EMA Guidance & Current Experience with New Drug Submissions

PQRI/USP Elemental Impurities November 2017
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Acknowledgement and Disclaimer

- This presentation is based on discussions within the ICH Q3D EWG and IWG, within the QWP as well as the experience from actual submissions assessed by the Swedish MPA
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Content

- Implementation Issues and EMA Guidance on them
- ICH Q3D on Elemental Impurities – Current Experience
  - What is the picture so far
  - Summary of Risk Assessment
    - A real example
    - Regulators expectations

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Q3D Implementation Timeframes

- 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

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Existing Marketed Products – Should Comply from December 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.

Q3D Implementation Issues

- After the adoption of the Q3D Guideline, discussions among Regulatory Assessors as well as with Industry Representatives have
  - revealed some areas that would benefit from some further clarification/interpretation
  - raised some questions in relation to the previous EMA Guideline on Catalysts and Reagents
  - indicated a need to clarify the role of the European ASMF and CEP systems in relation to Q3D

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Implementation of Q3D in the EU

- I will highlight some aspects
  - Use of the Control Threshold
  - Number of batches needed
  - Intentionally added elements in last step
  - Drug product approach
- Some of these are also discussed in a document
  - Implementation strategy of ICH Q3D guideline (EMA/CHMP/QWP/115498/2017)
    http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500222768.pdf

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Testing for Elemental Impurities

- In ICH Q3D compliance should be ascertained by ***testing when necessary***
- Companies want to know when it is not necessary
  - no further controls or measures are necessary, where the Risk Assessment/Management predict a low risk
- The basis for this prediction (the Risk Assessment) must be more than just an analytical snapshot
  - as it will provide an assurance for the future that the likelihood of exceeding the PDE is negligible

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The Use of the Control Threshold

- The concept of Control Threshold is introduced to facilitate the decision on when it is necessary to test
  - *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)

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What is Meant by *Consistently* Below the Control Threshold?

- The Control Threshold is not an extra limit needed to comply with
  - but between the Control Threshold and the PDE compliance must be ascertained by controls
- Therefore it is necessary to judge if being below the Control Threshold is likely also in the future
  - variability and uncertainty must be considered
- To justify not testing, it should be unlikely that the Control Threshold will be exceeded in the future
  - the decision will be easy when the levels are far below
  - the closer the levels are, the more difficult to judge

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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.*
- To justify no further controls, this number of batches is a minimum that could be sufficient
- Levels approaching the Control Threshold means that more batches may be necessary for concluding ”consistently below”
  - the number of batches should be commensurate with the risk of exceeding the Control Threshold

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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

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Intentionally Added Elements – ICH Q3D

- Intentionally added elements in active substance should 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 itself in case of an in-house synthesised substance
    - in an ASMF or
    - in a CEP dossier in case of an outsourced substance

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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

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Intentionally Added Elements – Catalyst used in the Last Step of the Synthesis

- Less reassurance from purging compared to a synthesis with multiple subsequent steps
- Therefore possibly greater impact in case of any unexpected events
- Due to this
  - the need to have a specification is more likely
  - the absence of a specification must be justified by evidence of purging
  - where evidence is scares but promising, skip testing may be possible

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Drug Product Approach

- The Drug Product Approach is an option in Q3D
- It is possible to comply with Q3D by testing the product
- To justify the omission of testing for an element,
  - there must be some level of understanding of possible sources (Risk Assessment)
  - representative batches tested e.g. covering all suppliers
- With a Risk Assessment – depending on its outcome – the number of batches tested should be commensurate with the risk of the elemental impurities present

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ICH Q3D on Elemental Impurities – Current Experiences after June 2016

- We have seen some nice examples where we have had nothing to complain about, but
  - a high number of applications
    - are completely missing any Summary of Risk Assessment
    - have included far too short (high level) Summary of Risk Assessment
- In between we have good examples that have been ambitious but may have missed some link in presenting a compelling ”story”

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Selection of Approach

- Analysis of Drug Product
  - usually with different levels of Component Risk Assessments to justify some omission of testing
  - but also some cases without Risk Assessment, routinely analysing all elements
- Component Approach
  - quite common
  - ending up with no or only limited routine testing
  - a large interest from API manufacturers to include an active substance Risk Assessment in the CEP (more than 150 so far)

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Approaches for Other Routes of Administration

- Development of an Acceptable Limit (AL)
  - recalculation of oral PDE considering bioavailability (topical)
- Applying existing PDE:s that can be argued to be sufficiently protective
  - complying with oral PDE (rectal)
  - complying with parenteral or inhalation PDE (nasal, ocular)
- Applying an extra safety margin
  - complying with oral PDE divided by 100 (vaginal)

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Any Observed Risks?

- The lack of, or deficient, Summary of Risk Assessments are usually updated and approved after one/two rounds.
- If not – applications are typically rejected/withdrawn on other grounds as well.
- We have not rejected an application based unacceptable presence of elemental impurities
  - summations based on LoQ:s has occasionally been insufficient to conclude levels being below the Control Threshold

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A Real Example – Summary of Risk Assessment
New application for an Oral Solution

- *The assessment examined all relevant sources of elemental impurities. During the evaluation of the drug substance, the excipient, the manufacturing process and the packaging material it was identified that the following elemental impurities should be further investigated: Cd, Pb, As, Hg and Ni*.

- *Using Option 2b in the guideline the permitted concentration limits of elemental impurities across drug product component material for a maximal daily dose was calculated and compared to the observed levels of the identified elemental impurities in the excipients and drug substance as declared by the vendor.*

A Real Example – Continued...

- *The results showed that none of the identified potential elemental impurities was above the permitted daily concentration. Of all the potential elemental impurities only lead was above the 30% PDE. However since the potential major contributor [Excipient] is controlled by Ph.Eur. no further control strategy was introduced.*

Potential risks	Action/mitigation
Elemental impurities from drug substance	No action required; process control strategy sufficient
Elemental impurities from equipment	No action required; Quality system control strategy sufficient
Elemental impurities from nitrogen	No action required; negligible risk
Elemental impurities from container closure systems	No action required; negligible risk
Elemental impurities from excipients	No action required; major component controlled by Ph.Eur.

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A Real Example – Continued…

- *The risk assessment for elemental impurities in [Product] was completed. The assessment show that the design and implementation of the inherent controls in the manufacturing and quality system processes ensure that the levels of identified elemental impurities are maintained at or below their respective PDEs.*

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A Real Example – The Assessors Concern

- This Summary is not telling a compelling “story”
  - which maximum daily intake of the product is used and how is that calculated?
  - how were the potential sources of EI examined?
  - on what grounds where elements selected or not selected for further investigation?
  - how was Option 2b implemented (individual concentration limits for each element in each component)?

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A Real Example – Continued…

- what were the observed or predicted levels of identified elemental impurities that were compared to the established limits?
- how far below the control threshold were these elemental impurities levels?
- how did the Ph.Eur. limit for lead fit into the Company's Option 2b model?
- there was no critical appraisal on the basis for vendor declaration and there validity (specifications, monitoring, other grounds etc.)

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A Real Example – Continued…

- Only vague statements without discussion where presented
  - Equipment – quality system control strategy sufficient
  - Nitrogen – negligible risk
  - CCS – negligible risk
- In conclusion it is stated ”The assessment show …”
  - But nothing is shown in the Company’s ”Summary of Risk Assessment” that enables the Quality Assessor to do a proper assessment

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So what are Regulators Expectations?

- The Summary of Risk Assessment should
  - follow the principles lined out in ICH Q3D
  - contain what is **needed to evaluate** the appropriateness and completeness of the Risk Assessment process.
  - tell a story to the assessor on what has been **considered, done and concluded**
    - a narrative that clearly explain the assessment made, including all assumptions, calculations etc. made

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Regulators Expectations – Continued…

- The Summary of Risk Assessment should
  - **be quantitative**, also when not based on own measurements
    - raw data not necessary, but summary of findings is expected where applicable
  - 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
  - contain a justification for the **Control Strategy** (what to control and not to control)

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Are there Good Examples of Summaries of Risk Assessment?

- The length of good examples submitted preclude introduction in this presentation
- Please,
  - learn from the calculation examples in Annex 4 of Guideline
  - be inspired by the Case studies of the Training Material on www.ich.org
    - Case study 1b is an illustrative example of what a submission could look like
- Important aspects are well illustrated in this Case study as extracted on the next slides

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Oversight of Scope of Risk Assessment
(Note: Case Study is an Example – not a Template)

Element	Class	Intentionally added?	Consider in risk assessment	Justification
Cd	1	no	Yes	Included in risk assessment for all components
Pb	1	no	Yes	Included in risk assessment for all components; vendor provided information on observed levels in talc and calcium dihydrogen dihydrate
As	1	no	Yes	Included in risk assessment for all components
Hg	1	no	Yes	Included in risk assessment for all components
Co	2A	no	Yes	Included in risk assessment for all components
V	2A	no	Yes	Included in risk assessment for all components
Ni	2A	no	Yes	Included in risk assessment for all components
Tl	2B	no	No	Not intentionally added in any component.
Au	2B	no	No	Not intentionally added in any component.
Pd	2B	Yes	Yes	Pd is used in the penultimate step of the drug substance process
Ir	2B	no	No	Not intentionally added in any component.
Os	2B	no	No	Not intentionally added in any component.
Rh	2B	yes	Yes	Rh is used to prepare one of the starting materials.
Ru	2B	no	No	Not intentionally added in any component.
Se	2B	no	No	Not intentionally added in any component.
Ag	2B	no	No	Not intentionally added in any component.
Pt	2B	no	No	Not intentionally added in any component.

Source: ICH

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Summarize Evaluation

Potential source of elemental impurities	Information evaluated	Further consideration in the risk assessment?
Drug substance	Pd is used in the penultimate step of the synthesis. Batch data and commercial scale data review. Class 1 or 2A elements are not intentionally added and are not found as impurities in the drug substance.	Consider potential impact of Pd levels in the drug substance on the drug product.
Excipients	Information supplied from vendors confirms no elements (Class 1, 2 or3) are intentionally added. Vendor certificates of analysis indicate negligible levels of the following Class 1 and 2A elements: Cd, As, Hg, Co, Ni and V. Vendor certificates of analysis for talc and calcium hydrogen phosphate dihydrate indicate the presence of Pb.	Consider the potential impact of Pb levels in the 2 identified excipients on the Pb levels in the drug product. The currently observed levels can be found in Table 1. Elemental impurity data are generated using a validated method where the Limits of quantitation are below the control threshold, based on the ICH Q3D: Table A2-2 concentrations.

Source: ICH

Summarize any Data

Component	No. of lots[1]	Element	Mean µg/g	Std. Dev.[2] µg/g	Min µg/g	Max µg/g	Upper 95% Confidence Limit µg/g
Drug substance	3	Pd	36	3	33	39	41
Talc	3	Pb	4	5	0.3	10	12
Calcium hydrogen phosphate dihydrate	3	Pb	4	4	1	8	10

Source: ICH

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Quantitative Summary

- Don´t forget to be quantitative in the Risk Assessment
  - Summarize any analytical results
  - Show the contribution of upstream controls
  - Explain the magnitude of any purging
  - Quantify worst case scenarios to justify negligible contributions
  - Etc.

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Show the Quantitative Relation to PDE

Component	Mass of Component in a 50 mg tablet g	Mass of Component in a daily dose (2 tablets) [1] g	Pb specification limit µg/g	Total lead contribution to the drug product µg
Greatstuff drug substance	0.05	0.1	-	-
Microcrystalline cellulose (PH102) (MCC)	0.09	0.18	-	-
Calcium hydrogen phosphate dihydrate	0.46	0.92	4	3.68
Magnesium stearate	0.003	0.006	-	-
Croscarmellose sodium	0.3	0.6	-	-
Talc	0.057	0.114	5	0.57
Hydroxypropylmethylcellulose	0.04	0.08	-	-
Total tablet weight, g	1	2		
Maximum lead per daily dose when excipient levels are at the specification limits, µg/daily dose				4.25
Lead (Pb) PDE, µg/day				5

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Relation to the PDE

- Don’t forget to show the relation to the PDE
- Also very important when you refer to the Control Threshold as justification for no further controls
  - The closer to the 30% of PDE results are – the more evidence is needed (e.g. more batch results)
  - Critically discuss the variability
    - Observed variability
    - Possible future variability – e.g. mined material

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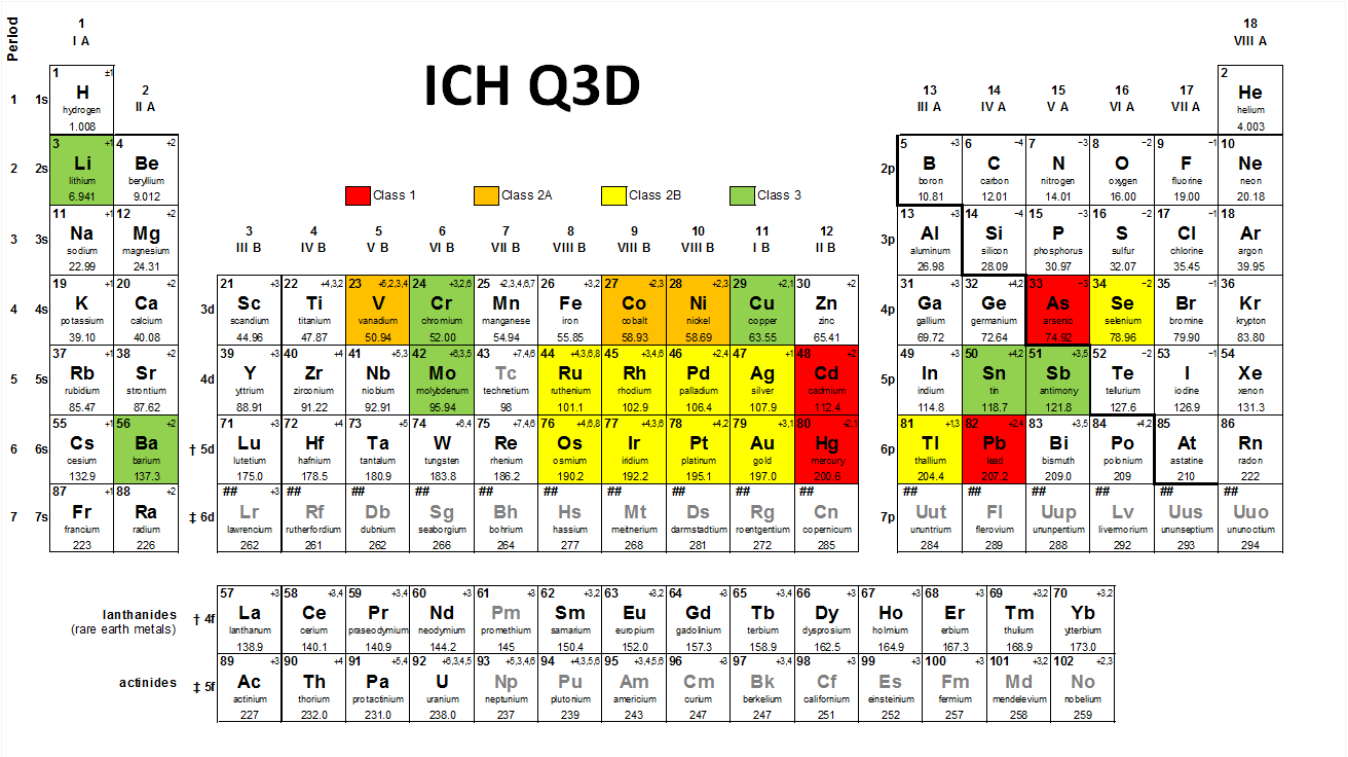
Thank you!



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