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

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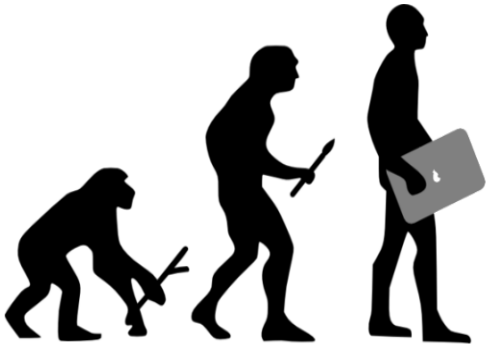
# Elemental impurities in the Ph. Eur.
## A revolution?!

# Elemental impurities in the Ph. Eur.

## ...Rather an 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

# EMA timelines

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

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.
- 11th January 2017: update on the Ph. Eur. implementation strategy

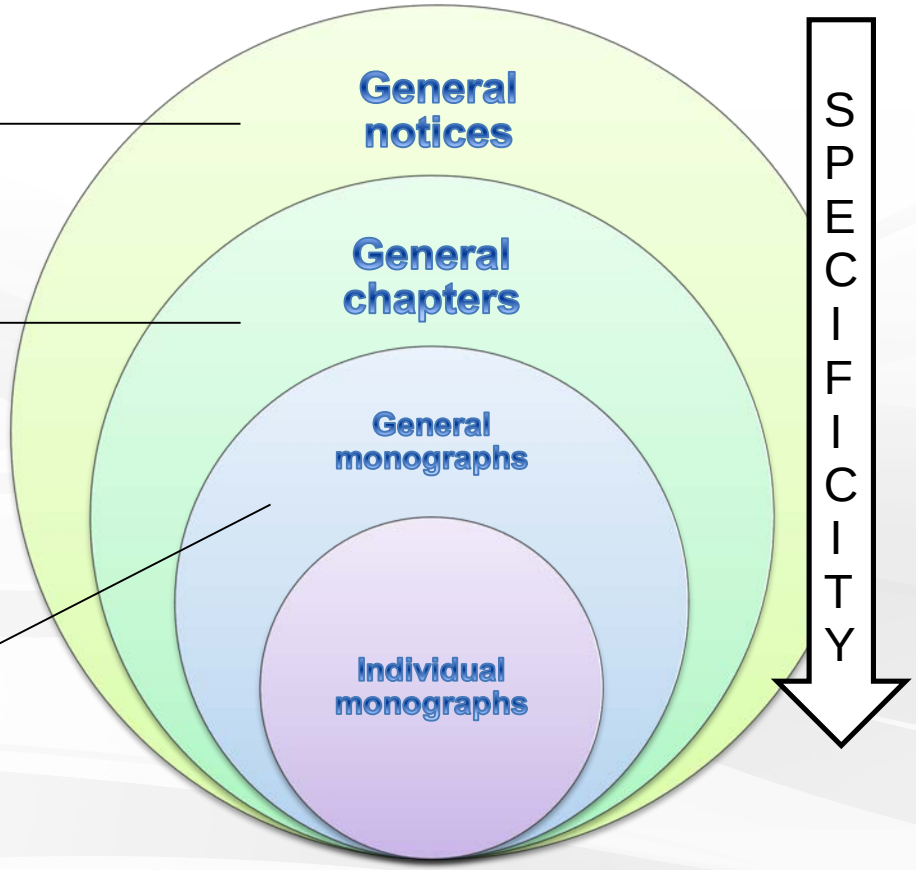
# Content and structure of the Ph. Eur.

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 requirements 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.



# What happened over the last year ?

We love it when a plan comes together...

# What happened over the last year ?

- 5.20: Replacement of the EMA guideline by parts of the introduction and the scope of ICH Q3D
- Pharmaceutical preparations (2619)
  - EIs must be part of the risk assessment for all preparations
  - ICH Q3D is legally binding for products in its scope
- Substances for pharmaceutical use (2034) :
  - Elements intentionally added are controlled during production.
  - Clarification for the deletion of specifications (unless otherwise prescribed) from monographs

# What happened over the last year ?

- Transition away from the heavy metals test to risk assessment or other methods in many texts

A little help for a “smooth” transition ?

# What are we up to now ?

Already practicing basketball with our versions of ICH Q3D ??..... Not quite yet !

# ICH Q3D still keeps us busy

- International harmonisation of chapter 2.4.20 Determination of EIs
- Monographs on containers under discussion
- Planning of revision of other chapters linked with EI testing (ICP methods)
- Early 2018: launch of Ph. Eur. EIs reference material for big 4 (Pb, Hg, Cd & As)
- Impact of the implementation strategy on individual monographs

➔Deletion/revision of specific metal tests

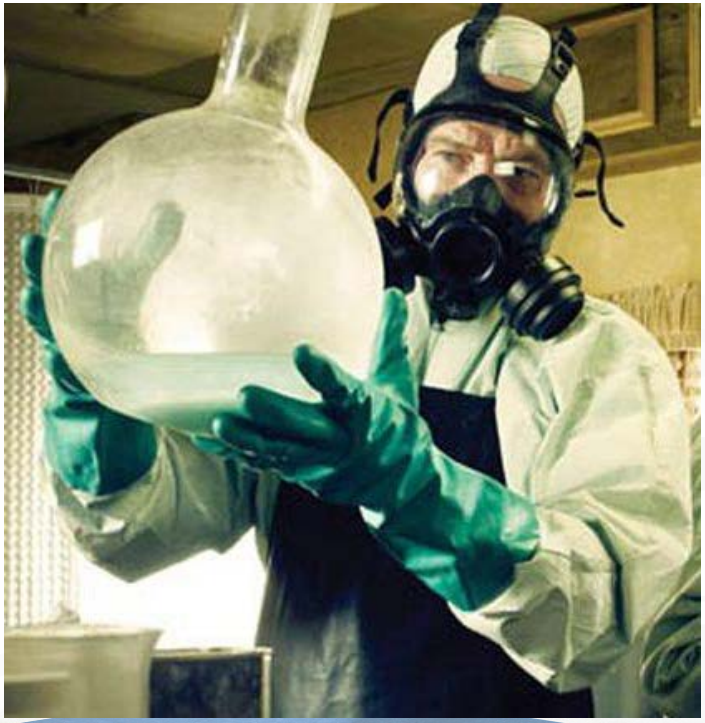
# Revision of specific metal tests
## - a differentiated approach -

5 categories based on potential sources of contamination as identified in ICH Q3D (§5.2)

1. Residuals resulting from elements intentionally added
2. not intentionally added but potentially present
3. potentially introduced from manufacturing equipment
4. potentially leached from container closure system
5. having no PDE (« Other elements »)

# Approach for specific EI tests

**1** Residuals resulting from elements intentionally added



- metal catalyst
- Specific of the production pathway
- Manufacturing secret
- No change control
- New sentence in substances for pharmaceutical use: must be controlled during production

➔ Delete the corresponding tests from monographs

**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

# Approach for specific EI tests

**2** not intentionally added but potentially present

- Elements naturally present in mined excipients
- Present the highest potential risk
- Purification very difficult
- Tests should remain with a mandatory status

➔ Delete tests for class 2B EI as highly unlikely to be naturally present (unless otherwise justified)

➔ Batch data needed to get the bigger picture (ICH classes 1,2A and 3)

# Approach for specific EI tests

❸ potentially introduced from manufacturing equipment

Out of scope ➔ GMP

❹ potentially leached from container closure system

Out of scope ➔ CCS studies

# Approach for specific EI tests

5 having no PDE (« Other elements »)


- Reduced toxicological risk

➔ Keep tests for defining the quality of the substance

# Specific metal tests – next steps

First phase (ongoing)

- Each group of experts involved to assess case by case whether the specific tests can be suppressed (categories ❶, ❸ and ❹) or maintained (category ❷)
- Special focus: Substances of natural origin (mainly mined excipients)
- First monographs have been published for consultation in Pharmeuropa 29.3

Second phase

- Obtain batch data and revise maintained tests / or add new ones, if necessary, based on batch data (also category ❺)

**Need for more expertise and support (especially from manufacturers) to revise / maintain these tests**

# Acknowledgments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Dr JL Robert, former chair of the EPC

Dr T Gosdschan present chair of the EPC

# Thank you for your attention!


HEAVY METALS DON'T ROCK