# ICH Q3D Implementation in Europe - EMA Perspective

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# Disclaimer

This presentation intends to share experiences from an EU quality assessor point of view.

The thoughts expressed represents the view of the presenter and do not necessarily reflect the opinion of MPA, EMA or QWP/BWP.

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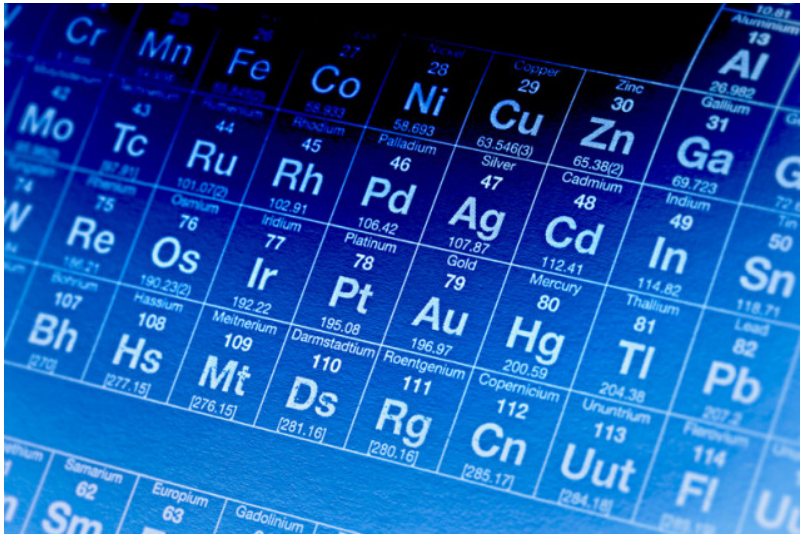

# Implementation timelines in EU

Products should comply with the ICH Q3D Guideline for Elemental Impurities from:

**June 2016**

New marketing authorisations for new products containing new or established active substance

**December 2017**

Marketed products (including new mutual recognition applications of already approved products and line extensions)

# Implementation - new marketing authorisations

- Initially, ICH Q3D requirements were not routinely addressed in new MAAs.
- Now, 4 years after implementation, information is usually provided in the initial submission.
- If old dossiers are re-used, this new requirement is sometimes forgotten.
- Increased awareness and understanding of EIs of all parties involved in drug manufacturing as well as regulators.
- Few products where EI needs to be controlled by final product specifications. Controls are applied only when needed based on science and risk management.

# Implementation - marketed products

- Guidance provided by EMA on the implementation to ensure a common approach among the national authorities in EU.

- If, based on the risk assessment, no additional control of EIs, no change of quality of materials or no change in manufacturing process is needed – no notification to authorities.

- Information supporting compliance with the guideline should be available for inspection.

- A few risk assessments of marketed products have been recieved for review. Generally, no testing needed.

# Drug product *vs* component approach

- Component risk management approach is used predominantly and has advantages from a science and transparency point of view.
- Drug product approach might be a suitable option when all information to progress with a component approach is not available to the MAH/drug product manufacturer.
- Both options includes risk assessment.
- Without risk assessment, routine testing of all elements would be required to comply with ICH Q3D.

# Drug product approach

- Scanning for EI's in finished product rather than in the different components of the product.
- The analytical data in itself do not predict EI levels in future drug product batches and is therefore not sufficient to justify omission of specification testing.
- The data should instead be used as part of the risk assessment.
- The extent of analytical testing needs to be in proportion to the identified risk.
- Frequent misconception that this approach involves only presentation of batch data to show EI levels below PDE. A risk assessment is also required.

# Risk assessment

- Typically, informal risk management processes are followed.
- Needs to be quantitative since the risk is related to the PDE.
- Relevant elements (based on the classification) are generally considered.
- Not always clear if intentionally added elements have been considered.
- Regularly we see additional elements included in the RA without explaining the reason for the inclusion.


Identify
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# Sources

- Sources pointed out in the guideline are generally covered.
- Low risk of EIs from water/utilities, manufacturing equipment and container closures for solid formulations. A general assessment (non-product specific) is often performed and usually accepted.
- For liquid and semi-solid dosage forms, leachables from the container closure should be investigated and considered in the RA.
- Drug substance and excipients considered main contributors and should be assessed more thoroughly.

# Drug substance

- Since the RA should be quantitative – data on EI levels in the drug substance is needed.
- Information usually provided but often unclear with regards to number of batches tested and if all manufacturers are covered.
- For ASMF/CEP:
  - Processes that provide an option for the drug substance manufacturer to compile a separate dossier with the drug substance information that is not fully disclosed to the drug product manufacturer.
  - EI information provided will be assessed but without confirming compliance with ICH Q3D. Sufficient information will be reported on CEP/in the assessment report to inform the drug product manufacturers risk assessment.
  - Introduction of test for elemental impurities in drug substance specification (by variation) is to some extent used as a mean to inform drug product manufacturers – mainly for ASMFs.
  - Submission of RA in CEP updates – information included in published certificate.

# Excipients

- Excipients that originate from mined material (e.g. calcium phosphate, titanium dioxide, calcium carbonate, talc ) may have a natural variability in elemental impurities level. The possible inherent variation is not always discussed and taken into account in the RA.

- If high amount of an excipient is used in the formulation and high maximum daily dose, compliance with PDEs could be challenging.

- If the excipient is controlled in accordance with Ph. Eur, the RA needs to take into account any potential EI controls in the monograph.

- Control in accordance with a Ph. Eur. monograph do not guarantee ICH Q3D compliance.


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# Analytical considerations

- It does not appear to be a problem to achieve required sensitivity of the analytical methods used to generate data.

- Analytical methods should be suitably validated. We do not require the validation report in the MAA but information needed to interpret the data, e.g. LoD/LoQ of the method, should be provided. This needs to be requested on a regular basis.

# Observed/predicted levels

- The origin of the data presented should be clearly specified – this is often missed.
  - Batch data/CoA
  - Specification limit
  - Literature data
  - etc.

- Variability should be considered when defining the data requirements and evaluating the data.

- Concentration limits derived from the PDE sometimes presented in the RA as the predicted maximum level in the components – this could be done only if the EI is controlled to this limit by e.g a specification.

# PDE

- PDEs for the relevant administration route are generally applied.
- Option to justify a level higher than the established PDE is not often seen.
- If an administration route not covered by the guideline:
  - A justification should be given for the use of oral/inhalation/parenteral PDE– not always included.
  - The option to apply a correction factor taking into account bioavailability of the element *via* the intended route of administration is rarely explored.

# Evaluation

- In the evaluation step, the control threshold (<30% of PDE) is generally used to justify omission of specification control.

- Level should be consistently below 30 % of PDE to justify not performing specification testing.

- If the risk to exceed the PDE (or control threshold) for an element is concluded high in the RA, it is not neccessarily sufficient to present analytical data from a few batches of drug product demonstrating low levels. Routine testing might be needed to manage the identified risk.

- However, if available analytical results indicate compliance with the guideline, skip testing (non-routine testing) could be an acceptable option until sufficient data has been generated.


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# Summarize and document

- The quality of the RA varies but majority of RA reviewed are deemed acceptable.
- Sometimes very brief and not always possible to follow the different steps of the RA – it should be clearly presented what has been considered, done and concluded.
- Elements are frequently missed out in discussions/result tables
- The summary should:
  - **be quantitative**, also when not based on own measurements
  - make it possible to **follow the calculations** leading to the numbers that are compared with the PDE's
    - tables may be a good way to be transparent and give an overview
    - do not leave steps out
  - contain a **justification** for the **Control Strategy** (what to control and not to control)
- Example for component approach RA available in appendix 4 and in the training material.

# Control

- In most cases – the conclusion of the risk assessment is that no further control is needed for any element. Routine testing of drug product is rarely proposed.

- The link between level of risk and the control strategy is however not always clear. Sometimes a risk to exceed the PDE is identified but no control proposed.

- Is the RA seen as a formal exercise where the outcome ’no further control needed’ is always expected?

# Challenges – from an assessors perspective

- Risk-based approach more difficult to assess
  - How to determine if the impurity level is consistently below 30 % of PDE? How many batches?
  - How much data is needed to assure that an intentionally added element will not exceed PDE in the final product.

- Increased risk for divergent views between assessors
  - Training for assessors available
  - Local alignment activities
  - Difficult cases are discussed in QWP/BWP

# Top 6 deficiencies:

- Data is missing – could be for a specific element or a specific component.
- Data is presented but source not clear.
- Information of LoD/LoQ missing – what does ’not detected’ means?
- Intentionally added elements are not discussed.
- Difficult/impossible to follow the risk assessment – part of the story is missing.
- Link between the RA and proposed control strategy is missing.

# Thank you for your attention!