Module 5

Product Risk Assessment General Approaches

ICH Q3D Elemental Impurities

Disclaimer:
This presentation includes the authors' views on Elemental Impurities theory and practice.
The presentation does not represent official guidance or policy of authorities or industry.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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Purpose

- **To provide an overview of an elemental impurities risk assessment for a product consistent with ICH Q3D.**
- **To provide illustrative examples for developing product risk assessments**
  - Other approaches may also be acceptable
- **The information presented here does not provide new guidance, rather, it elaborates on how the recommendations in the guidance may be implemented**

Overview

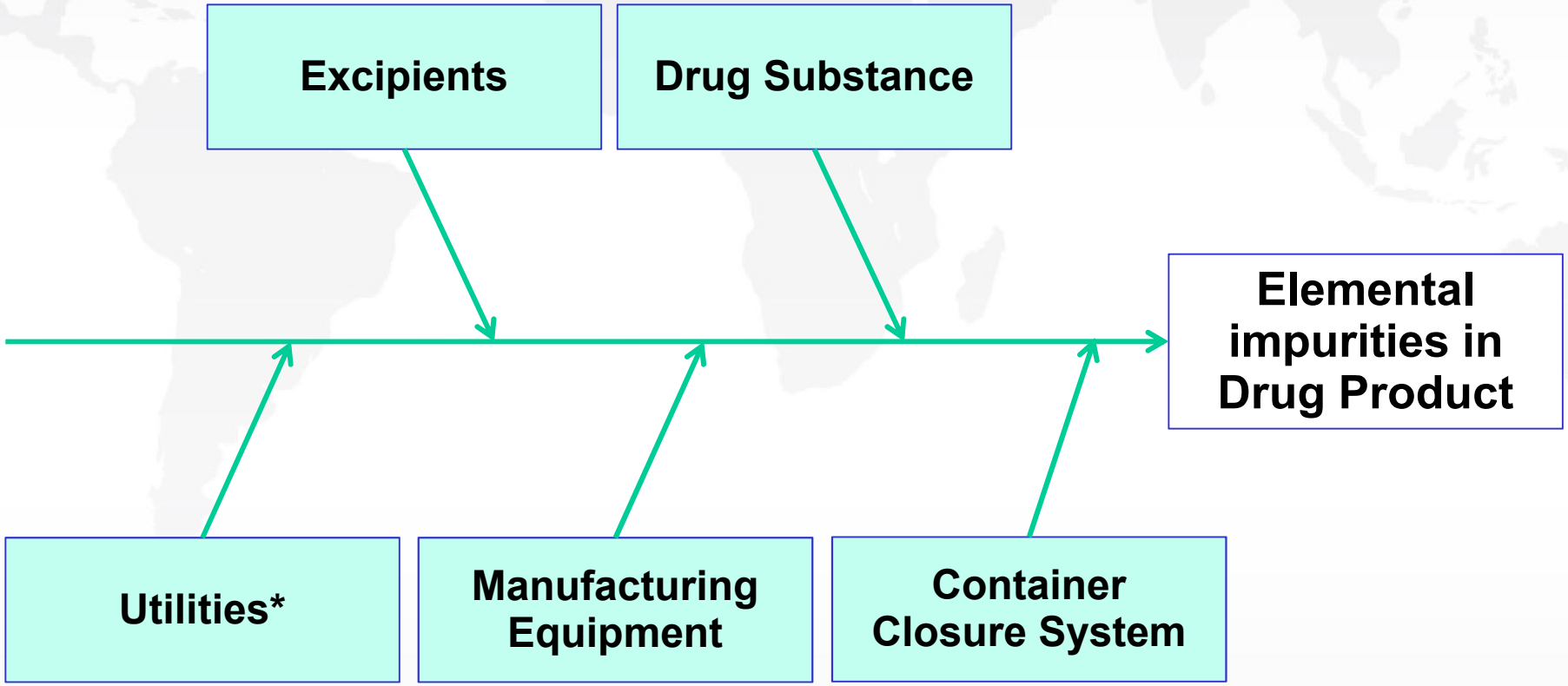
- Potential sources of elemental impurities
- Risk assessment approaches
- Output of elemental risk assessment
- Product risk assessment Process
  - Drug product based
  - Drug product component based
- Evaluation

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

Risk assessment approaches

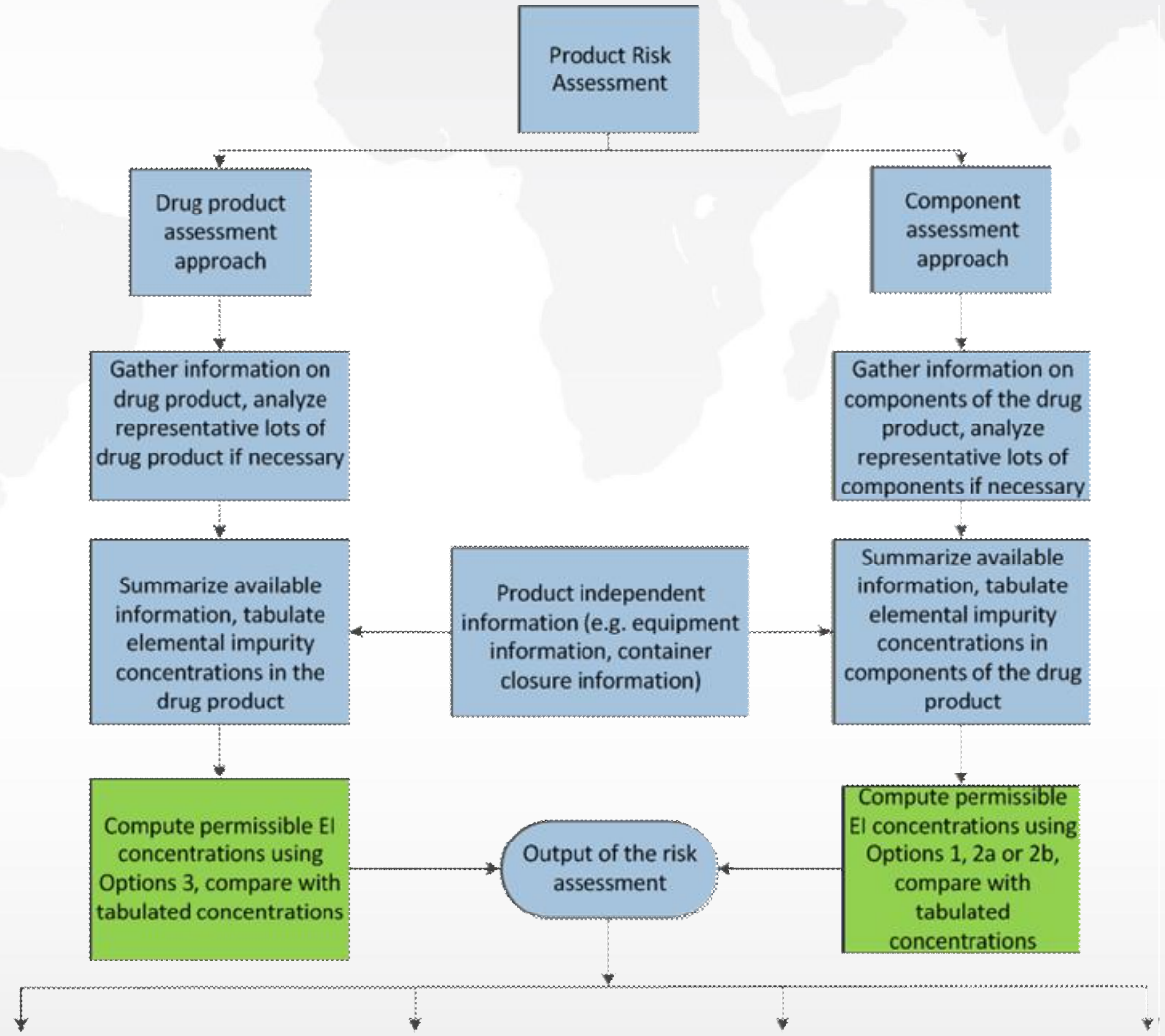
- **Examples of general approaches that may be considered during elemental impurities risk assessment are:**
  - These approaches or others may change as information becomes available or additional experience is gained.
- **Assessment of potential elemental impurities in the drug product**
  - Determine 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)**

Q3D Table 5-1: Elements to be considered in the risk assessment

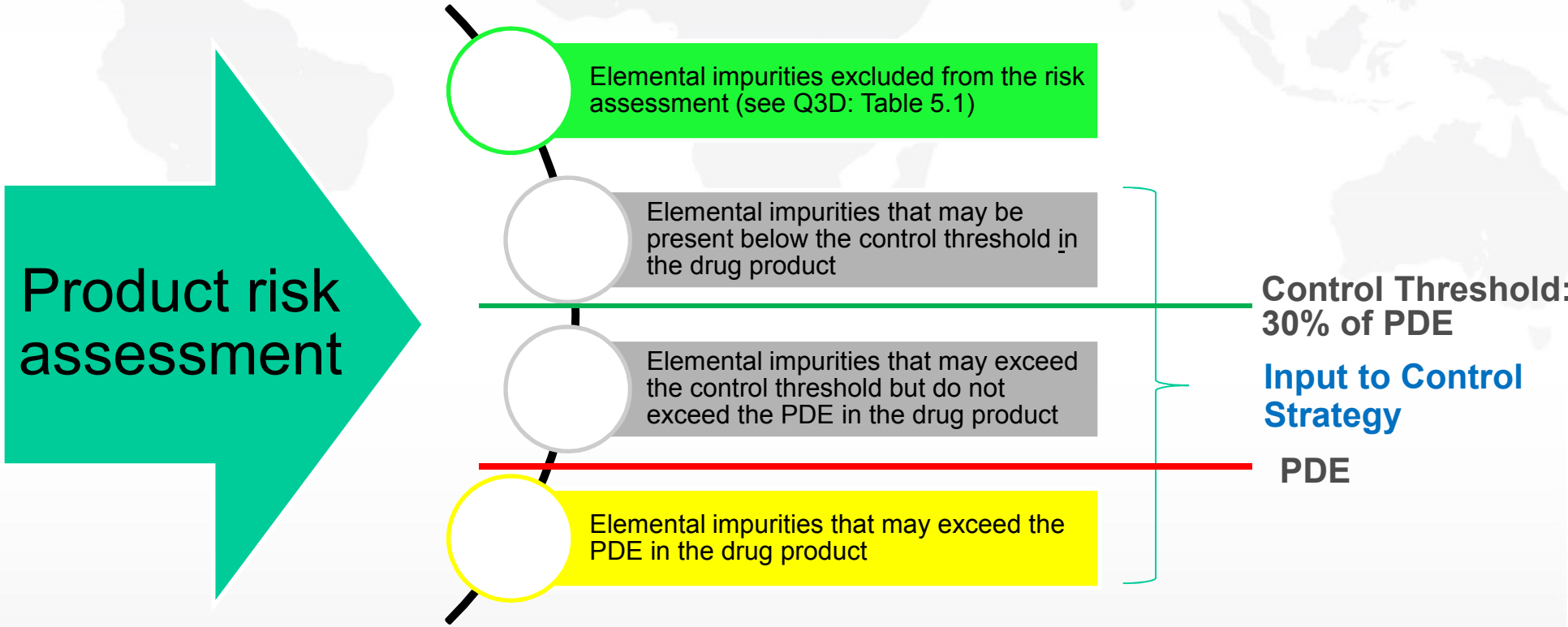
Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	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.

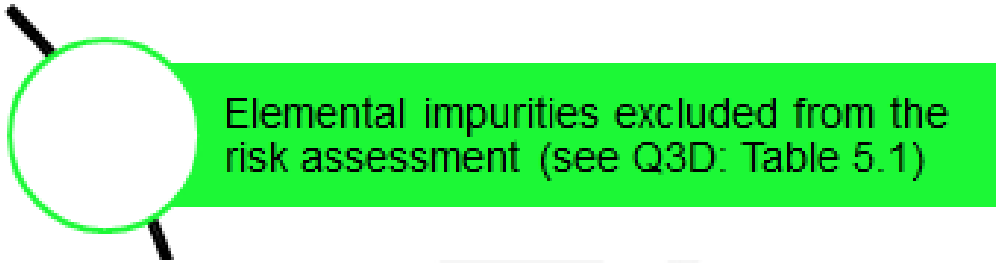
Generalized risk assessment process flow



Risk Assessment Output



Examples of potential outputs of the risk assessment

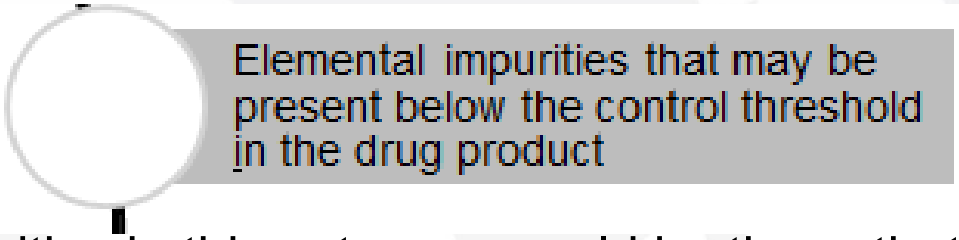


- Class 2B elements that are not intentionally added
- Elements in Table 5.1 that may be excluded based on the route of administration

Example:

- For a solid oral drug product, the following class 3 elemental impurities were not intentionally added and therefore were not considered in the risk assessment: Li, Sb, Ba, Mo, Cu, Sn, and Cr.

Examples of potential outputs of the risk assessment

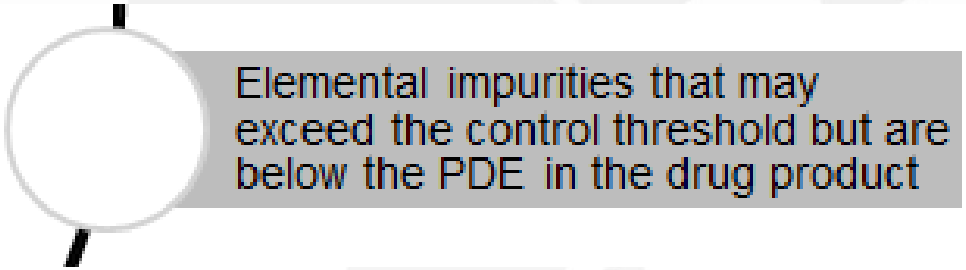


Elemental impurities in this category would be those that have the potential to be found, but if present would be found at low levels They are often associated as low level impurities in components that can be handled through incoming material controls or with GMP Quality System elements (e.g. vendor/supplier qualification processes and procedures).

Example:

- Pb is a potential impurity in TiO_2. If the formulation contained 10 mg TiO_2 in a 1 g tablet (1% TiO_2) and the observed Pb level in TiO_2 was 1-10 µg/g; the total amount of Pb contribution to the drug product would be (0.01-0.1 µg/day), less than the control threshold of Pb (1.5 µg/g) in the drug product.

Examples of potential outputs of the risk assessment

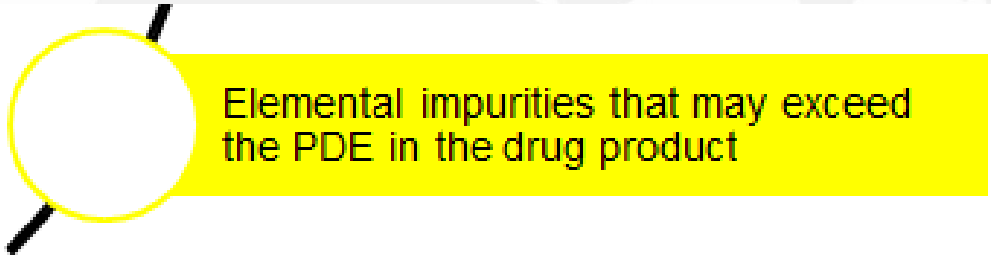


Elemental impurities in this category would be those that have the potential to be found in the drug product or in drug product components.

Example:

- Pb is a potential impurity in K_2CO_3. If the formulation contained 500 mg K_2CO_3 in a 1 g tablet and the observed Pb level in K_2CO_3 was 1-8 µg/g, the total amount of Pb contribution to the drug product would be 0.5-4 ppm. The range of observed levels is above the control threshold but below the PDE (5 µg/g).

Examples of potential outputs of the risk assessment



Elemental impurities in this category would be those that exceed the PDE in the drug product. (See Module 2 for justification)

Example:

- Cd is a potential impurity in $CaHPO_4$. If the formulation contained 500 mg $CaHPO_4$ in a 750 mg tablet and the observed Cd level in Ca_2HPO_4 was 8-9 µg/g, the total amount of Cd contribution to the drug product (5.3 - 6 µg) would exceed the PDE for Cd 5 (µg/day).

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

Special considerations for biotechnologically derived products

- It is recognized that the risks associated with the presence of elemental impurities at levels of safety concerns for biotechnology-derived products are low
  - This is generally due to the absence of use of inorganic catalysts or reagents and to the typical purification schemes used in the manufacture of biotechnology-derived products

Documentation

Documentation to be maintained in Company Pharmaceutical Quality System	Documentation to be included in regulatory dossiers (new or updates)
Complete risk assessment document describing process, data used, data references and information needed to support dossier summary	Summary of product risk assessment process used
GMP related processes to limit the inclusion of elemental impurities	Summary of identified elemental impurities and observed or projected levels
Change management processes (defining triggers for product assessment or control strategy updates)	Data from representative commercial or pilot scale batches (component or drug product as appropriate)
Periodic review processes	Conclusion of the product risk assessment
Original data used in the product risk assessments, quality agreements, supplier qualification, etc.	

Elemental Impurity risk assessment process – general considerations

Considerations in determining drug product assessment approach

The decision of the risk assessment approach (component or drug product) is dependent on many factors, including but not limited to the following;

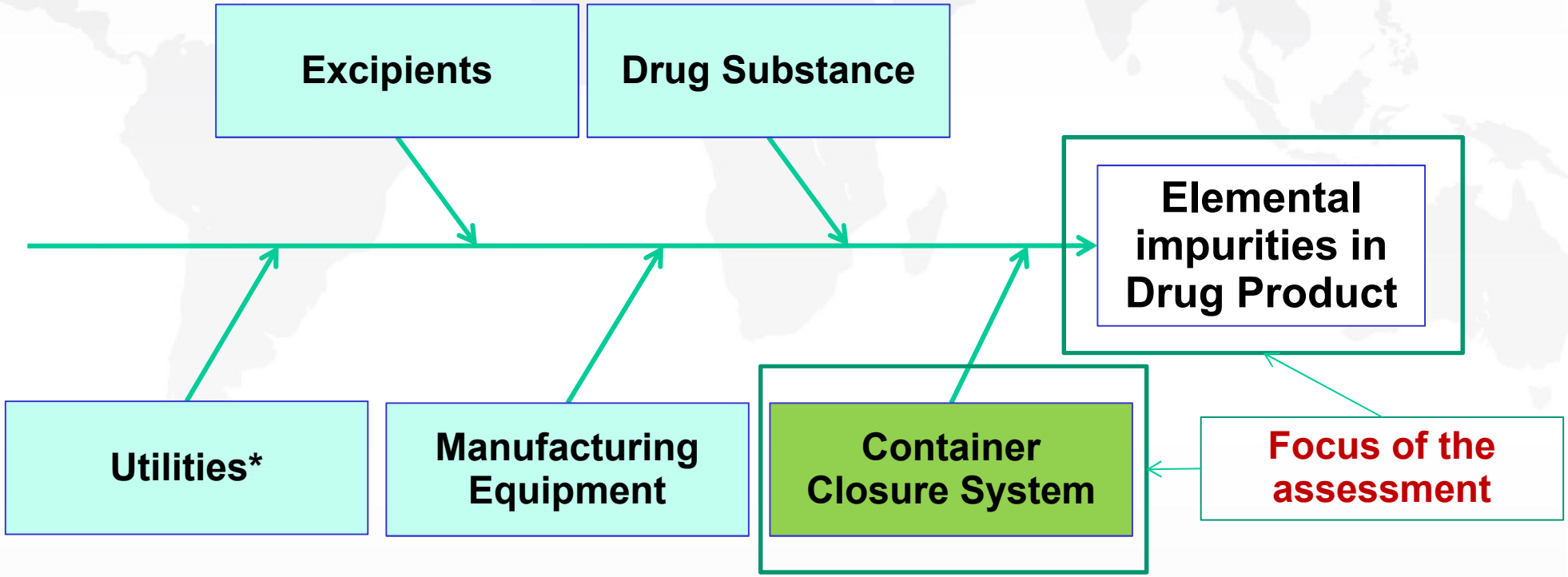
- Knowledge of the elemental impurity levels of components of the drug product
- Situations where the drug substance (or drug product or both) is managed by a third party manufacturer with potentially different internal quality systems and controls
- Demonstrated high variability of the elemental impurity levels in one or more components of the drug product
- High formulation percentages of excipients known to have concomitant elemental impurities
- Knowledge of the levels of elemental impurities in the drug product components or excipients that have been established as having limited potential to introduce elemental impurities
- Primary contribution of elemental impurities to the drug product can be traced to a limited number of components
- Identification of one or more components that contribute the greatest to the elemental impurity 'burden' providing improved control options (material controls, periodic verification testing, etc.)

In many situations, the risk assessment may be a combination of both the component approach and the drug product approach. Knowledge of components that have potential elemental impurities can provide information to improve the drug product assessment approach

Product Assessment – Drug Product Approach

Potential sources of elemental impurities

For an assessment focused on the drug product



*** Water is the primary utility of potential concern**

- **This risk assessment focuses on the measured levels of potential elemental impurities in the drug product**
- **The assessment may require the evaluation of the impact of the container closure system on the drug product and the potential to contribute elemental impurities to the drug product**

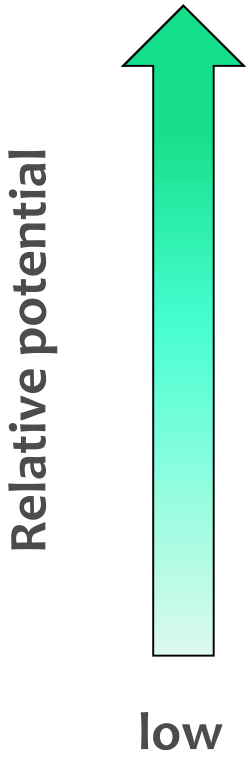
Drug product assessment approach

- **Implicit in the drug product risk assessment approach is the availability of data concerning elemental impurity levels in the drug product**
- **Justification of the elemental impurities included in the assessment**
  - Preliminary multiple element screening methods can establish the elemental impurities of interest (if any)
  - Table 5.1 in the guideline provides guidance on what elements should be considered in the assessment
- **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.**
  - For some components that have inherent variability (e.g., mined excipients), additional data may be needed

Drug product assessment approach – container closure systems

- **Depending on the drug product type, additional evaluation for potential elemental impurity introduction into the drug product may be needed**
  - Solid oral dosage forms
    - The interaction of solid oral dosage forms with packaging components has essentially a negligible risk of transferring elemental impurities from the container closure system (packaging) to the drug product.
    - No further evaluation is required
  - Liquid, suspension and semi-solid dosage forms
    - Depending on the packaging material and the formulation components, there may be a potential for leaching of elemental impurities from the packaging components
    - Data may be generated in leachable studies (evaluating the potential for inclusion of elemental impurities using an appropriate methodology)
    - Table 1 provides additional information on the level of risk associated with various drug products and container closure systems.
- **Questions for consideration**
  - Does the packaging inherently contain large quantities of metals which might leach?
  - Is the drug product likely to leach metals from its packaging over the shelf-life?

Relative potential of interaction of CCS with drug product categories



Potential for inclusion of elemental impurities introduced to the drug product from the container closure system	Specific drug product classes	Example considerations/potential packaging components of concern
	Injections and Injectable Suspensions	Glass containers – potential to leach As
	Inhalation Aerosols and Solutions;	
	Parenteral solutions	
	Ophthalmic Solutions and Suspensions;	Glass containers - potential to leach As
	Transdermal patches	Metal containers – potential to leach elemental impurities (dependent upon composition of CCS and composition/pH of formulation
	Ointments and Creams	
	Nasal Aerosols and Sprays	
	Topical Solutions and Suspensions;	Plastic containers - potential to leach elemental impurities from polymeric materials is low
	Topical and Lingual Aerosols;	
	Oral Solutions and Suspensions	
	Oral Tablets	Solid – solid interaction provides little or no opportunity to transfer elemental impurities from CCS to drug product
	Oral (Hard and Soft) Capsules	
	Oral Powders	
	Sterile Powders	
	Inhalation Powders	
	Powders for Injection	
	Topical Powders	

Evaluation

- Using the data from the drug product testing results, obtained from 3 commercial or 6 pilot scale batches, the observed elemental impurities need to be calculated as a total daily amount based on the total daily dose of the drug.

Daily amount of elemental impurity = (impurity conc.,(µg)/g)×(mass of drug g/day)

- Compare the total daily amount of each elemental impurity with the established Permitted Daily Exposure value (PDE)[1].
  - Elemental impurities consistently below the control threshold do not require additional controls
  - Elemental impurities that exceed the control threshold require additional evaluation during the development of the controls

[1] Or proposed Acceptable Levels (AL) for those routes of administration not included in ICH Q3D (see Module 1 for AL determination)

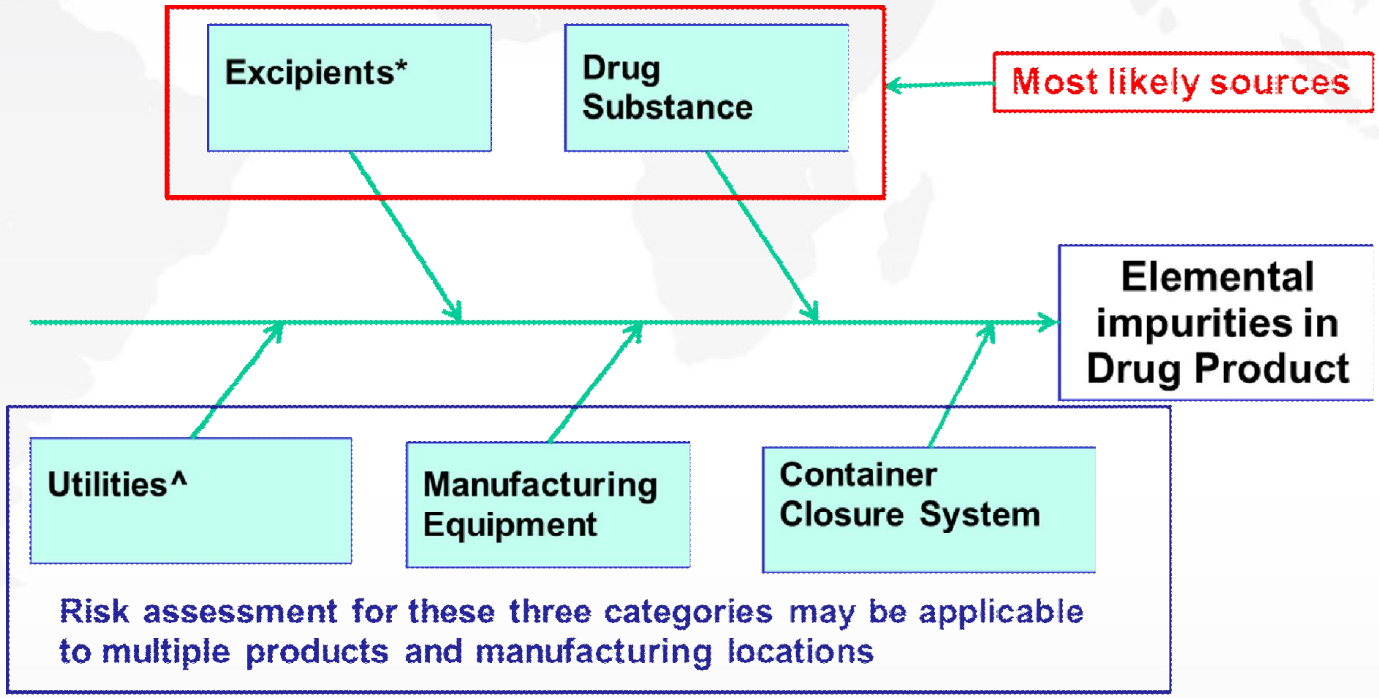
Comparison of Observed Levels with PDE

- 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 to ensure 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 acceptable level (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. Module 1 contains additional information on the establishment of ALs.

Product Assessment – Component Approach

Potential sources of elemental impurities – component approach



* Water may need to be considered as an excipient (component) depending on the formulation

^ Water is the primary utility of potential concern

Following the component approach, all the potential sources of elemental impurities should be considered and evaluated for contribution to the drug product

Lower risk sources of elemental impurities – assessment for utilities contributions

- **In general GMP policies, processes and procedures ensure that the contribution of elemental impurities to drug products is low.**
  - Facility & utility design and qualification
  - Facility & utility maintenance procedures
- **Water produced under GMP controls ensures that the contribution of elemental impurities from water to the drug product is low**
  - Qualification and maintenance of water systems
  - Specification for water quality
  - Routine monitoring of the water quality
- **Use of compendial grade water (*e.g. PW, WFI)* further reduces the potential contribution of elemental impurities**
  - The source water used to prepare WFI or PW is first required to meet drinking water standards which already include strict control on the levels of elemental impurities of concern.
  - The purification processes employed to produce WFI or PW provide a mechanism to further reduce the elemental impurity content

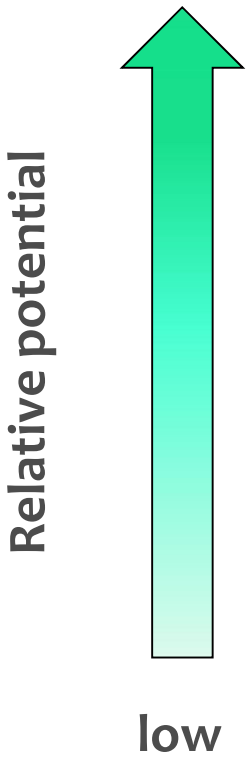
Lower risk sources of elemental impurities – assessment for Manufacturing Equipment Contributions

- **In general GMP policies, processes and procedures ensure that the contribution of elemental impurities to the drug products is low.**
  - Equipment design and qualification
  - Equipment maintenance procedures
  - Equipment cleaning/visual inspection procedures
- **Knowledge of the elemental impurity profile of drug substance can assist in the evaluation of potential contributions from manufacturing equipment**
  - Drug substance processes often are more chemically aggressive than drug product processes.
  - Monitoring of drug substance for potential impurities from manufacturing equipment (e.g. stainless steel – Cr, Mn, Mo, V, Ni) can provide insight into potential impact to the drug product

Lower risk sources of elemental impurities – assessment for CCS contributions

- **The potential of release of elemental impurities from CCS components into the drug product depends on the dosage form**
- **Empirical results confirmed low potential of introduction of elemental impurities to the drug product from the CCS**
  - *Jenke, D. et.al.,* "A Compilation of Metals and Trace Elements Extracted from Materials Relevant to Pharmaceutical Applications Such as Packaging Systems and Devices", PDA J. Pharm. Sci. Technol., 67(4):354-75, 2013
- **Potential risk may be further explored by use of prior knowledge or conducting an appropriate leachables study.**

Relative potential of interaction of CCS with drug product categories

Potential for inclusion of elemental impurities introduced to the drug product from the container closure system	Specific drug product classes	Example considerations/potential packaging components of concern
	Injections and Injectable Suspensions	Glass containers – potential to leach As
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	Oral Powders	
	Sterile Powders	
	Inhalation Powders	
	Powders for Injection	
	Topical Powders	

Product risk assessment – Excipient contribution

- **A limited number of excipients of mineral origin may include elemental impurities that are embedded in or tightly bound to the solid matrix preventing their release except with extreme extraction procedures**
  - *e.g.* smectic (mineral) clays[1,2]
- **Some mined excipients (e.g. Talc, Titanium dioxide) are known to have low but variable levels of some elemental impurities of concern (e.g. As and Pb)**
  - Due to the nature of the isolation of the excipients, it is often not possible to reduce the level of elemental impurity
  - Some demonstrate variation in the observed level based on mine location as well as variation within the same mine

[1] Morman SA, Plumlee GS, Smith DB (2009) Application of in vitro extraction studies to evaluate element bioaccessibility in soils from a transect across the United States and Canada, Applied Geochemistry 24, 1454–1463

[2] Oomen AG, Hack A, Minekus M, Zeijdner E, Cornelis C, Schoeters G, Verstraete W,Van de Wiele T, Wragg J, Rompelberg CJM, Sips A, Van Wijnen JH, (2002) Comparison of five in vitro digestion models to study the bioaccessibility of soil contaminants. Environmental Science & Technology, 36, 3326-3334

Product risk assessment – drug substance contribution

- **A significant potential source of elemental impurities arises from the use of metal catalysts in the synthesis of drug substances, especially if used in the latter stages of synthesis**
  - Knowledge of potential elemental impurities in synthetic steps prior to the final drug substance may provide information that can assist in the preparation of the risk assessment

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. Module 1 contains additional information on the establishment of ALs.

This portion of the training material was intended to provide an overview of the processes that may be used to complete the risk assessment.

Related topics are:

Module 6: Controls

Module 8: Case studies

