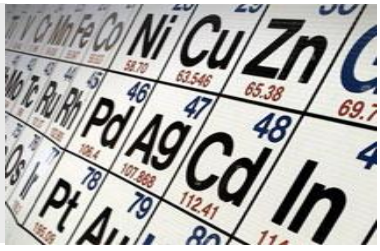
EUROPEAN PHARMACOPOEIA & QUALITY OF MEDICINES: TACKLING FUTURE CHALLENGES TOGETHER

27-28 September 2016

Tallinn, Estonia



Implementation of ICH Q3D: Challenges and opportunities

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27 September 2016

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Overview

- ICH Q3D overview – guideline development
- Safety evaluation – development of PDEs
- Product elemental impurity risk assessments
- Aligning assessment conclusions and control strategy
- Implementation challenges and opporunities

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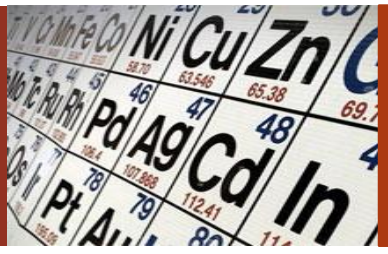

ICH Q3D Guideline development

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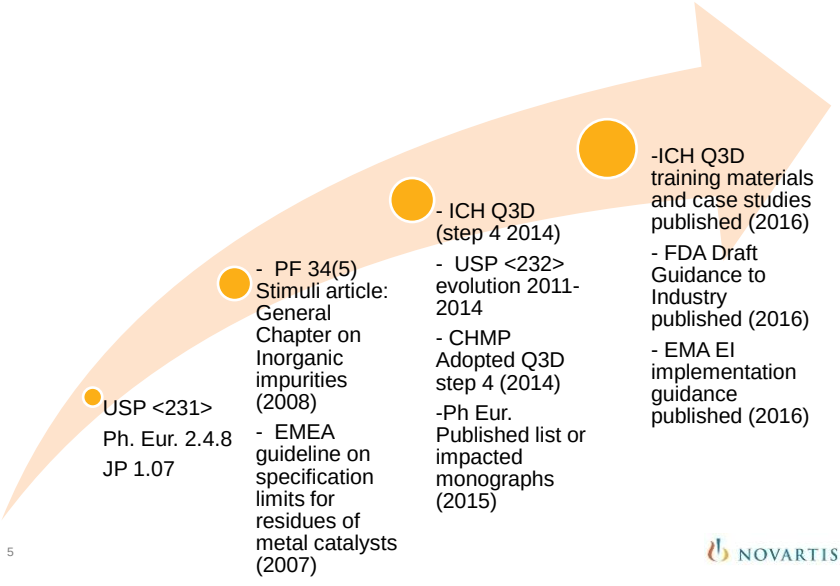
Evolution of elemental impurity standards



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ICH Q3D Deliverables

Original direction

- Globally harmonized policy for limiting elemental impurities in drug products
- Harmonised, safety-based limits for elemental impurities, especially those of highest toxicological concern
  - Selection of elements to control
  - Methodology for establishing safety-based limits
  - Permitted daily exposures for specific elements
- Appropriate risk-based approach to ensure control for elements likely to be present in drug products and ingredients.
- Guideline document
  - Main body, references and glossary (pages 1-17)
  - Appendix 1: Method for Establishing Exposure Limits (pages 18-20)
  - Appendix 2: Established Permitted daily exposures (PDEs) for Elemental Impurities by oral, parenteral and inhalation routes of administration (pages 21-22)
  - Appendix 3: Individual Safety Assessments for 24 elements (pages 23-67)
  - Appendix 4: Illustrative Examples (pages 68-73)

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ICH Q3D Deliverables

Final guideline structure

Document organization

- Main body, references and glossary (pages 1-17)
- Appendix 1: Method for Establishing Exposure Limits (pages 18-20)
- Appendix 2: Established Permitted daily exposures (PDEs) for Elemental Impurities by oral, parenteral and inhalation routes of administration (pages 21-22)
- Appendix 3: Individual Safety Assessments for 24 elements (pages 23-67)
- Appendix 4: Illustrative Examples (pages 68-73)

ICH Q3D Deliverables

Implementation Working Group – Posted /soon to be posted on the ICH website

- Training Module 0: Introduction to the Q3D Guideline
- Training Module 1: Other Routes of Administration
- Training Module 2: Justification for Elemental Impurity Levels Higher than an Established PDE
- Training Module 3: Acceptable Exposures for Elements without a PDE
- Training Module 4: Large Volume Parenteral Products
- Training Module 5: Risk Assessment and Control of Elemental Impurities
- Training Module 6: Control of Elemental Impurities
- Training Module 7: Converting between PDEs and Concentration Limits
- Training Module 8: Case studies (1a: Solid oral dosage form – internal documentation, 1b: Solid oral dosage form – example dossier submission, 2: Parenteral product, 3: Biotechnological product
- Training Module 9: Frequently Asked Questions

Safety evaluation

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Key evaluation definitions

- **Permitted Daily Exposure (PDE)**: The maximum acceptable intake of elemental impurity in pharmaceutical products per day.
- **Minimal Risk Level (MRL)**: An *MRL* is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure
- **Modifying Factor (MF)**: An individual factor determined by professional judgment of a toxicologist and applied to bioassay data to relate that data to human safety. (ICH Q3C)
- **Safety Factor (SF)**: A composite (reductive) factor applied by the risk assessment experts to the No-Observed-Adverse-Effect Level (NOAEL) or other reference point, such as the benchmark dose or benchmark dose lower confidence limit, to derive a reference dose that is considered safe or without appreciable risk, such as an acceptable daily intake or tolerable daily intake (the NOAEL or other reference point is divided by the safety factor to calculate the reference dose). The value of the safety factor depends on the nature of the toxic effect, the size and type of population to be protected, and the quality of the toxicological information available. See related terms: Assessment factor, Uncertainty factor. (IPCS, 2004)

Safety evaluation considerations

- The factors considered:
  - The likely oxidation state of the element in the drug product;
  - Human exposure and safety data when it provided applicable information;
  - The most relevant animal toxicity study;
  - Route of administration, and
  - The relevant endpoint(s) – what are the specific endpoints of concern
  - Standards for daily intake for some EI exist for food, water, air, and occupational exposure. Where appropriate, these standards were considered in the safety assessment and establishment of the PDEs
    - MRL, threshold limit value—time weighted approach (TLV-TWA), reference dose (RfD)

High level safety assessment process

- STEP 1 Hazard identification by reviewing all relevant data
  - Is there a specific hazard?
- STEP 2 identification of "critical effects"
  - What is the most sensitive endpoint/critical toxicity?
- STEP 3 determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects
  - Has a NOEL, NOAEL, or LOAEL been established in the "best" study
- STEP 4 specify one or more adjustment factors to account for various uncertainties (Modifying Factors)

The process employed in ICH Q3D was previously applied in ICH Q3C for developing residual solvent PDEs

Modifying factor approach

$$PDE = \frac{\text{Tox End Point} \times \text{Weight Adjustment}}{F1 \times F2 \times F3 \times F4 \times F5}$$

F1: Inter species
F2: Inter individual
F3: Tox. EP vs Time exp
F4: Severity Tox. Effect
F5: NOEL not established

(50 kg) PDE apply for all patient populations

Modifying Factor	Value 1	Value 2	Value 3
F1	Human = 1	Rat = 5	Mouse = 12
F2	Individual variation between subjects – typically set = 10		
F3	Lifetime study = 1 (at least ½ lifetime	6 month study in rodent = 2	3 month study in rodents = 5
F4 (fetal effects)	Fetal toxicity with maternal toxicity = 1	Fetal toxicity without maternal toxicity = 5	Teratogenic effect without maternal toxicity = 10
F5	NOEL = 1	NOAEL = 1-5	LOEL = 5-10

For additional details see Appendix 1 of ICH Q3D

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Establishing an acceptable daily intake (ADL)

Levels acceptable for elements of potential concern that do not have an established PDE

- In situations where a limit needs to be considered for an element not included in ICH Q3D, the process used to establish PDEs should be followed

- STEP 1 Hazard identification by reviewing all relevant data
- Is there a specific hazard?
- STEP 2 identification of "critical effects"
- What is the most sensitive endpoint/critical toxicity?
- STEP 3 determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects
- Has a NOEL, NOAEL, or LOAEL been established in the "best" study
- STEP 4 specify one or more adjustment factors to account for various uncertainties (Modifying Factors)

The end product of this level is a proposed Acceptable Level – to be proposed and reviewed with the relevant Health Authority

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Other routes of administration

Setting appropriate limits

- Consider the oral PDEs in Appendix 3 as a starting point
- Training material is available with case examples – Module 1
- Based on a scientific evaluation, the parenteral and inhalation PDEs may be a more appropriate starting point than the oral PDE
- Assess if there are local effects are expected when administered by the intended route of administration.
  - If local effects are expected, a modification to an established PDE may be required.
  - If local effects are not expected, no adjustment to an established PDE is necessary.

Other routes of administration - continued

Setting appropriate limits

- If available, evaluate the bioavailability of the element via the intended route of administration and compare this to the bioavailability of the element by the route with an established PDE.
  - Information may not be readily available
  - Literature data may not be sufficiently detailed or may describe a different form
- When a difference is observed in proposed limits, a correction factor (CF) may be applied to an established PDE effectively converting it to a proposed Acceptable Level (AL)
  - For example, when no local effects are expected, if the oral bioavailability of an element is 50% and the bioavailability of an element by the intended route is 10%, a correction factor of 5 may be applied.
  - Dermal CF = absorption oral / absorption dermal
    - If a range is available, use highest dermal absorption and lowest absorption values
- Once the AL has been established, the level can be transformed into a permitted concentration for use in the product risk assessment and evaluation of EI controls

Product Risk Assessments

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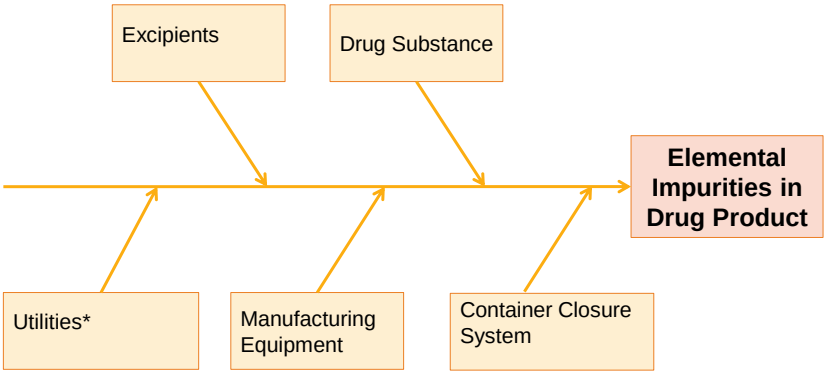
Elemental impurity risk assessment process

ICH Q3D defines a science and risk based assessment process to identify, evaluate, and define controls to limit elemental impurities in drug products

- Identify known and potential sources of elemental impurities that may find their way into the drug product.
- Evaluate the presence of a particular elemental impurity in the drug product by determining the observed or predicted level of the impurity and comparing with the established PDE.
- Summarize and document the risk assessment. Identify if controls built into the process are sufficient or identify additional controls to be considered to limit elemental impurities in the drug product.

Potential sources of elemental impurities



* Water is the primary utility of potential concern

The product assessment should consider the potential of each of these categories to contribute elemental impurities to the drug product

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Risk assessment approaches

Examples of general approaches that may be considered during elemental impurities risk assessment are:

- Assessment of potential elemental impurities in the drug product
  - Determine or assess the levels of elemental impurities in the final drug product
  - Depending on the formulation type, an evaluation from the container closure system may also be required
- Assessment of potential elemental impurities from each component of the drug product (API, excipients, container closure system)
  - Assess each component for potential sources of elemental impurities
  - Identify known or likely elemental impurities
  - Determine the contribution of each component or source of elemental impurity to the levels in the final drug product
- Irrespective of the approach chosen – consider the elemental impurity classification and recommendations in Table 5-1 (see following slide)
- These approaches or others may change as information becomes available or additional experience is gained.

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Q3D 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

Reference this table in the summary of the risk assessment.

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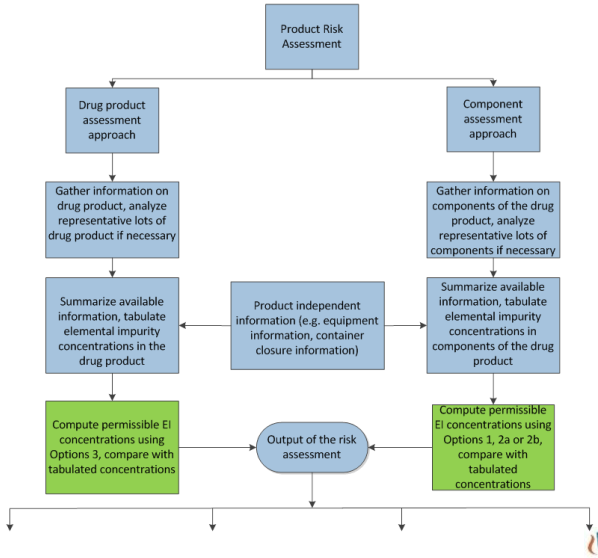
Generalized risk assessment process flow



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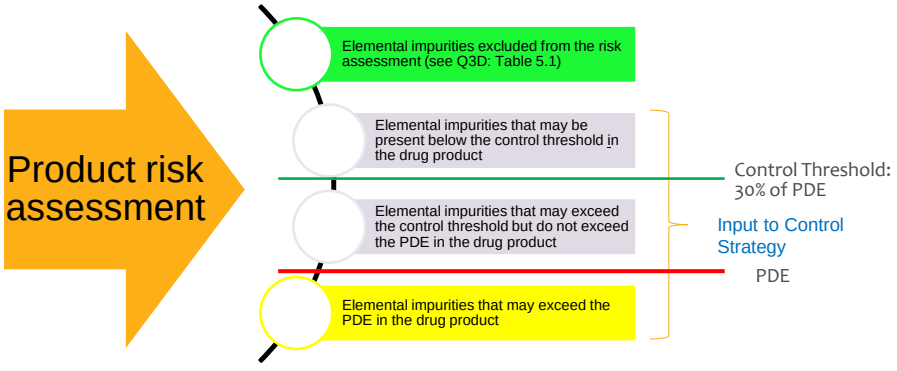
Risk Assessment Output



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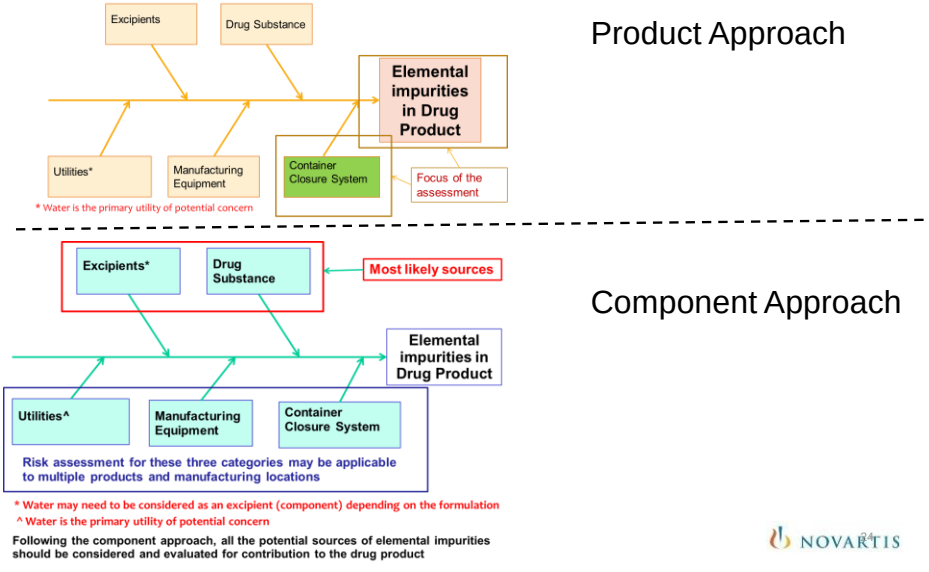
Comparison of Risk Assessment Approaches



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Information to consider in the risk assessment

- Assumptions, risks considered and identified, controls inherent in the process and product evaluated
- Data where available and estimated levels when literature or published data or calculations are used to justify exclusion of elemental impurities from further consideration
- The rationale for elemental impurity clearance steps/reduction steps included or inherent in the process design
- Consideration of using compendial quality components
- Consideration of GMP controls and
- Discussion of any additional controls to be considered when developing the drug product control strategy

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Sources of information on elemental impurities in excipients

The amount of information in refereed publications and sources is increasing

RESEARCH ARTICLE – *Pharmaceutics, Drug Delivery and Pharmaceutical Technology*

Elemental Impurities in Pharmaceutical Excipients

GANG LI,[1] DAVE SCHONEKER,[2,3] KATHERINE L. ULMAN,[2,3] JASON J. STURM,[4] LISA M. THACKERY,[4] JOHN F. KAUFFMAN[1]

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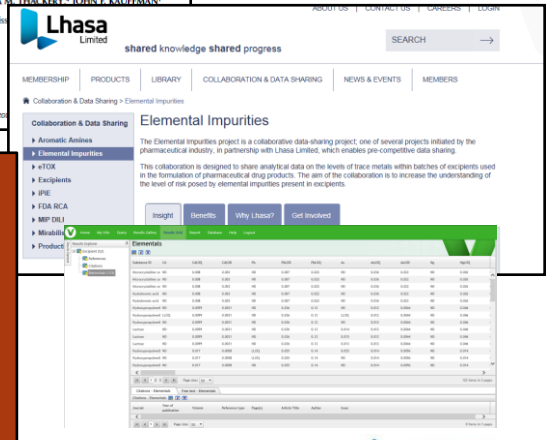

Excipient database rel. 1

- Consortium of 8 pharma companies donating data
- 125 data points generated using validated methods
- 50 excipients
- Rel. 2 with additional data uploaded anticipated in Q4 2016

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Evaluation

- Compile data for components of the drug product
  - Published information
  - Data generated by the applicant or suppliers
  - Where data are not available, consider if surrogate information can be used to establish a reasonable estimate of the elemental impurity potential for inclusion
- Calculate the observed elemental impurities for each component, in which elemental impurities are identified, as a function of the percent composition of the formulation and the total daily dose of the drug.
- The level of each elemental impurity should be determined by summing the contribution from each component to determine the final amount in the drug product

$$Amount\ of\ Elemental\ Impurity\ in\ drug\ product\ = \sum_{i=1}^{n} Ci \times Mi$$

where, i = an index for each of N components in the drug product, C_i = permitted concentration of the elemental impurity in component i (µg/g), and M_i = mass of component i in the maximum daily intake of the drug product (g)

- Compare the total daily amount of each elemental impurity with the established Permitted Daily Exposure value (PDE).

Comparison of Observed Levels with PDE

- Elemental impurities excluded from the risk assessment (see Table 5.1)
- The elemental impurity level is <30% of the PDE. If this is the case, then no additional controls are deemed necessary.
- The elemental impurity level in the drug product is greater than the control threshold but does not exceed the PDE; additional measures may be implemented to insure that the level does not exceed the PDE
- The elemental impurity level exceeds the PDE,
  - Additional measures should be considered so that the levels do not exceed the PDE.
  - When additional measures are either not feasible or unsuccessful, levels of elemental impurities higher than the established PDE may be justified in certain circumstances.
    - The safety impact of the elemental impurity level should be evaluated as described in Q3D and Training Module 2.

It should be noted that if an AL is the level forming the basis of the comparison, the final acceptance of the proposed limit is dependent on approval by the appropriate regulatory authority.

Summary and conclusions

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Conclusions

- ICH Q3D EWG and IWG have delivered
  - Comprehensive science and risk- based approach to evaluating the impact of elemental impurities in drug products
  - Training materials to provide more detailed discussion of the guideline with no new guidance
  - Case studies illustrating potential approaches to documenting risk assessments
  - Processes to consider other routes of administration, intermittent dosing assessments (evaluation for less than chronic exposure)
- Guideline and training material provide a framework to permit applicants and regulators to focus review and evaluation on the most important/significant potential elemental impurities
- Data available to assist with product risk assessments is rapidly expanding – current knowledge base expansion is expected

Acknowledgements

The members of the ICH Q3D EWG and IWG

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Lhasa (managers of the EI Data sharing databse) for permission to use the image of the Vitic EI database

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Impact of the Guideline in Europe

European Pharmacopoeia: Tackling future challenges of the quality of medicines together September 2016, Tallinn

Sven-Erik Hillver
Senior expert, CHMP/CVMP Quality Working Party delegate
Medical Products Agency, Sweden

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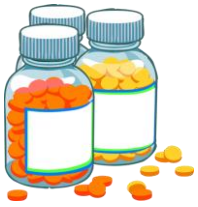
Impact of the Guideline in Europe

- **Impact on the quality of medicines**
- **Impact on the pharmaceutical industry**
- **Impact on the regulatory processes**



Impact on the quality of medicines

- What impact will the guideline have on the actual quality of medicines in Europe?
  - Rather limited!
- Why is that?
  - The most important potential sources of elemental impurities are already under control.
  - It is anticipated that most approved medicines contain levels of elemental impurities that are below the PDE:s.

Intentionally added elements

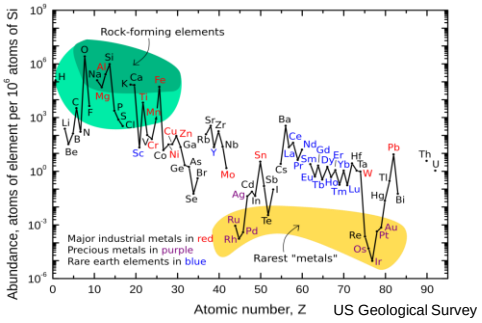
- Intentionally added catalysts and reagents are recognized as in practise the most likely source of contamination
  - The new guideline more clearly cover all sources of elemental impurities
  - The EMA guideline covers the intentionally added catalysts and reagents
- **Thus for these EI, comparable PDE:s are already implemented**

Other sources

- **Other sources of elemental impurities**
  - Utilities
  - Manufacturing equipment
  - Container-closure system
- They constitute a low risk in the majority of cases
- GMP control
- General qualification of facilities, packaging materials etc.

Mined material – a potential source

- Excipients that originate from mined material is a potential source that may have been overlooked in the past
- Now needs to be taken into account in the Risk Assessment



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

Why then Q3D?

- **The new guideline**
  - is not elaborated to meet an apparent risk to patients
    - medicines currently approved are generally believed to be safe with respect to elemental impurities
  - introduces a science and risk based approach to the control of elemental impurities with a holistic perspective
    - controls to be made only when necessary
    - defines manufacturers‘s responsibility with respect to EI from all sources

Impact on the quality of medicines

- **European medicines will continue to be safe with regard to elemental impurities with ICH Q3D**
- **The regulatory framework for how acceptable levels of elemental impurities is ascertained will be**
  - modern
  - risk based
  - more robust

Impact on the pharmaceutical industry

- *This is of course primarily for industry itself to tell – but if I should give my opinion I believe:*
- Q3D **will have an impact** on the pharmaceutical industry
- Basically, a more thorough assessment of the risk for elemental impurities will be needed
  - Some of the work will be product specific
  - Other parts will be more general and applicable to multiple applications

Impact on the pharmaceutical industry

- Eventually this will be a natural part of the pharmaceutical development
- The challenge is to start doing this in the **absence of experience**
- The **time frame** is perceived as short
  - In particular with regard to existing products
  - In particular for companies that may not have followed the elaboration of the guideline and therefore were unprepared when it was adopted.

Time frame for implementation

- **Compliance with the guideline is expected**
  - 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
- **These were chosen based on the experience with the implementation of ICH Q3C Residual solvents**

Impact on the pharmaceutical industry

- In the short perspective the new guideline can be anticipated to have a medium to strong impact
- The difficulty is most likely not to produce a product compliant with the PDE:s but to perform and document the risk assessment
  - Lack of examples of risk assessments
  - Difficulty to get information from vendors and suppliers
  - Challenging to develop necessary analytical methods
  - Unfamiliar to compile GMP related data to inform the risk assessment
  - Uncertainty on regulators expectations

Expectations for existing marketed products

- 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.

Expectations 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.

Submission expectation

- **A Summary of the Risk Assessment to be submitted**
  - Full documentation of Risk Assessment available at site
- **What should the Summary look like?**
  - 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
  - Raw data not expected, but summary of findings may be necessary
  - The justification for the Control Strategy (what to control and not to control)

Impact on the regulatory processes

- **Potential issues**
  - New information to assess in MA applications
  - Variations due to non-compliance
  - Changed focus from drug substance to drug product
  - Finding ways for ASMF and CEP to be useful tools for information exchange

New information to be assessed

- **Summary of risk assessment**
  - This is new information – what will it look like?
    - will it contain the necessary information?
    - will it tell a convincing story on the risk assessment done?
    - how to assess control threshold in borderline cases?
    - how to assess justifications for higher levels, new elements or new routes of administration?
    - etc.
- We still **lack practical experience** of assessing elemental impurities according to ICH Q3D

Assessing Q3D vs. EMA-GL dossiers

- Risk based approach vs. strictly defined rules
- A scientifically sound approach but …
- …considerably more difficult to assess
- There is an increased risk for divergent views between assessors
  - In worst case leading to referrals
- QWP is dedicated to continue the efforts to prevent this and to facilitate the implementation

Examples of difficulties - Application of Control Threshold (consistently < 30 % of PDE)

- The Control Threshold to give an assurance of negligible likelihood of exceeding the PDE
  - All sources of variability/uncertainty to be considered
  - When levels are far below the decision will be easy
- How to assess “consistently” when levels are close?
- Will the minimum number of batches in the GL be sufficient when results are close to the threshold?
- Can material with inherent unpredictable levels be precluded from using the control threshold?

Example of difficulties – catalysts used in the last step of the synthesis

- Less reassurance from purging compared to a synthesis with multiple subsequent steps
  - Possibly greater impact of any unexpected events
- Up to now mandatory to have a specification but in Q3D to be based on the risk assessment
  - Would it still be a normal expectation to have a specification in these cases?
  - Would there be a role for skip testing?
  - What evidence of robust purging will be needed to justify the absence of a specification?
  - Control Threshold – How to assess borderline results?

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Examples of difficulties – drug product approach

- It is an option in Q3D to decide on a control strategy based on scanning of Drug Product batches
- How to assess with only results from DP analysis?
  - What will the Risk Assessment look like?
  - Without an Risk Assessment, can full routing testing be enough for compliance with the guideline?
  - Can analytical data only (with no Risk Assessment) be sufficient to justify the omission of testing for an element?

Role of ASMF and CEP

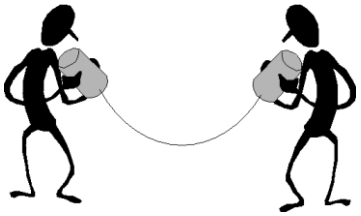
- Previously, intentionally added EI:s was controlled in DS
- PDE:s now apply to the drug product.
- Q3D not mandatory at the level of DS
- Elemental impurities can still be controlled at DS level
- In-house made substances as well as outsourced with ASMFs & CEPs will be assessed in the same way
- ASMFs and CEPs to be useful for substance manufacturers and MAH also in the future
  - A mechanism for exchanging information that can inform the DPMs Risk Assessment

Role of API and excipient suppliers

- It is acknowledged that the choice of a Drug Product vs. a Component approach is at the discretion of the DPM
- From a science and a transparency point of view, manufacturers & suppliers are encouraged to cooperate
  - To facilitate the Risk Assessment by exchanging information
    - Information from DPM on intended use (dose, RoA)
    - 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

Smooth implementation – The way forward

Continued dialogue between industry and regulators to give further guidance as more experience is gained



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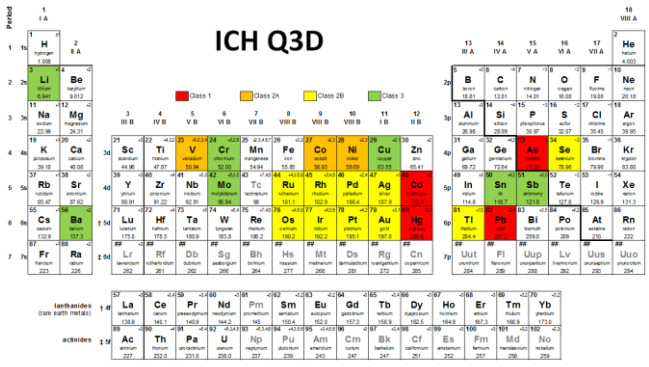

Impact of ICH Q3D in the CEP procedure

Ph. Eur conference, Tallinn,
27-28 September 2016

Hélène BRUGUERA
Head of the Certification Division, EDQM

Certification (CEP) procedure

- Managed by the EDQM, Council of Europe (Strasbourg)
- Centralised assessment of the quality of substances for pharmaceutical use covered by Ph. Eur monographs
- Contributes to updating Ph. Eur monographs

H. Bruguera, Ph. Eur conference, Tallinn @2016, EDQM, Council of Europe, all rights reserved

Former CEP policy for metal catalysts in substances (until 08/2016)

- EU gdl on "Specification limits for residues of metal catalysts" (General Chapter 5.20 of Ph. Eur) and related Q&A
- Catalysts used should be declared in the dossier, together with control strategy
- Limits as in the EMA gdl

Former policy (2)

- Catalysts used : control strategy (cf EMA Q&A)
  - Class 1 catalysts introduced in the last synthetic step to be limited in the specification of the API, whatever levels found in the API
  - Class 1 catalysts used earlier in the synthesis and present in the API to be included in the API specification
  - Class 1 catalysts used earlier in the synthesis and demonstrated absent to be limited in an intermediate specification or in the API specification
  - Other classes => flexibility possible when absent
  - Skip testing not addressed in Certification

Former policy and CEPs

- CEPs granted until 31/08/2016 carry:
  - ➢ Test & limit for catalysts as included in the specification of the API

Q3D: a shift in mindset

CEP new policy

- Published on the EDQM website in August 2016:

https://www.edqm.eu/sites/default/files/implementation_of_ich_q3d_in_the_certification_procedure_august_2016.pdf

- Implementation since 1 September 2016

Q3D: General Principles for CEPs

- No mandatory implementation of ICH Q3D at the level of pharmaceutical substances
- Same basic principles for ASMF & CEPs
- Serve the Component Approach of ICH Q3D:
  - Provide necessary information to MAH for their Risk Management on the Drug Product
- Be useful for substances manufacturers and MAH and keep the benefits of the centralised assessment

In the CEP application

- For substances used in products which are within scope of ICH Q3D
- 2 possible options:
  - Risk Management (RM) is made at the level of the substance (Component Approach)
  - No Risk Management is made
- **EDQM encourages the submission of a RM Summary in the CEP dossier**

RM Summary submitted in the CEP dossier

- Identify this option in the CEP dossier
- Use and declare known route(s) of administration for the substance
- Preferably tabulated format (example given in the EDQM guideline)
- Include all sources of EI, and contribution of raw materials (water), equipment and packaging:
  - the 4 Class 1 (As, Cd, Hg, Pb) and Class 2A (Co, V, Ni) elements
  - Class 2B intentionally added
  - any Class 3 intentionally added, and other Class 3 if relevant for the use of the substance (parenteral, inhalation)

RM Summary submitted (2)

- Control strategy:
  - Address absence/presence of EI in the final substance
  - Describe any controls applied
    - Specification and analytical method
    - Method validation elements as needed
- Screening of batches alone is not a RM Summary, but is useful supportive information
- CEP assessors will look at:
  - Completeness and relevance of the RM
  - Controls applied

No RM Summary in the CEP dossier

- In the dossier, describe Class 1, 2, 3 elements intentionally added, as part of process description
- Data showing levels of those EI in the final substance
- Controls applied as needed
  - Limits and analytical methods
- CEP assessors will look at controls applied, specification, batch results, methods validation

Control Strategy

- Limits introduced in the substance specification should reflect process capability
  - PDE of ICH Q3D **may** be used as reference
- For elements intentionally added in the last chemical step, a specification in the final substance is expected, unless the EI is demonstrated consistently **absent**
- Demonstration of absence:
  - Less than 30% of calculated concentration limit based on declared route of administration and option 1 daily intake of Table A.2.2 of ICH Q3D
  - 3 commercial or 6 pilot batches

EI in Ph. Eur monographs

- If there is a test for an EI in a Ph. Eur monograph, this test should be included in the specification of the substance (as far as relevant)

On the CEPs from 1 September 2016

- If RM Summary submitted:
  - Info on the CEP that it has been submitted, and annexed to the CEP
  - Specification of the final substance with regards EI as proposed by the manufacturer (limit + test appended)
- If RM Summary not submitted:
  - Statement that "No EI is intentionally introduced", OR
  - A list of EI intentionally introduced in the synthesis (regardless of levels found in the substance)
  - Specification of the final substance with regards EI as proposed by the manufacturer (limit + test appended)

Update of existing CEPs

- No plan to revise all existing CEPs
  - A small number of CEPs which referred to "*option 2a of Chapter 5.20 of Ph. Eur*" (EMA guideline) to be revised. CEP holders will be contacted individually by EDQM
- Deletion of reference to Ph. Eur 2.4.8 from individual monographs
  - Test can be removed from the specification of the substance (similarly to implementation of revised monographs)
  - CEP holders will not be contacted by EDQM, and no request for revision should be submitted
  - Exception: if the removal of the Ph. Eur 2.4.8 test prevents the control of presence of EI in the substance.

Update of CEPs (2)

- At renewal, good opportunity to update the CEP dossier
  - Submission of RM Summary (preferred!)
  - Update of control strategy: Data + justification to be provided
  - EDQM reviews EI in renewal applications and grants CEPs against the new policy
- Requests for revision:
  - Changes to the process affecting EI: new policy applied
  - Introduction of RM Summary in the CEP dossier (minor)
  - Changes to the control strategy for EI ➔ use EDQM guideline to define the kind of revision
  - CEPs revised accordingly

Use of a CEP in Marketing Applications (MA)

- For "new" CEPs
  - In a **new** MA, include info carried by the CEP in the Drug Product Risk Management
  - In a **variation** to a MA, use info carried by the CEP to determine **impact** on the Drug Product ➔ impact on type of variation!

Use of a CEP in a Marketing Application (2)

- For "old" CEPs
  - Use information from CEP: metals present or introduced in the last step, according to EMA guideline
  - Drug Product manufacturers to get info from CEP holder, to feed the Risk Management of the Drug Product, OR use Drug Product approach

Conclusion

- **Need to gain practical experience…**

WATCH THIS SPACE!

Acknowledgements

S-E Hillver from MPA

EDQM working group
(A. Degardin, C. Feeney, L. Seidler, C. Thouvenel)

COMMENTS WELCOME!

THANK YOU FOR YOUR ATTENTION

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

Ph. Eur. International Conference, Tallinn
27-28 September 2016

Bruno Spieldenner, Ph. Eur. division, EDQM

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

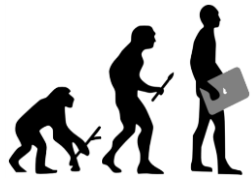
Source: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/03/WC500184920.pdf

Ph. Eur aligned to the extent possible with these implementation dates

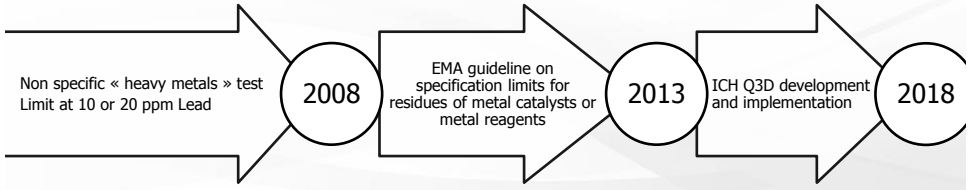
Press releases on Ph. Eur. strategy

- 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.

Elemental impurities in the Ph. Eur.



- A (r)evolution



Risk management

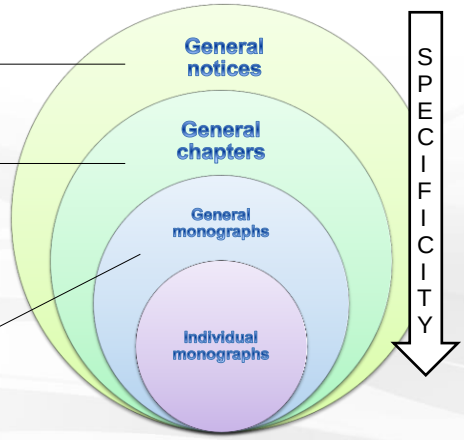
Content and structure of the Ph. Eur.

Provide basic and very general information that are true for all texts. Help to understand aspects of wording, structure and requirements of the Ph. Eur.

- General methods: general recommendations 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.



Implementation in general text 5.20 (1/2)

- Replacement of the EMA guideline on metal catalysts and metal reagents by the principles of the ICH Q3D guideline
- No verbatim reproduction to avoid introducing a "Ph. Eur. Copy" of the guideline. The enforceable text is the version as published by the EMA.
- Foreseen publication: Ph. Eur. Suppl. 9.3 [impl. date 01/2018]

Implementation in general text 5.20 (2/2)

- Only the introduction and the scope of ICH Q3D are reproduced and supplemented with information specific to Q3D in the Ph. Eur.
- Extracts of the draft proposal for chapter 5.20: (work ongoing)

[…] The European Pharmacopoeia (Ph. Eur.) applies this guideline to all medicinal products (except for veterinary use and unlicensed preparations) via the general monograph Pharmaceutical preparations (2619) whether or not they are the subject of an individual monograph and unless excluded from the scope of the guideline. […]

[…] Unless otherwise prescribed, tests for elemental impurities are not mentioned in individual monographs (either on substances for pharmaceutical use or on medicinal products) since the elemental impurities potentially present may vary from one source to another. According to the guideline, manufacturers of medicinal products shall assess and control elemental impurities in the medicinal product using the principles of risk management. […]

Implementation in general method

General method 2.4.20:

1. Editorial revision to align wording with ICH Q3D guideline
   Foreseen publication: Ph. Eur. Suppl. 9.3 (no public consultation)
   "*metal catalyst and metal reagent residues*" to "*elemental impurities*"

2. International harmonisation (coordinating pharmacopoeia: USP)
   Work ongoing with high priority within the PDG.
   (public consultation hoped in 2017)

Other general methods : e.g. Heavy metals (2.4.8), Arsenic (2.4.2)

Will be kept in the Ph. Eur.

Proposed implementation in general monographs

- Pharmaceutical Preparations (2619) :
  Addition of a cross reference to general text 5.20 (principles of ICH Q3D) to render the text legally binding for medicinal products in scope of Q3D.
- Substances for pharmaceutical use (2034) : clarification for substances used in drug products outside of the scope of ICH Q3D guideline. Mention of elements intentionally added in the production section.

Public consultation ended on 31st August 2016.
For publication in Ph Eur suppl. 9.3 *[impl. date 01/2018]*

Proposed revision of general monograph 2619

PHARMACEUTICAL PREPARATIONS

Pharmaceutica

Elemental impurities. *For pharmaceutical preparations within the scope of general chapter 5.20, the requirements for the control of elemental impurities are defined in general chapter 5.20.*

For pharmaceutical preparations outside the scope of general chapter 5.20, manufacturers of these products remain responsible for controlling the levels of elemental impurities using the principles of risk management.

If appropriate, testing is performed using analytical procedures developed and validated according to general chapter 2.4.20.

General chapter 5.20 is not applicable to unlicensed pharmaceutical preparations and to medicinal products for veterinary use.

Proposed revision of general monograph 2034 (1/2)

SUBSTANCES FOR PHARMACEUTICAL USE

Corpora ad usum pharmaceuticum

PRODUCTION SECTION

"Potential elemental impurities derived from intentionally added catalysts and reagents are considered in a risk assessment (e.g. according to Table 5.20.-1(1) in general chapter 5.20). The identity of the potential elemental impurities is known and techniques for controlling them are available."

➔ Compatible with latest statements by regulators (EMA, EDQM CEP) that there will be a special focus on elements intentionally added

Proposed revision of general monograph 2034 (2/2)

SUBSTANCES FOR PHARMACEUTICAL USE

Corpora ad usum pharmaceuticum

Elemental impurities. *According to general chapter 5.20 the limits for elemental impurities apply to the medicinal product; therefore, individual monographs on substances for pharmaceutical use do not contain a test for elemental impurities unless otherwise prescribed.*

For medicinal products outside the scope of general chapter 5.20, even in the absence of a test for elemental impurities in an individual monograph on a substance used for their production, the manufacturer is still responsible for controlling the levels of elemental impurities in their medicinal product, using the principles of risk management and applying validated analytical procedures, as appropriate.

Outcome of public consultation

Concern that additional requirements would be introduced for products out of scope of ICH Q3D:

- ➔ **No intent to extend the scope of Q3D**
- ➔ Q3D sets human toxicological limits (PDE)
- ➔ with respect to medicinal products for veterinary use Consider to clarify that they are out of scope of Q3D

NEVERTHELESS:
With suppression of HM tests, EIs should still be considered an important quality attribute of substances and products to guarantee meaningfulness of EP monographs as quality standards (at least via RM)

Implementation in individual monographs – 1st Phase

- ✓ Suppression of heavy metals tests (2.4.8) from individual monographs (except those for vet. use only). Published in the 9th Edition.
- Total number of texts: 754 monographs (43%) ➔ combined with a new edition for practical reasons
- No anticipated entry into force expected for already marketed products: from a regulatory point of view manufacturers are expected to comply with ICH Q3D by december 2017.
- See press release from April 2015:

"The absence of the heavy metals test from an individual monograph does not preclude substance manufacturers from controlling the levels of elemental impurities in their products. Control of heavy metals according to method 2.4.8 is still acceptable until ICH Q3D comes into force for a given finished product."

- No test for elemental impurities in individual finished products monographs

Other monographs

- Water, purified (0008) : is in public consultation until 30/09 (Pharmeuropa 28.3)

Elemental impurities. *If purified water in bulk does not meet the requirement for conductivity prescribed for Water for injections (0169) in bulk, a risk assessment according to general chapter 5.20. Metal catalyst or metal reagent residues is carried out, taking into consideration the role of water in the manufacturing process, in particular when water is used in a process but is no longer present in the final product.*

- Materials/containers : discussion ongoing in Group of experts

Thank you for your attention!

HEAVY METALS DON'T ROCK

Impact of the ICH Q3D Guideline on the Ph. Eur.

- Specific Monographs

Dr. Michael Türck
Tallin, 27th and 28th September 2016

MERCK

Setting

- ICH Q3D defines limits for elemental impurities (EI) solely for drug products.
- These limits are given in the form of PDE in µg/day and are dependent from the route of administration.
- Limits for EI in components of drug products become dependent form the route of administration and of the amount used in the drug product.
- General limits for drug substances may be calculated based on a worst case scenario (concentration of the limit may be calculated from PDE, from maximum daily dose and from most critical route of administration).
- No universally valid limits for excipients can be set.

Current situation

- The pharmacopoeia contains about 1700 monographs (including 28 homeopathic products and 33 products for veterinary use only).
- Limits for heavy metals (method 2.4.8) are defined in about 780 monographs. Limits and method are not in line with guidance of ICH Q3D.
- In some cases individual limits for EI are given (Ag, As, Ba, Cd, Cr, Cu, Hg, Ni, Pd, Sb, Se, Sn).
- 14 (out of 33) monographs for veterinary use only refer to method 2.4.8.

Actions already agreed

- Test for heavy metals (method 2.4.8) will be deleted from all individual monographs except from monographs of substances for veterinary use only (9th edition).
- Other tests for specific EIs in individual monographs will be reviewed by groups of experts on a case by case basis.
  Secretariat provided lists of monographs concerned to the groups.
- Specific tests in individual monographs for elements not covered by ICH Q3D will remain untouched but me be considered upon discussion of a monograph in the group.

Options for consideration of test on specific EI

a. Delete all tests for specific EIs from individual monographs.
b. Keep tests for EIs with limits justified higher than the PDE.
   Delete all other tests.
c. Delete all tests for specific EIs from individual monographs of synthetic organic substances (unless option b. applies).
   Keep tests for EIs in individual monographs of inorganic substances or natural products (tests for natural contaminants).
d. Delete all test for intentionally added EIs from all monographs (unless option b. applies) and keep all other tests.
e. Keep all tests for specific EIs in individual monographs; introduce new tests if necessary.

Option a.

Delete all tests for specific EIs from individual monographs.

Advantages

- Clear, distinct solution
- Full in line with ICH Q3D
- Simple action, no discussions

Disadvantages

- Considerable loss of information
- Virtually meaningless monographs for inorganic substances

Option b.

Keep tests for EIs with limits justified higher than the PDE.
Delete all other tests.

Advantages

- Only rare exceptions from option a.
- Full in line with ICH Q3D
- Essential information retained or even added

Disadvantages

- Considerable loss of information
- Virtually meaningless monographs for inorganic substances

Justification of EI levels higher than PDE

Paragraph 3.3 of The ICH Q3d guideline reads:

Levels of EI higher than the established PDE may be acceptable in certain cases. These cases could include, but are not limited to the following situations:

- Intermittent dosing;
- Short term treatment (i.e. 30 days or less);
- Specific indications (e.g. life threatening, unmet medical needs, rare disease).

Examples of EIs retained under option b.

1. Cisplatin

- Test for silver (Ag): maximum 250 ppm
- Cisplatin is an anticancer drug. It is produced via a silver salt
- PDE of silver (parenterally) is 10 µg/day
- For drugs containing cisplatin paragraph 3.3 of the ICH Q3D is applicable.

  3.3 Justification for Elemental Impurity Levels higher than the established PDE:
  - Intermittent dosing
  - Specific indication (life threatening disease)

Examples of EIs retained under option b.

2. Meglumine

- Test for nickel (Ni): maximum 5 ppm
- Meglumine is used in contrast products for diagnosis in large quantities. Meglumine is usually applied just one time.
- PDE of nickel (parenterally) is 20 µg/day
- For drugs containing meglumine paragraph 3.3 of the ICH Q3D is applicable.

  3.3 Justification for Elemental Impurity Levels higher than the established PDE:
  - Short term treatment

Option c.

Delete all tests for specific EIs from individual monographs of synthetic organic substances (unless option b. applies).
Keep tests for EIs in individual monographs of inorganic substances or natural products (tests for natural contaminants).

Advantages

- Meaningful monographs for inorganic substances

Disadvantages

- Limits derived from quality considerations may collide with PDEs of ICH Q3D
- Different approaches for organic and inorganic compounds may confuse users.

Special case inorganic compounds

Organic compounds

- Origin of EI is commonly the production process (intentionally added as reagent or catalyst).
- Production and purification process runs predominantly in non-aqueous solvent systems.
- Complete depletion of EI during down stream processing is likely and can be validated.
- Risk analysis, based on knowledge of the production process, is feasible and leads to rational decisions.
- EIs may be treated like “residual solvents”

Special case inorganic compounds

Inorganic compounds

- Inorganic compounds are usually produced from mineral sources (mined materials) by simple production steps in aqueous systems (dissolution and precipitation or crystallization).
- EIs origin from natural contamination and the concentration may vary widely depending from the source of the raw material.
- Depletion of EI during down stream processing is possible, but can be hardly validated.
- Risk analysis based on knowledge of the production process is not feasible.
- EIs may be treated like "related substances"

Special case inorganic compounds

Inorganic compounds

- Applying option a) or option b) leads for inorganic compounds to essentially meaningless monographs since practically all tests for relevant impurities will be deleted.
- Example: Ferrous fumarate

Current monograph	Possible monograph under assumption of options a. or b.	Possible monograph under assumption of option c.
Test for	Tests for	Test for
Identity, ph, sulfates, ferric ions,	Identity, ph, sulfates, ferric ions,	Identity, ph, sulfates, ferric ions,
As, Cd, Cr, Pb, Hg, Ni, Zn,	Zn,	As, Co, Pb, Ni, V,
loss on drying, assay	loss on drying, assay	loss on drying, assay

Option d.

Delete all test for intentionally added EIs from all monographs (unless option b. applies) and keep all other tests.

Advantages

- Clear rule, equal approach for all kind of monographs.

Disadvantages

- Limits derived from quality considerations may collide with PDEs of ICH Q3D.

Option e.

Keep all tests for specific EIs in from individual monographs; introduce new tests if necessary.

Advantages

- Maximum of information about possible EIs.

Disadvantages

- Limits derived from quality considerations may collide with PDEs of ICH Q3D.
- High risk of missing potential EIs, especially if reagents or catalysts get changed or new ways of production get introduced.

Possible representation of EI in monographs

- Option A:
  Individual tests for specific EIs with description of the test or reference to a specific general method
  (Current form of representing tests for cationic impurities.)

Possible representation of EI in monographs

- Option B:
  New "general test"
  Elemental Impurities (2.4.20)
  followed by a list of impurities which should be mandatory assessed and corresponding limits.
  Considered will be in any case EIs of class 1 and 2A;
  EIs of class 3 only for relevant indications;
  EIs of class 2B only if relevant for the quality of the substance.
  Limits will be oriented on good pharmaceutical quality currently on the market.

Impact on the Users: Perspective of an Excipient Manufacturer

David R. Schoneker
Director of Global Regulatory Affairs
Colorcon
Email: dschoneker@colorcon.com

Outline

- **What is ICH Q3D from an Excipient Manufacturers Perspective?**
- **Excipient Manufacturers are much different than API and Drug Product Manufacturers?**
- **What Data exists for Excipients Today?**
- **Limited Information available from Suppliers – Reality!**
- **Excipient EI Predictability? Excursions!**
- **Removal of Specific Element Requirements from Monographs**
- **Improvements in Communication Needed between Users and Makers**

What is ICH Q3D?

From an Excipient Manufacturer's Perspective

Colorcon®

What is it? – ICH Q3D Overview

- **A Requirement for Drug Manufacturers:**
  - Requires an assessment of the **potential elemental impurities present in drug products.**
    - Potential sources: Drug substance, **excipients**, manufacturing equipment and packaging.
- **ICH Q3D <u>applies</u> to:**
  - **All** human drug products - Emphasizes the use of risk assessment as opposed to testing wherever possible
- **Does <u>not apply</u> to:**
  - Components, i.e. Drug Substance/ **Excipients**
  - **No compliance requirement for excipient suppliers other than to share what they may know and what they do not know about EI in their excipients – may be very little! This is appropriate!**

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Pharmaceutical Excipient Industry – Different than Drugs!

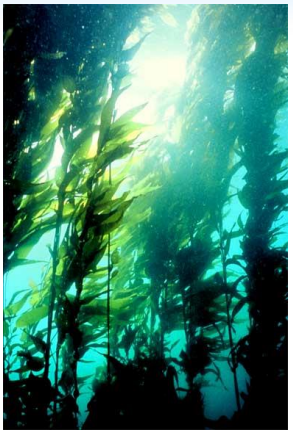
Majority of Pharmaceutical Excipient Suppliers are Chemical Industry subsidiaries

- **Products targeted at Food, Beverage, Industrial, and Cosmetic**
- **Small fraction of Main Production Volumes for excipient – sometimes less than 0.1% of business**
- **Varying degrees of dedicated R&D related to excipient uses**
- **Specifications-driven by main market (usually not Pharma)**
- **Global Market and Manufacturing Base**

What is the Excipient Industry?

Diverse Materials Base

- **Chemical synthesis**
  (Polymer mixtures, Cellulose derivatives – substances often less defined than low mol wt entities)
- **Mining of minerals**
- **Harvesting of vegetation**
- **Formulated Products**
- **Biotechnology & Fermentation**
- **Genetic Modification**
- **Animal by-products**



Excipient Industry is significantly different than the Pharma Industry

Excipients CANNOT be regulated like APIs or Drug Products!

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Excipients may come from the farm or natural environment and are processed and packaged into excipients

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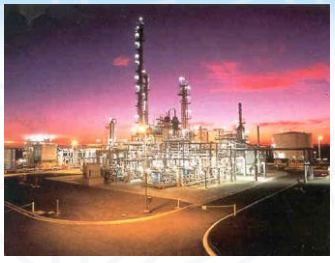
Excipients are produced and packaged in many ways typically by chemical companies





The journey from the manufacturing site





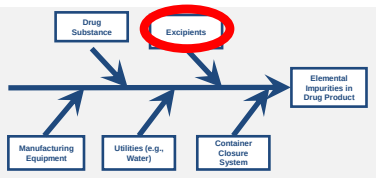




ICH Q3D – Risk Assessment

- ICH Q3D advocates a risk assessment approach to determine the level of elemental impurities in drug products and the risk posed to patients.

- "The data that support the risk assessment can come from:
  - Prior knowledge,
  - Published literature,
  - Information provided from suppliers
  - Data generated from testing of components of the drug product,
  - Data generated from testing the drug product"



USP – US Pharmacopeal Convention

- Intention is to use testing to evaluate risk…….not test every batch…..unless needed due to unpredictability

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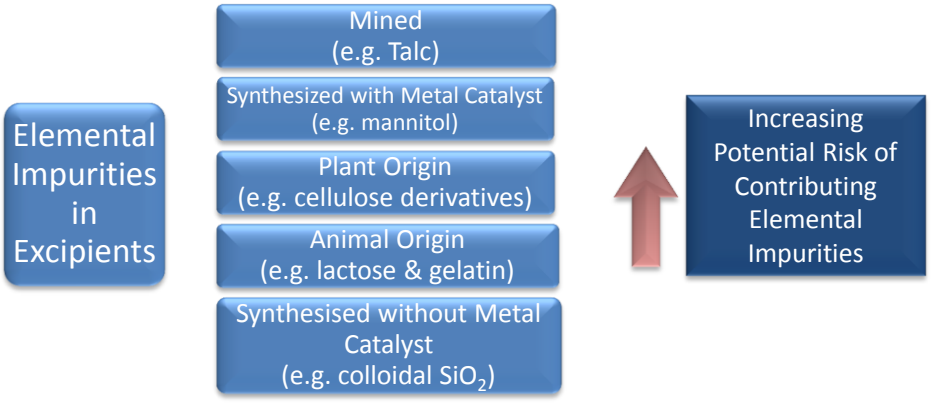
Risk Potential for Elemental Impurities in Excipients



What data exists today?

Unknowns - Analysis by FDA lab

IPEC Americas
request for "blinded samples" to be tested by FDA lab

Q1 2012
Law office for IPEC – Americas collected, blinded and submitted excipient samples to FDA lab for analysis

Q1 2013
Law office un-blinded and sent results to original submitters.

2014
Study completed - Industry assessed FDA results vs industry results

FDA & IPEC published data in journal - Fall 2015

Q2-Q4 2012
FDA analyzed samples using ICP-MS

Q1 2013
Additional samples sent to FDA


RESEARCH ARTICLE – *Pharmaceutics, Drug Delivery and Pharmaceutical Technology*

Elemental Impurities in Pharmaceutical Excipients

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The Problem with Available Data

- Data in the literature (such as the FDA study) or that may exist from shared study information is general and not specific to the actual grade and supplier of an excipient used in your particular drug product!
- This information may be useful to give you an idea of what elemental impurities **"might"** exist in the excipients you use in your drugs, however, without knowing that the data applies **specifically to the grades you use**, this data is fairly irrelevant for use in a risk assessment of the components in **YOUR** drug product!
- **Users** must still do appropriate testing of their grades or get supplier specific information to properly do their risk assessments
- The suppliers of the excipients which were included in the FDA study were provided with the results for their specific samples through the blinding exercise. Therefore, they have some good information about what might be present in the grades they supply

Limited Supplier EI Information

- Some excipient suppliers are fully engaged with this initiative, while others will not engage at all
- This will depend on whether the pharmaceutical uses of the excipient make up a significant share of their business or not – **business potential will drive decisions, not regulatory requirements**
- Most suppliers will only have EI information for elements which may have previously been listed in a compendial monograph or is of interest to their other markets which usually will drive their testing (ie; food, electronics, industrial)
- Most suppliers **do not** plan to do any additional routine testing for elemental impurities due to ICH Q3D and have no intention of agreeing to any new specifications – there may be some exceptions
- Some suppliers have done some designed studies on a limited number of batches to improve their knowledge of potential EI in their products so they can provide some risk assessment assistance to their customers

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Limited Supplier EI Information

ICH Q3D for Elemental Impurities is NOTHING like ICH Q3C for Residual Solvents!

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Can we Really Predict EI Levels in Various Types of Excipients?

Sometimes……..but not Always!

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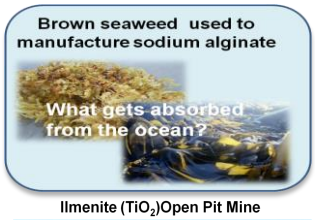
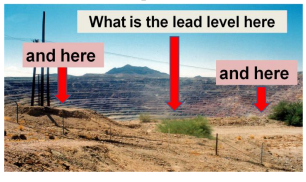
EI Content from Excipient Sources

Metal content is often inherent (due to sourcing) and cannot be "easily" reduced or removed

- **Plant-derived Excipients**
  - Grown in soil (e.g. cellulose derivatives)
  - Harvested from the ocean (e.g. alginates, carageenan)
- **Synthetic Excipients**
  - Derived from oil through synthetic processes – may use metal catalysts (e.g. povidone, PEG, silicones)
- **Mineral-based Excipients**
  - Conversion of ores from mines (e.g. TiO_2)



Ilmenite (TiO_2)Open Pit Mine



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Excursion Potential

Ilmenite (TiO_2)Open Pit Mine

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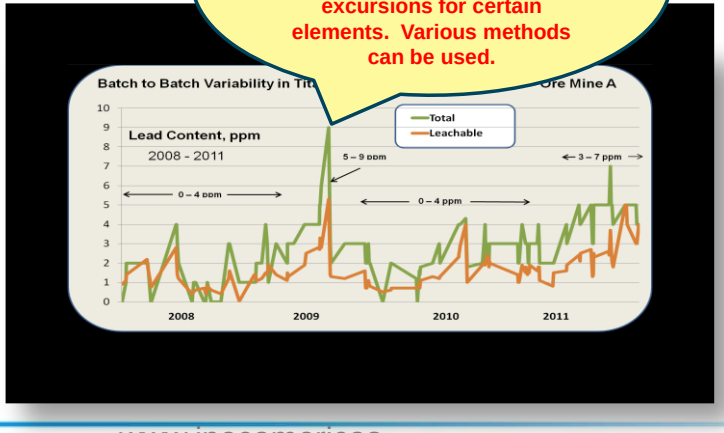
Excursions - Potential Normal Variation

- Many metal impurities are naturally [illegible] in **mined excipients** and cannot be further [illegible] it is important to understand the

Excursions can occur in any excipient derived from nature depending on process capability

Normal variation can be expected from **excursions** that occur in the raw material source – **CANNOT be predicted!**

Ongoing trend analysis will need to be done by excipient manufacturers and users for materials with a potential for excursions for certain elements. Various methods can be used.



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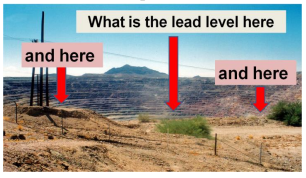
Potential for Predictability of EI Content

- **Plant-derived Excipients**
  - Depending on the **understanding** of source variability and level of processing, worst case predictions may be able to be made
  - Probably need a significant test result history for accurate predictions – MORE THAN 3-6 batches!
- **Synthetic Excipients**
  - Dependent on process capability – highest likelihood of predictability
- **Mineral-based Excipients**
  - **CANNOT** be accurately predicted unless significant processing is done
  - **Years of data** needed for a semi-accurate idea of worst case! – MORE THAN 3-6 batches!

Ilmenite (TiO_2)Open Pit Mine



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Removal of Monograph Requirements for Specific Elements

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Specific Element Requirements in Monographs

- Pharmacopeias should **not** change the existing specific element requirements (methods/limits) in the monographs unless they are evaluated as part of an individual monograph modernization to establish their overall need for the specific metal requirement.
  - Existing element limit requirements and test methods **should stay in the monographs and not be removed** – represents what has typically been used in the past
  - History supports these limits/test methods which can be used in risk assessments as a worst case example – provide useful information to users since actual detailed information is limited
  - **No changes should be made to the limits and no new elements should be added based on a limited amount of batch testing since excursions will not show up except over long-term history**
- As part of Monograph Modernization, Pharmacopeias could request from industry information regarding whether the elements(s) in the current monograph are still representative of material on the market. Some monographs have been established for many years and material on the market may have changed over time.

Specific Element Requirements in Monographs

- Because the **current monograph limits and test methods are linked**, Pharmacopeias should not change the monographs to use approaches for methodology which are different than what has been historically used in the monograph even if the methods are less sophisticated – if changed, limits could be impacted due to differences in sensitivity or sample prep!
- No changes to the test methods should be made unless validation work conducted demonstrates that the current methods in the monograph and any alternative methods **give equivalent results**.
- Basic process described in Ph.Eur. 2.4.20 can be used provided no changes are made in the limits or procedures currently listed in excipient monographs – a pathway exists for this….

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Ph.Eur. 2.4.20 – Determination of Metal Catalyst or Metal Reagent Residues

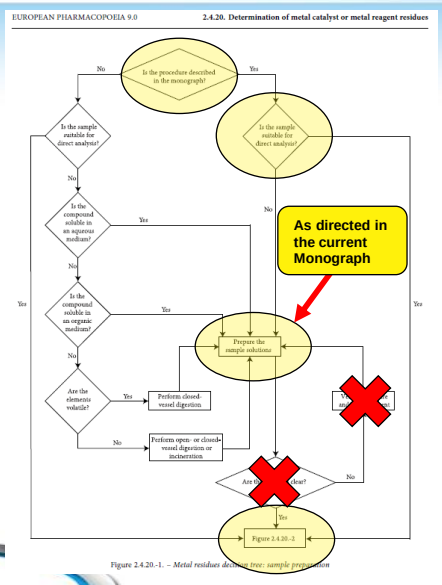

Figure 2.4.20.-1. – *Metal residues decision tree: sample preparation*

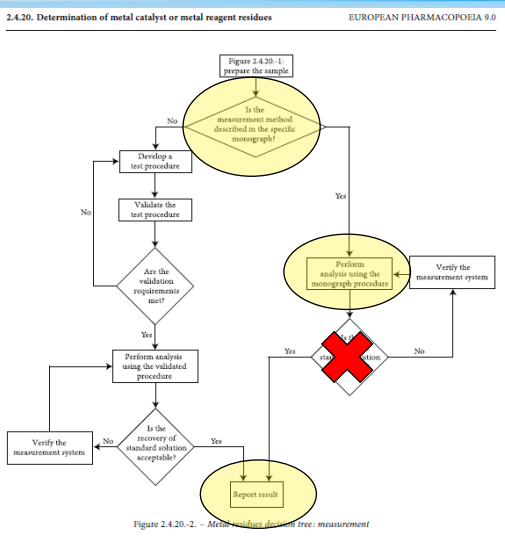

Figure 2.4.20.-2. – *Metal residues decision tree: measurement*

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Specific Element Requirements in Monographs

- If, after significant assessment, a decision is made to update or change the monographs in any way, USP, Ph.Eur. And JP should **harmonize** regarding which elements should remain in the monographs along with their appropriate limits.

- **Communication** with a number of the global excipient manufacturers for the material **is essential** to assess the necessary limits based on data from products currently in the market and the process knowledge of the excipient manufacturers.

- It is critical that no changes are made which could impact the acceptability of excipients (from their existing suppliers) **that are currently used in existing drug products** on the market !
  - **These excipients do not represent any significant risk on their own!**

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The Need for Improved Communication between Users and Makers is Significant to Improve Understanding of the Realities!

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Sharing Information between Makers & Users

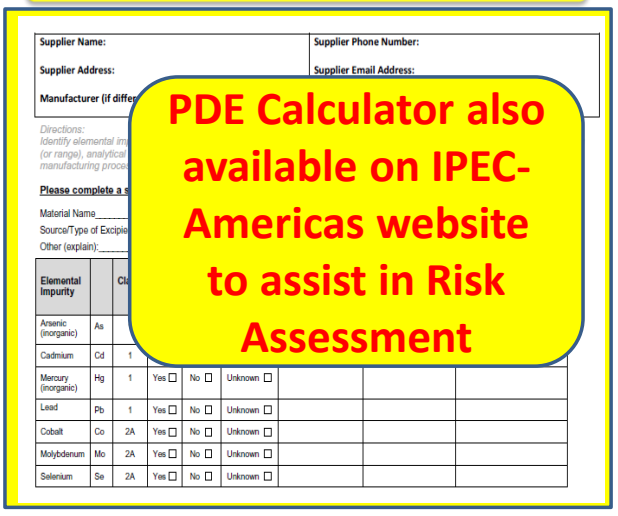
EI Coalition developed **standardized request letter and form templates** to help facilitate industry communication between users and makers of APIs and excipients. Template created and designed to help pharmaceutical companies:

- **Gather information from suppliers pertaining to potential metals/concentrations (and the potential for excursions) in both APIs and excipients used in the production of drug products.**
- **Use information from suppliers (when available) to determine potential presence / concentration of each metal in the assessment of a finished drug product Permitted Daily Exposure (PDE) level.**

NOTE: both API and excipient manufacturers are encouraged to utilize the Information Exchange request template form to **proactively develop** their own product documentation/information. However, other formats are also acceptable if appropriate.

Sharing Information between Makers & Users
IPEC Template Information Exchange Request

URGENT industry need for BASE-LINE DATA!



Supplier Name: | Supplier Phone Number:

Supplier Address: | Supplier Email Address:

Manufacturer (if differ

Directions:
Identify elemental im
(or range), analytical
manufacturing proces

Please complete a s

Material Name_____
Source/Type of Excipie
Other (explain):_____

Elemental Impurity		Cl						
Arsenic (inorganic)	As							
Cadmium	Cd	1						
Mercury (inorganic)	Hg	1	Yes ☐	No ☐	Unknown ☐			
Lead	Pb	1	Yes ☐	No ☐	Unknown ☐			
Cobalt	Co	2A	Yes ☐	No ☐	Unknown ☐			
Molybdenum	Mo	2A	Yes ☐	No ☐	Unknown ☐			
Selenium	Se	2A	Yes ☐	No ☐	Unknown ☐			

PDE Calculator also available on IPEC-Americas website to assist in Risk Assessment

IDEAL WORLD….

Pro-actively completed by suppliers and sent to users

REAL WORLD…

A limited number of suppliers have data or will complete and return the form to users

download THE LETTER

download THE TEMPLATE

Your Questions – Thank You!

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