EU Regulatory Perspective and Expectations

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Disclaimer

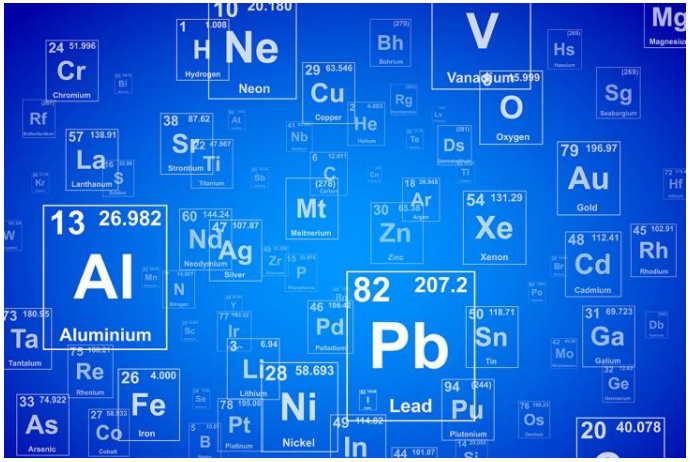
- EU regulators still have to build up an experience of applications based on ICH Q3D
- EU regulators still discuss how to apply ICH Q3D in practice
- EU regulators cannot yet be said to have a final understanding on how to implement ICH Q3D
- This is my attempt to share with you thoughts, ideas and concerns from EU regulators
- Quality Working Party will continue to work on the implementation of ICH Q3D – not at least taking into account the outcome of this workshop

EU regulators challenges

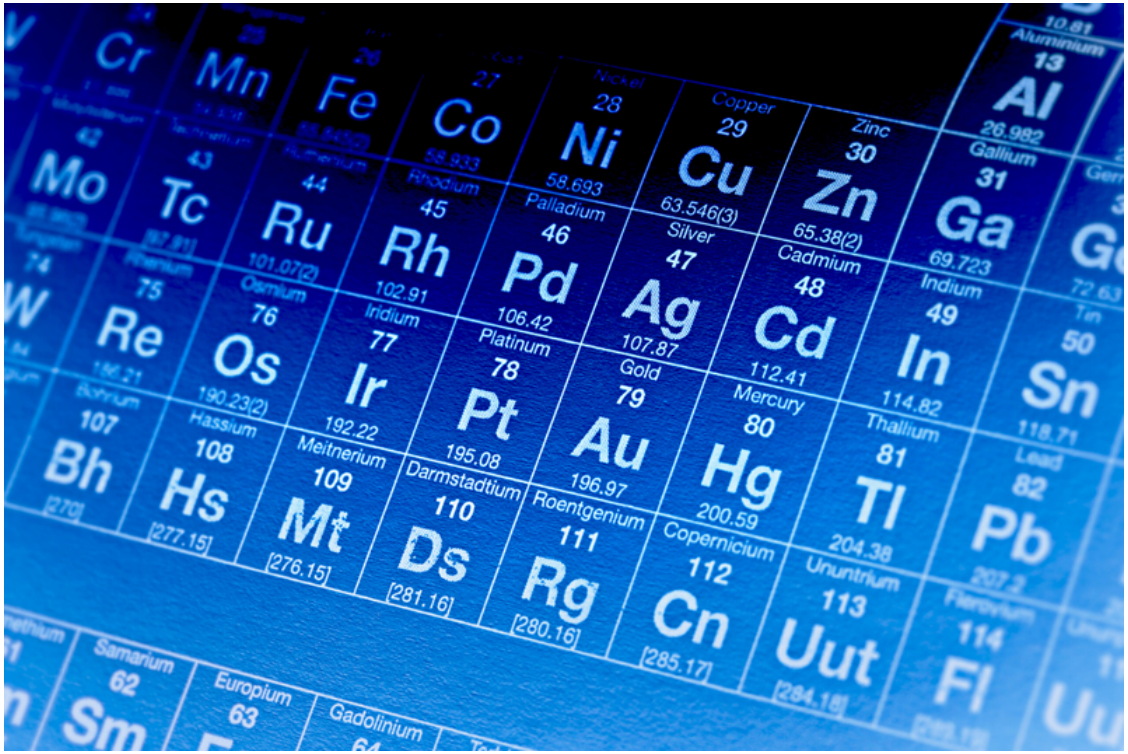
- A shift in paradigm
- Q9 Risk Management to be assessed with every application
- Leaving stricter rules for more flexibility – harmonised assessment?
- Challenges for ASMF:s and CEP:s?

Overview

- **Background**
- **Implementation scheme**
- **General expectations and considerations**



Background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The Guideline EMEA/CHMP/SWP/4446/2000

- Took 10 years and 3 consultations from start until coming into effect
- Addresses **intentionally added** elements (metals) in drug substance
  - because they are of the greatest concern
- Other sources of these elements also mentioned
  - *the concentration limits in this guideline are **in principle also applicable to residues from other sources** than catalysts and reagents. However, for these other sources adoption of a concentration limit and a validated method in the specification is only necessary in the very exceptional cases where these residues are known to be insufficiently limited by GMP, GDP or any other relevant provision.*

Differences at a Glance

ICH Q3D

- All sources of elemental impurities
- Focused on drug product contamination
- PDE:s for 24 elements
- Classification based on safety and occurrence
- Focused on risk management in line with ICH Q8-11

EU Guideline

- Catalysts and reagents
- Focused on drug substance contamination
- PDE:s for 15 elements
- Classification based on safety
- Does neither mention nor contradict the use of risk assessment

Comparison of PDE:s in Q3D vs. EU Guideline

New elements		Higher PDE	Lower PDE	Excluded
Cd	Pb	Pt (oral + inh.)	V	Mn
As	Hg	Ni (inh.)	Ni (oral + par.)	Fe
Co	Tl	Mo		Zn
Au	Se	Cu		
Ag	Li	Cr		
Sb	Ba			
Sn				

Risk based approach vs. strictly defined rules

- This is a scientifically sound approach
- It will however be more challenging to assess
- There is an increased risk for divergent views between assessors
  - In worst case leading to referrals
- QWP is dedicated to facilitate the implementation
- We still lack practical experience of assessing elemental impurities according to ICH Q3D

Implementation of ICH Q3D in the EU – a schedule

When should products comply with ICH Q3D in the EU?

- **CHMP has decided that**
  - New MA for new product (new active substance)
    - June 2016
  - New MA for product with existing active substance
    - June 2016
  - Marketed products including new MR applications of already approved products
    - December 2017

New Marketing Authorisations should comply from June 2016

- **This means**
  - Compliance with the Q3D PDE:s
  - The applicant should document the Risk Assessment and control approaches in an appropriate manner
- **On site**
  - The documentation of the Risk Assessment should be kept available for inspection
- **In file**
  - A summary of the Risk Assessment and any measures taken to ascertain compliance
  - The overall Control Strategy for elemental impurities including any specifications as needed

Existing marketed products should comply from Dec. 2017

- Risk Assessment should be performed, documented and be kept available.
- No variation is necessary if the Risk Assessment show that for compliance:
  - **No further controls** on elemental impurities to materials such as the designated active substance starting material, synthesis intermediates, active substance, excipients or the finished product are needed.
  - **No replacement or change of quality of materials** such as the designated active substance starting material, synthesis intermediates, active substance, excipients or of the manufacturing equipment is needed.
  - **No change of the manufacturing process** is needed.
- In other cases a variation is needed.
  - Categorised according the Variation Guidelines (Official Journal 2013/C 223/01)
  - Accompanied with the documentation required in the Variation Guideline.
  - In addition contain a summary of the Risk Assessment and the conclusions drawn.

During the products Lifecycle

- Product and process knowledge gained during the lifecycle to be used for improvements (ICH Q10)
- Risk Assessment to be **re-evaluated** upon changes e.g.
  - Synthetic routes
  - API or Excipient suppliers
  - Raw materials
  - Processes
  - Equipment
- Subject to internal Change Management process (ICH Q10) and where applicable regulatory Variations.

General expectations and considerations

- **Drug Product vs. Components approach**
- **Summary of Risk Assessment**
- **Control Threshold**
- **Number of batches**
- **Intentionally added elements**
- **Mined excipients**
- **Drug Product scanning**

Drug Product vs. Component approach

- The guideline describes different approaches to the Risk Management
- It is acknowledged that the choice may rely on factors not fully in the hand of the Drug Product manufacturer
- It is understood that for a particular product a mix of approaches may have to be applied
- From a science and a transparency point of view, EU regulators nevertheless strongly encourage the use of a Component approach

Component suppliers

- EU regulators urge on Drug Product manufacturers and suppliers to cooperate
  - To facilitate the Risk Assessment by exchanging information
    - Information from DP manufacturer on intended use
    - Information from supplier on possible elemental impurities
  - To use the ASMF or the CEP procedures whenever possible as a way to supply information useful for the Risk Assessment

Summary of Risk Assessment – in the File

- The purpose is to **tell a story** on what is done and the outcome
- Should contain the information needed to evaluate the **appropriateness and completeness** of the elemental impurity Risk Assessment.
- Raw data not expected, but **summary of findings** may be necessary
- The **justification** for the Control Strategy (what to control and not to control)

Application of Control Threshold

- In ICH Q3D compliance should be ascertained by **testing when necessary**
- The concept of Control Threshold is introduced to facilitate the decision on when it is necessary
  - *If the total elemental impurity level from all sources in the drug product is expected to be **consistently less than 30%** of the PDE, then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities.* (ICH Q3D)

What means *consistently below the Control Threshold*?

- An assurance that the likelihood of exceeding the PDE is negligible
- For many elements the observed or predicted levels will be far below this threshold and the decision will be easy
- The closer the levels are to the threshold, the more difficult to judge whether no further controls are needed.
- All sources of variability and uncertainty must be considered
- To allow the absence of controls, regulators must be convinced that the threshold will never be exceeded.

Application of Control Threshold – Number of batches

- The guideline states
  - *At the time of submission, in the absence of other justification, the level and variability of an elemental impurity can be established by providing the data from three (3) representative production scale lots or six (6) representative pilot scale lots of the component or components or drug product.*
- This number of batches **is a minimum** that may be sufficient for the decision unless the results are approaching the threshold
- Being close to the Control Threshold means that more batches may be necessary for concluding ”consistently below”.

Intentionally added elements – EMA guideline

- Until now – in line with the EMA guideline a **specification has been needed** (except for Fe and Zn)
  - *"If the synthetic or manufacturing processes have shown to result in the removal of a potential metal residue, routine testing of that metal residue may be replaced by non-routine (skip) testing. A metal residue can be considered adequately removed if, in 6 consecutive pilot scale batches or 3 consecutive industrial scale batches less than 30 % of the appropriate concentration limit was found.* ***A change from routine to non-routine testing does not mean that the test may also be deleted from the specification*****.**"

Intentionally added elements – ICH Q3D

- To comply with Q3D
  - Intentionally added elements must **always be included** in the Risk Assessment
- The need for a specification will **depend on the outcome** of the Risk Assessment
- It is preferred that the applicant, also for outsourced active substances, are fully **informed by the supplier** on the use of any sources of elemental impurities in the synthesis of the active substance.

Intentionally added elements – ICH Q3D

- Intentionally added elements in active substance should normally be known to applicant and authorities since
  - Details of the synthetic route including the use of catalysts or reagents is mandatory either
    - in the dossier for an in-house synthesised substance
    - in an ASMF or
    - in a CEP dossier for an outsourced substance
  - In case of not updated CEP:s – applicants may have to request information to the risk assessment from the CEP holder or generate data on his own.

Intentionally added elements – catalyst used in the last step of the synthesis

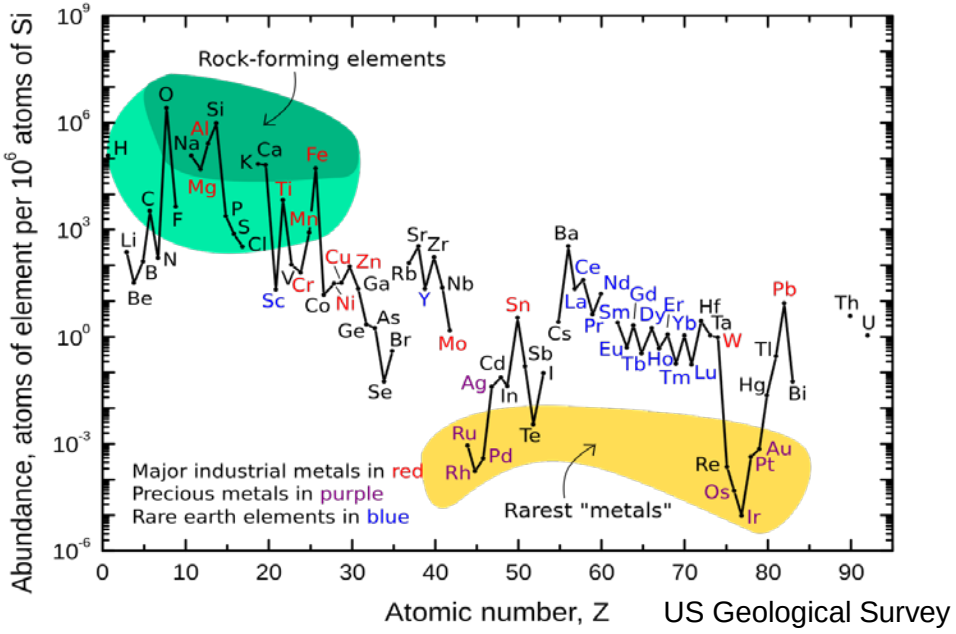
- This constitutes an elevated risk
  - *Impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations (e.g., washing, crystallisation of isolated intermediates) than impurities generated late in the manufacturing process, and are therefore less likely to be carried into the drug substance* (ICH Q11).
- Special considerations are warranted

Intentionally added elements – catalyst used in the last step of the synthesis

- Less purging reassurance compared to a synthesis with multiple subsequent steps
- Possibly greater impact of any unexpected events
- Due to this elevated risk
  - The normal expectation will be **to have a specification**
    - skip testing may be possible
  - The absence of a specification must be justified by **strong evidence** of robust purging
  - To apply the Control Threshold to eliminate a testing, borderline results will most likely not be accepted
    - Consistently below = well below (order of magnitude)

Mined material – originating from the Earth Crust

- In some geological environments certain elemental impurities may be abundant
- Needs to be taken into account in Risk Assessment when material is sourced from minerals



Mined material

- **Directly mined material, e.g.**
  - Sodium chloride
  - Titanium dioxide
  - Calcium carbonate
  - Talc
- **Inorganic salts derived from mined material e.g.**
  - Calcium hydrogen phosphate
- **Simple organic salts made with mined material e.g.**
  - Ferrous fumarate

Mined material – special considerations

- **The natural level of elemental impurities may vary from one mine/quarry to another**
  - It may even vary within a pit
- **Compliance with Q3D may require**
  - Specifications with routine testing
  - Selection of vendors
  - Selection of batches

Drug Product scanning

- It has sometimes been proposed that the simplest way of complying with the guideline would be
  - to scan a number of batches of Drug Product
  - to decide on the need for controls based on this
- From a regulatory point of view
  - Analytical data only without a risk assessment will not be sufficient to justify the omission of testing for an element
  - Without an acceptable risk assessment, only full routing scanning of all elements can ensure compliance with the guideline

Thank you for your attention!