Elemental impurities

Expectations for APIs and Excipients in the EU

Implementation strategy in the European Pharmacopoeia

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Elemental impurities

Content of the presentation

- EDQM/European Pharmacopoeia in Europe
- Current situation
- New situation after adoption of Q3D
- What will now happen in Europe
- Implementation strategy Ph. Eur.

Position of the EDQM/Ph. Eur. in Europe

Key words:

- Council of Europe, European Union and EDQM
- The EU regulatory framework in pharmaceuticals and its key players

The Council of Europe

Founded in 1949

Development of European common and democratic principles

47 member countries

Headquarters in Strasbourg

Core values:

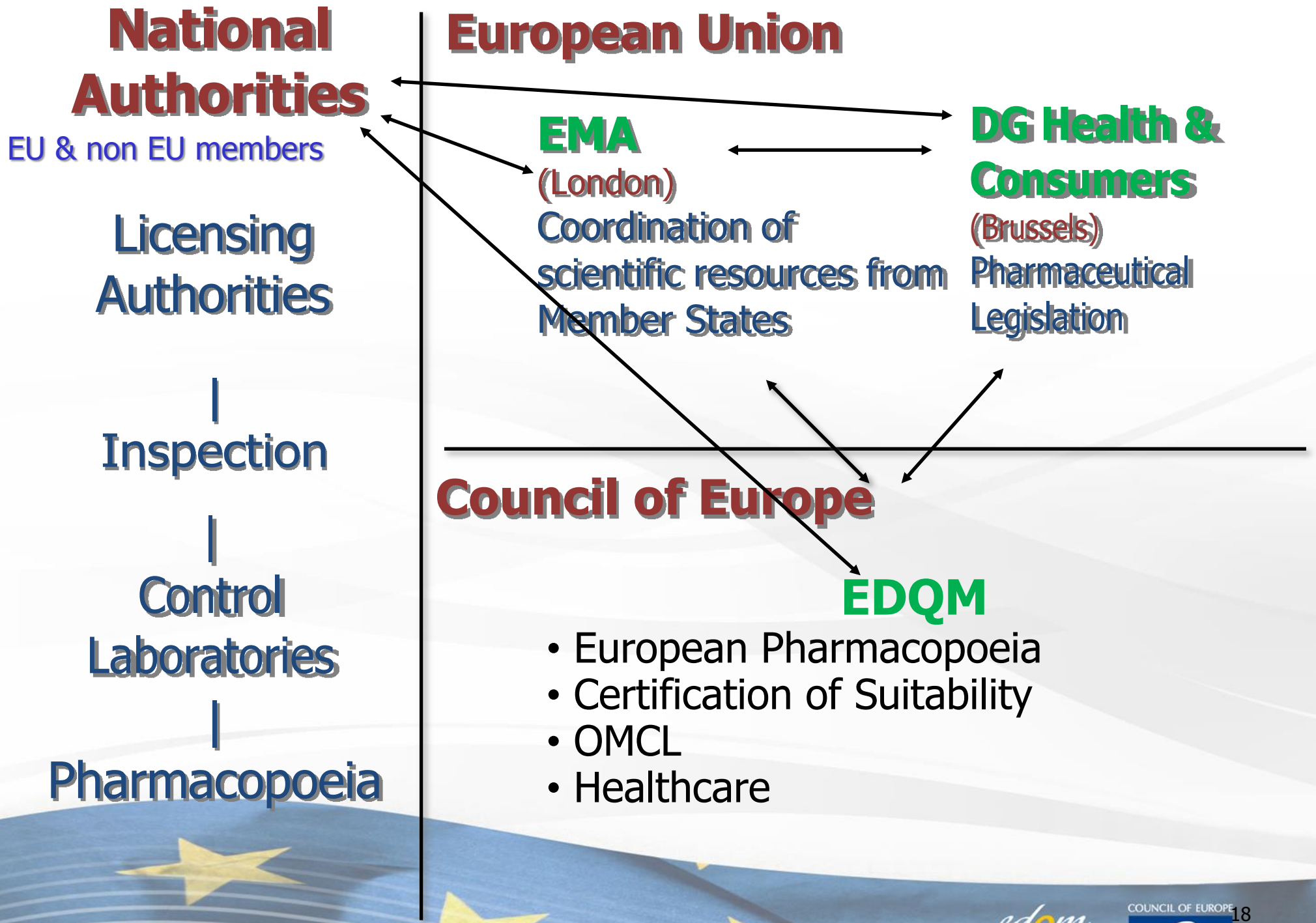
– protection of human rights
– pluralist democracy and the rule of law

The Council of Europe is not the European Union!

- **European Union (EU):** a unique economic and political partnership between currently 28 European countries ⇒ > 500 million citizens.
- **European Council:** The EU's main decision-making body. It defines the general political direction and priorities of the European Union.

Quality « Players » in the EU

- EMA and national competent authorities (NCA)
- CHMP/CVMP/HMPC Working parties:
  - Quality Working Party (+ CVMP + HMPC)
  - Biologicals Working Party
  - GMP/GDP Inspectors Working Group ….
- EDQM:
  - European Pharmacopoeia
  - OMCL network
  - Certification of Suitability ….



History of Heavy Metals test

- More than 100 years ago the classical heavy metals test was introduced in some Pharmacopoeias
- Initially based on sulphide precipitation in acidic and alkaline medium of metal impurities like As, Sb, Pb, Cd, Cu, Zn
- Later: precipitation medium changed to weak acid: useful to limit Pb and/or Cu used for water pipes and in factory equipment and lead contained in sulphuric acid produced by the lead chamber process

Current Situation

- Ph. Eur. monographs for APIs and excipients describe the classical « heavy metals » test (precipitate with sulphide)
- General chapter 2.4.8 « Heavy Metals » describing methods A to H (digestion methods)
- Some monographs describe specific tests, e. g. for arsenic, mercury, lead and others, sometimes using chemical methods, sometimes instrumental techniques (AAS, AES…)

Current Situation

- Advantage of 2.4.8 ☺:

Basically, no major instrumentation required, simple test

But:

Current Situation

- Disadvantage ☹:

Current Situation

Further disadvantages :

- Test is not selective
- Test is not sensitive
- Reagent is toxic and smells
- Under the given conditions only few metals are controlled (e. g. Pb, Pd, Cu)

General texts on elemental impurities in Ph. Eur.

5.20: reproducing EMA GL on catalysts and metal reagents

2.4.20: test for catalysts and metal reagents

2.4.2 Arsenic: 1-10 ppm (58 monographs)

2.4.8 Heavy metals: 1-50 ppm (771 monographs)

2.4.9 Iron: 1-500 ppm (145 monographs)

2.4.10 Lead in sugars: 0,5 ppm (16 monographs)

2.4.15 Nickel in polyols: 1 ppm (10 monographs)

2.4.27 Heavy metals in herbals: out of scope of Q3D

2.4.31 Nickel in hydrogenated oils: 1 ppm (10 monographs)

2.3.1 Identification of ions and functional groups

General monographs may contains limits for metals (extracts…)

Now: ICH Q3D adopted

- For new finished products, including new drug products with existing drug substances
- Including Biologicals and Biotech products
- Excluding: Herbals, radiopharmaceuticals, vaccines, blood
- *No longer excluded:* « crude products of animal and plant origin »
- Natural abondance 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 covers 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)

What will now happen in Europe?

CHMP (Committee for Medicinal Products for Human Use):

Approved as scientific EMA-guideline « ICH guideline on elemental impurities » in December 2014 *(EMA/CHMP/ICH/353369/2013)*

- Deadlines ->

- For new marketing autorisation applications: June 2016

- For authorised medicinal products: December 2017

What will now happen in Europe?

CVMP (Committee for Medicinal Products for Veterinary Use):

Decided not to apply the guideline for « products for veterinary use only » ->

Consequence: No change in current policy, APIs still to be controlled by the test given in the individual monograph

Implementation Strategy for Ph. Eur. (1)

Revision of general text 5.20 on « Metal Catalyst or Metal Reagent Residues »:

- Replacement of the current EMA guideline by the new ICH Q3D guideline

- Revision of general chapter 2.4.20 on « Determination of Metal Catalyst or Metal Reagent Residues »

Implementation Strategy for Ph. Eur. (2)

2.4.20 : « Determination of Metal Catalyst or Metal Reagent Residues »

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 for Ph. Eur. (3)

2.4.20 : « Determination of Metal Catalysts or Metal Reagent Residues »

- A revision is envisaged at least to adapt the wording (« elemental impurities »), further modifications may be necessary
- Chapter has been added on the work program of PDG (G07). USP currently describes two « reference procedures ». Reply from Ph. Eur. is underway.

Implementation Strategy for Ph. Eur. (3a)

And usually we find a solution with USP…

Joke !

Implementation Strategy for Ph. Eur. (4)

General monographs 2034 and 2619

- 2034: *Substances for pharmaceutical use*:

Does not necessarily require revision, as the guideline applies to drug products, not to APIs, a non-mandatory sentence may be introduced, still needs to be confirmed.

- 2619: *Pharmaceutical preparations:*

Will cross-reference the revised chapter 5.20.

Implementation Strategy for Ph. Eur. (5)

Specific monographs:

For human use (and human or veterinary use):

Reference to classical heavy metals test (chapter 2.4.8) will be deleted from individual monographs

For « veterinary use only »:

Reference to 2.4.8 will remain in these monographs

Chapter 2.4.8 will therefore remain unchanged for the time being

Implementation Strategy for Ph. Eur. (6)

Other chapters (e.g. 2.4.9 Iron; 2.4.10 Lead in sugars) and individual metal tests in scope of ICH Q3D :

No systematic deletion from individual monographs **but a review, case by case**, by the group of experts concerned to assess **the purpose and the added value of the test**; discussion whether it shall be kept or deleted

Objective

- Individual monographs and general chapters are revised until 1st January 2018 when ICH Q3D comes in force for existing medicinal products
- Suitable testing methods to be chosen by the manufacturer, in accordance with requirements provided in general chapter 2.4.20

Flexibility

- And at the end the Pharmacopoeias are always flexible:

Thank you for your attention