 (2)



FERROUS FUMARATE

Ferrosi fumaras

MODIFIED

$C_4H_2FeO_4$ [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 ?

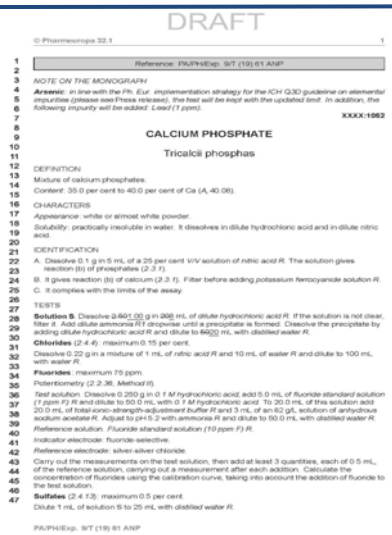
Final revision of ferrous fumarate monograph

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

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

Element	Maximum content (ppm)
Arsenic	1.5
Chromium	200
Cobalt	20
Lead	3
Nickel	50
Vanadium	40

Example monograph (3): Calcium phosphate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Reference: PA/PH/Exp. 9/T (19) 61 ANP

NOTE ON THE MONOGRAPH

***Arsenic**: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see Press release), the test will be kept with the updated limit. In addition, the following impurity will be added: Lead (1 ppm).*

XXXX:1052

CALCIUM PHOSPHATE

Tricalcii phosphas

DEFINITION

Mixture of calcium phosphates.

Content: 35.0 per cent to 40.0 per cent of Ca (*A*, 40.08).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water. It dissolves in dilute hydrochloric acid and in dilute nitric acid.

IDENTIFICATION

A. Dissolve 0.1 g in 5 mL of a 25 per cent *V/V* solution of *nitric acid R*. The solution gives reaction (b) of phosphates (*2.3.1*).

B. It gives reaction (b) of calcium (*2.3.1*). Filter before adding *potassium ferrocyanide solution R*.

C. It complies with the limits of the assay.

TESTS

Solution S. Dissolve 2.601.00 g in 200 mL of *dilute hydrochloric acid R*. If the solution is not clear, filter it. Add *dilute ammonia R1* dropwise until a precipitate is formed. Dissolve the precipitate by adding *dilute hydrochloric acid R* and dilute to 5000 mL with *distilled water R*.

Chlorides (*2.4.4*): maximum 0.15 per cent.

Dissolve 0.22 g in a mixture of 1 mL of *nitric acid R* and 10 mL of *water R* and dilute to 100 mL with *water R*.

Fluorides: maximum 75 ppm.

Potentiometry (*2.2.36, Method II*).

Test solution. Dissolve 0.250 g in 0.1 *M hydrochloric acid*, add 5.0 mL of *fluoride standard solution (1 ppm F) R* and dilute to 50.0 mL with *0.1 M hydrochloric acid*. To 30.0 mL of this solution add 20.0 mL of *total-ionic-strength-adjustment buffer R* and 3 mL of an 82 g/L solution of *anhydrous sodium acetate R*. Adjust to pH 5.2 with *ammonia R* and dilute to 50.0 mL with *distilled water R*.

Reference solution. *Fluoride standard solution (10 ppm F) R*.

Indicator electrode: fluoride-selective.

Reference electrode: silver-silver chloride.

Carry out the measurements on the test solution, then add at least 3 quantities, each of 0.5 mL, of the reference solution, carrying out a measurement after each addition. Calculate the concentration of fluorides using the calibration curve, taking into account the addition of fluoride to the test solution.

Sulfates (*2.4.13*): maximum 0.5 per cent.

Dilute 1 mL of solution S to 25 mL with *distilled water R*.

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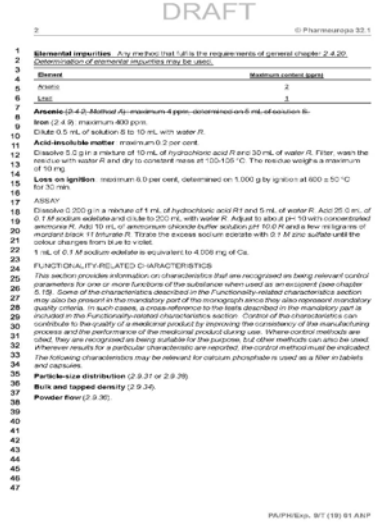
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Elemental impurities. Any method that fulfils the requirements of general chapter *2.4.20. Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Arsenic	2
Lead	3

Arsenic ~~(*2.4.2. Method A*): maximum 4 ppm, determined on 5 mL of solution S~~.

Iron (*2.4.9*): maximum 400 ppm.

Dilute 0.5 mL of solution S to 10 mL with *water R*.

Acid-insoluble matter: maximum 0.2 per cent.

Dissolve 5.0 g in a mixture of 10 mL of *hydrochloric acid R* and 30 mL of *water R*. Filter, wash the residue with *water R* and dry to constant mass at 100-105 °C. The residue weighs a maximum of 10 mg.

Loss on ignition: maximum 6.0 per cent, determined on 1.000 g by ignition at 600 ± 50 °C for 30 min.

ASSAY

Dissolve 0.200 g in a mixture of 1 mL of *hydrochloric acid R1* and 5 mL of *water R*. Add 25.0 mL of *0.1 M sodium edetate* and dilute to 200 mL with *water R*. Adjust to about pH 10 with *concentrated ammonia R*. Add 10 mL of *ammonium chloride buffer solution pH 10.0 R* and a few milligrams of *mordant black 11 triturate R*. Titrate the excess sodium edetate with *0.1 M zinc sulfate* until the colour changes from blue to violet.

1 mL of *0.1 M sodium edetate* is equivalent to 4.008 mg of Ca.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated. The following characteristics may be relevant for calcium phosphate is used as a filler in tablets and capsules.

Particle-size distribution (*2.9.31 or 2.9.39*).

Bulk and tapped density (*2.9.34*).

Powder flow (*2.9.36*).

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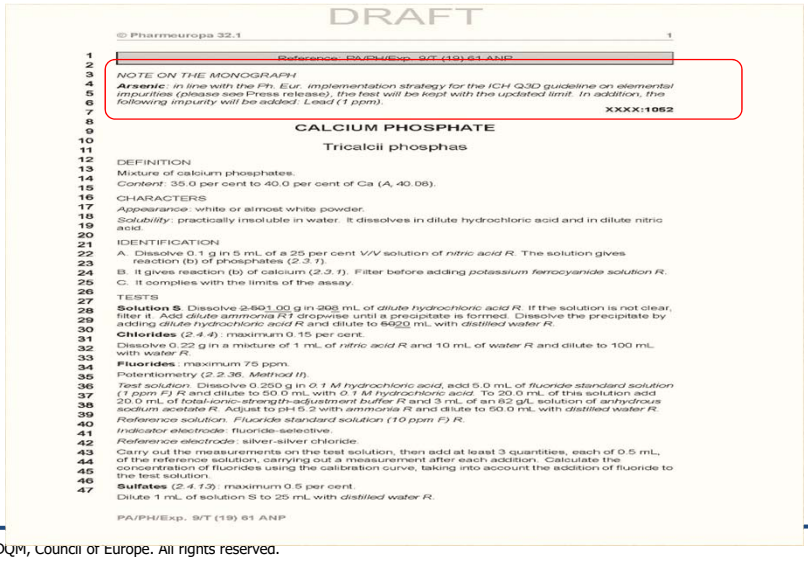
Example monograph (4): Calcium phosphate



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Reference: PA/PH/Exp. 9/T (19) 61 ANP

NOTE ON THE MONOGRAPH

***Arsenic**: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see Press release), the test will be kept with the updated limit. In addition, the following impurity will be added: Lead (1 ppm).*

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CALCIUM PHOSPHATE

Tricalcii phosphas

DEFINITION

Mixture of calcium phosphates.

Content: 35.0 per cent to 40.0 per cent of Ca (*A*, 40.08).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water. It dissolves in dilute hydrochloric acid and in dilute nitric acid.

IDENTIFICATION

A. Dissolve 0.1 g in 5 mL of a 25 per cent *V/V* solution of *nitric acid R*. The solution gives reaction (b) of phosphates (*2.3.1*).

B. It gives reaction (b) of calcium (*2.3.1*). Filter before adding *potassium ferrocyanide solution R*.

C. It complies with the limits of the assay.

TESTS

Solution S. Dissolve ~~2.50~~ 1.00 g in ~~20~~8 mL of *dilute hydrochloric acid R*. If the solution is not clear, filter it. Add *dilute ammonia R1* dropwise until a precipitate is formed. Dissolve the precipitate by adding *dilute hydrochloric acid R* and dilute to ~~50~~20 mL with *distilled water R*.

Chlorides (*2.4.4*): maximum 0.15 per cent.

Dissolve 0.22 g in a mixture of 1 mL of *nitric acid R* and 10 mL of *water R* and dilute to 100 mL with *water R*.

Fluorides: maximum 75 ppm.

Potentiometry (*2.2.36, Method II*).

Test solution. Dissolve 0.250 g in *0.1 M hydrochloric acid*; add 5.0 mL of *fluoride standard solution (1 ppm F) R* and dilute to 50.0 mL with *0.1 M hydrochloric acid*. To 20.0 mL of this solution add 20.0 mL of *total-ionic-strength-adjustment buffer R* and 3 mL of an 82 g/L solution of *anhydrous sodium acetate R*. Adjust to pH 5.2 with *ammonia R* and dilute to 50.0 mL with *distilled water R*.

Reference solution. *Fluoride standard solution (10 ppm F) R*.

Indicator electrode: fluoride-selective.

Reference electrode: silver-silver chloride.

Carry out the measurements on the test solution, then add at least 3 quantities, each of 0.5 mL, of the reference solution, carrying out a measurement after each addition. Calculate the concentration of fluorides using the calibration curve, taking into account the addition of fluoride to the test solution.

Sulfates (*2.4.13*): maximum 0.5 per cent.

Dilute 1 mL of solution S to 25 mL with *distilled water R*.

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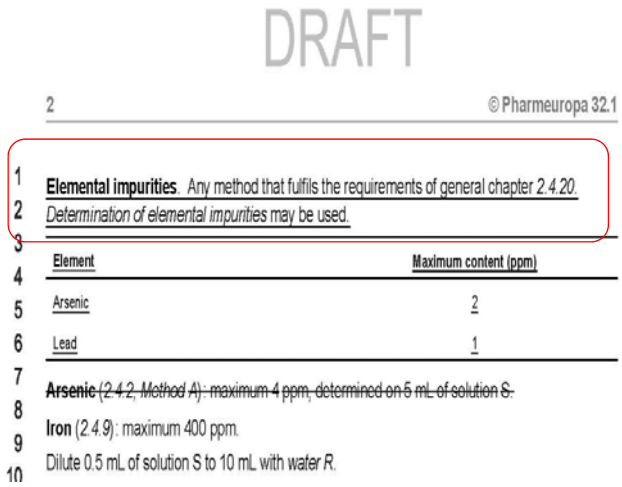
Example monograph (5): Calcium phosphate



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

Element	Maximum content (ppm)
Arsenic	2
Lead	1

~~**Arsenic** (*2.4.2, Method A*): maximum 4 ppm, determined on 5 mL of solution S.~~

Iron (*2.4.9*): maximum 400 ppm.

Dilute 0.5 mL of solution S to 10 mL with *water R*.

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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