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General Approaches to Elemental Impurity Product Assessments

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Outline

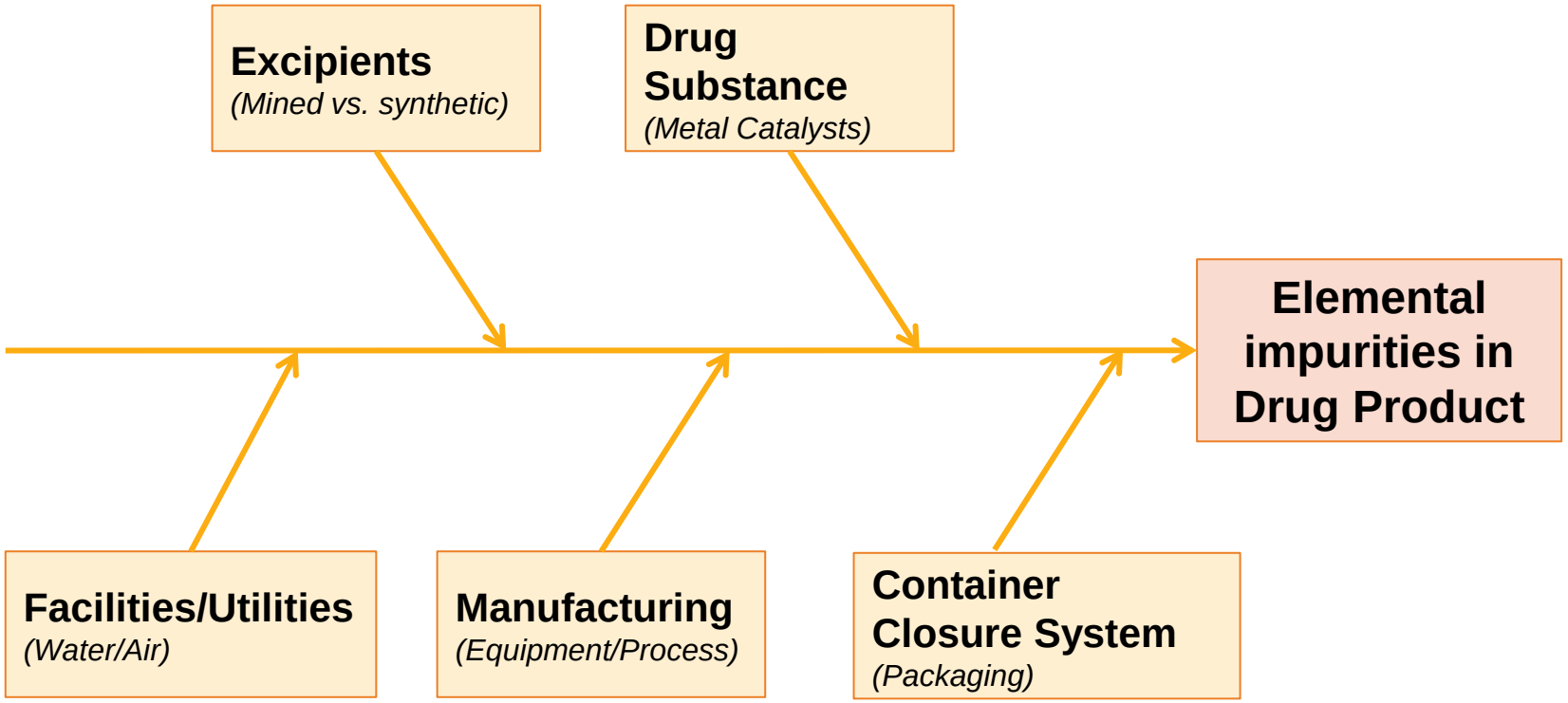
- Overview of Risk Assessment Process
- Product Assessment Process
  - Product Based
  - Component Based
- Documentation and Conclusions of Product Risk Assessments

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 or suspected sources of elemental impurities with the potential to be included in the finished product
- **Analyze:** Determine the probability of elemental impurity occurrence
- **Evaluate:** Compare actual or predicted elemental impurity levels with PDE's
- **Control:** Develop, document and implement a control strategy

Potential sources of elemental impurities



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

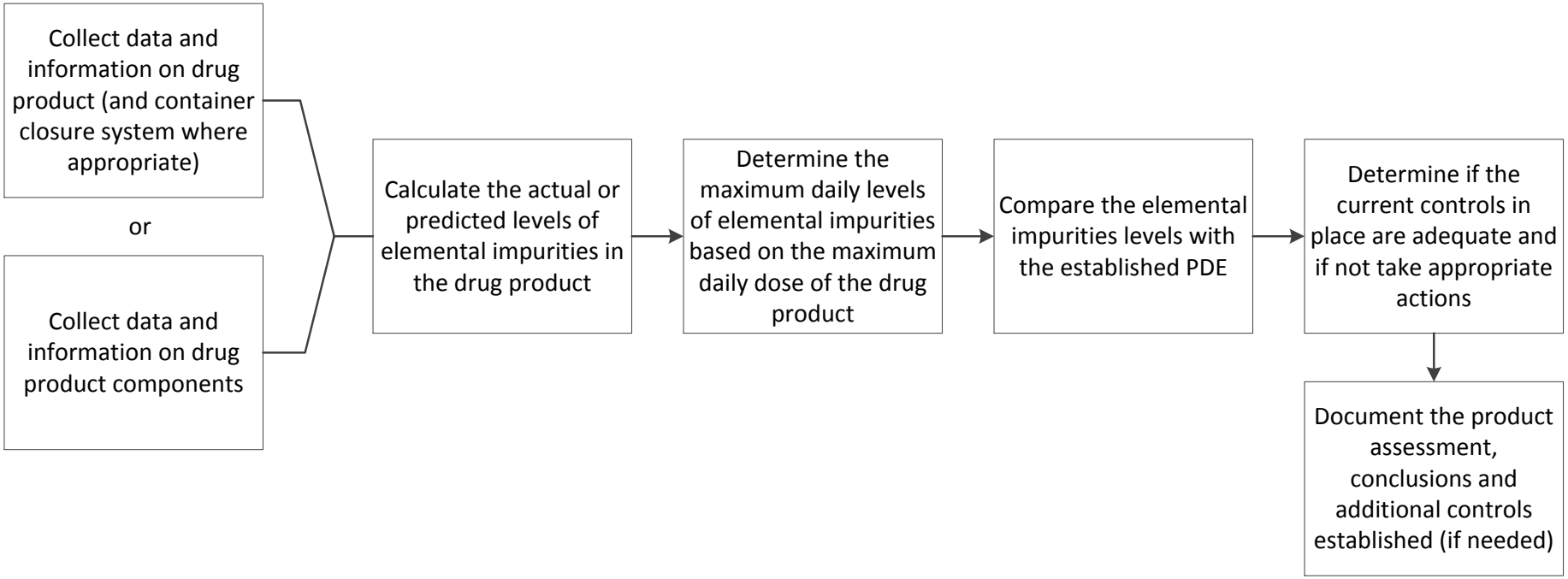
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Risk assessment approaches

There are two general approaches that may be considered in determining the potential for elemental impurities in the drug product.

- 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 of the container closure system may also be required
- Assessment of potential elemental impurities from each component of the drug product
  - Assess all 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

Generalized assessment process flow



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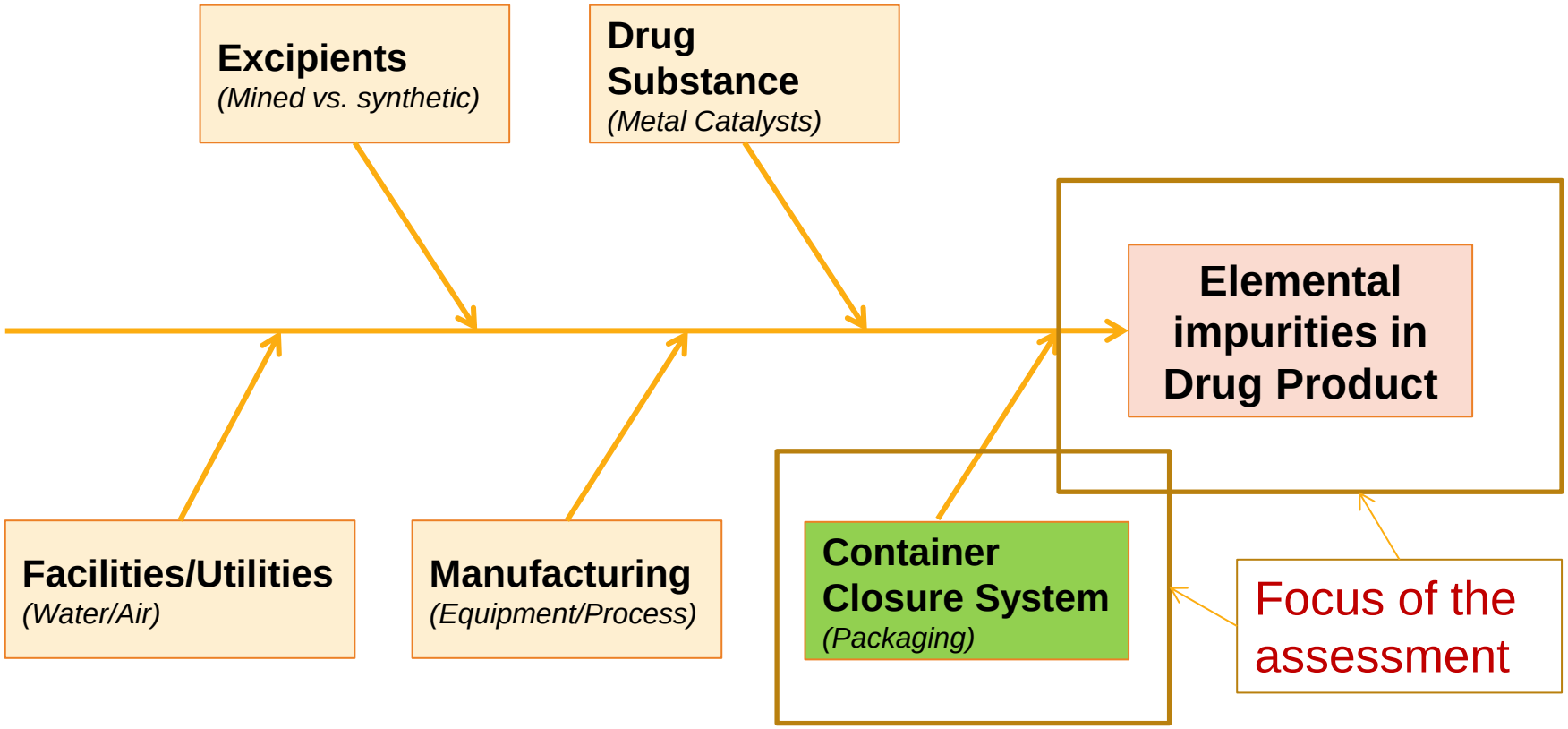
Some considerations in determining assessment approach

Assessment based on final drug product	Assessment based on product components
• Limited knowledge of the elemental impurity levels of components of the drug product • Manufacture of the drug substance (or drug product or both) by a third party manufacturer • 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	• Significant body of data on the levels of elemental impurities in the drug product components • Primary contribution of elemental impurities to the drug product can be traced to a limited number of components • Use of well characterized excipients • Limited use of excipients known to have concomitant elemental impurities • High formulation percentages of excipients known to have concomitant elemental impurities

Product Assessment – Drug Product Approach

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Potential sources of elemental impurities



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Drug product assessment approach

- Implicit in taking this approach is the availability of data concerning elemental impurity levels in the drug product
- Minimum data expectations
  - Data from 3 commercial lots or 6 pilot scale lots of drug product
- Justification of the elemental impurities included in the assessment
  - Preliminary multiple element screening method 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 evaluation
- Potential contribution from manufacturing equipment can be evaluated in several ways
  - Screening of drug substance for presence of elements from manufacturing equipment (e.g. Cr, Mo, V)
  - Inclusion in the drug product elemental impurity testing

Drug product assessment approach - packaging

- 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?

Drug Product assessment –Packaging component risk analysis

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Inject able Suspensions	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral Powders	Oral Tablets and Oral (Hard and Soft) Capsules

To components

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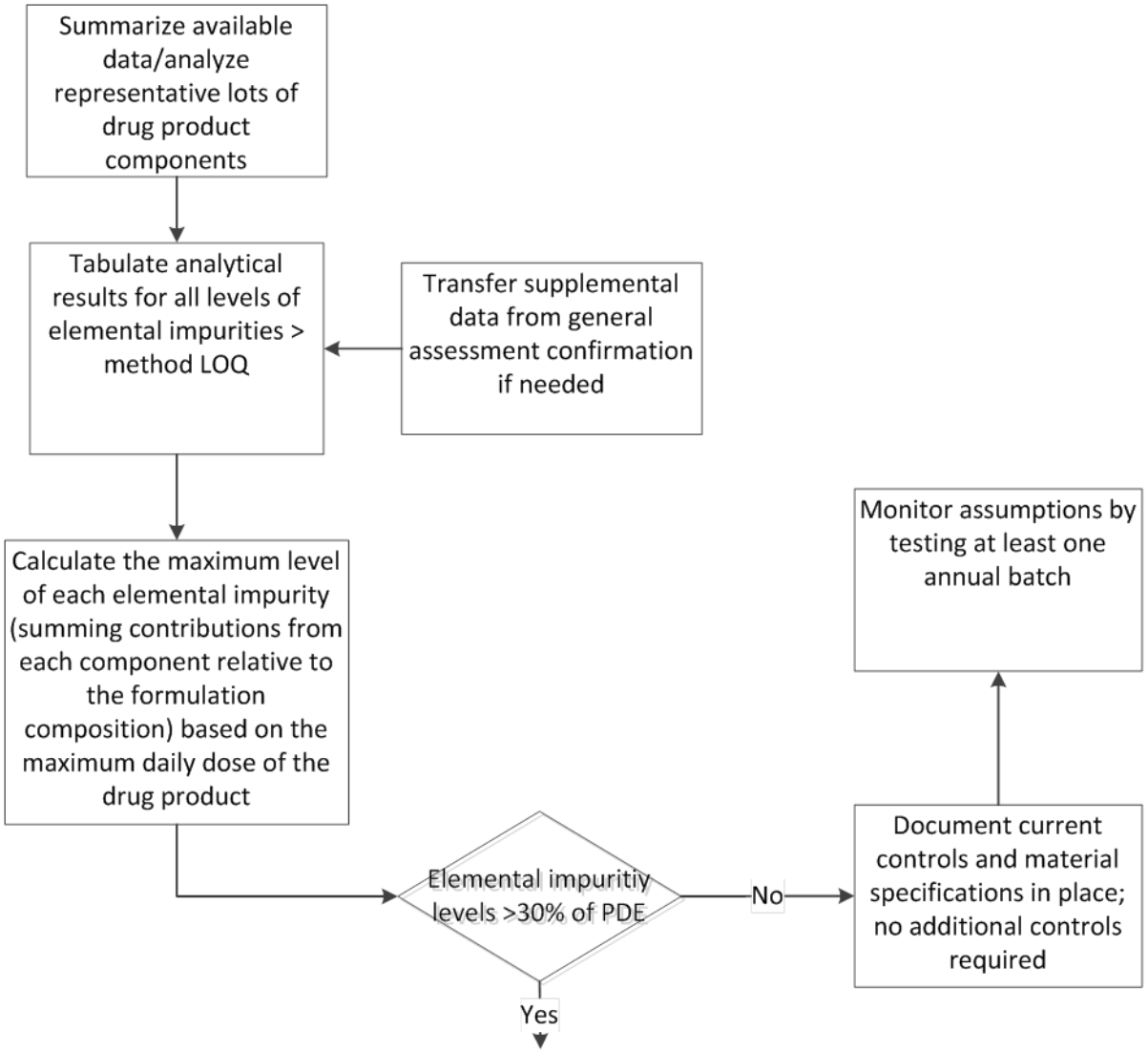
Evaluation

- Using the data from the drug product testing results, 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 µg/day)

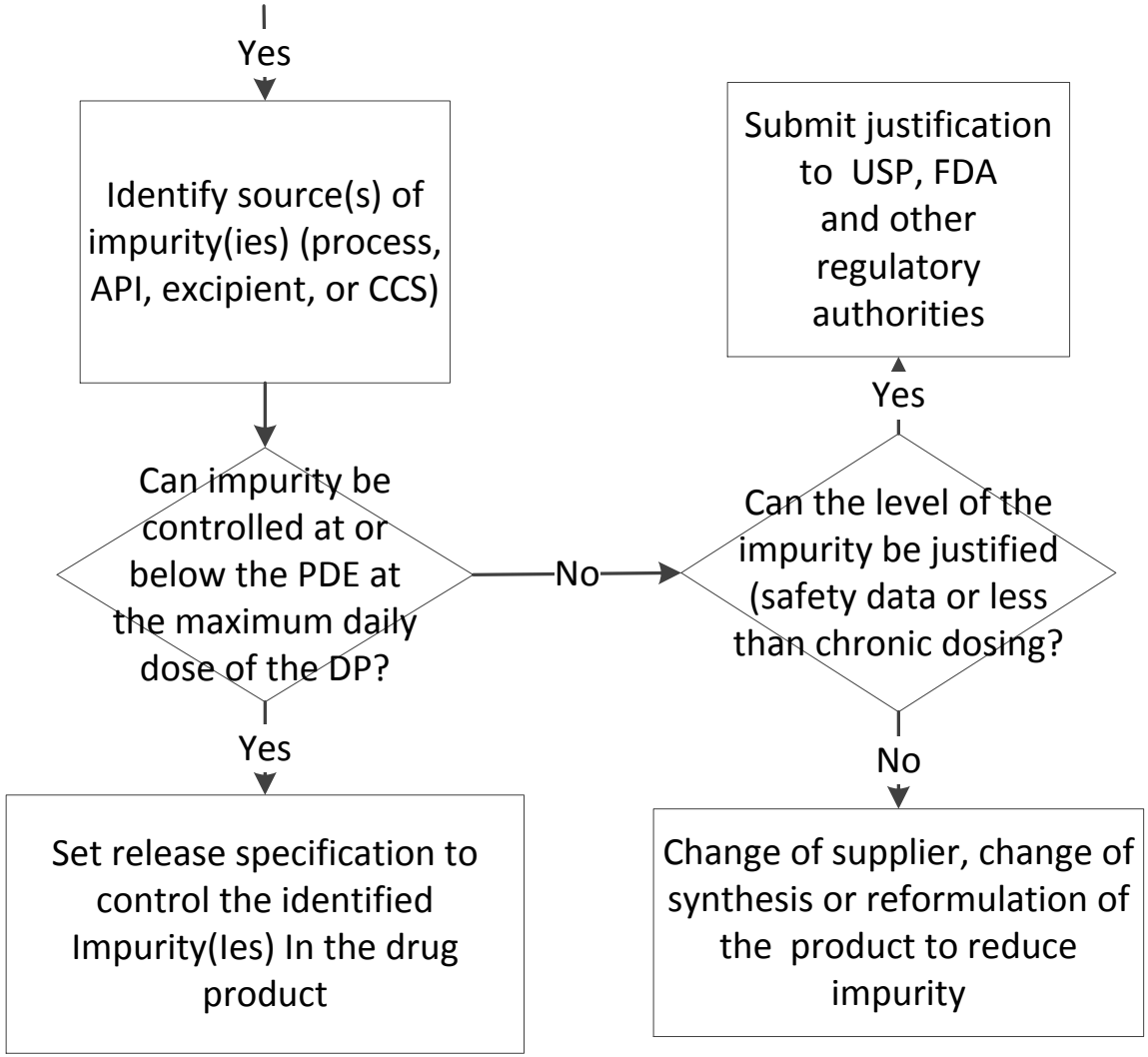
- Compare the total daily amount of each elemental impurity with the established Permitted Daily Exposure value (PDE).

Expanded view of process flow – Part 1



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Expanded view of process flow – Part 2



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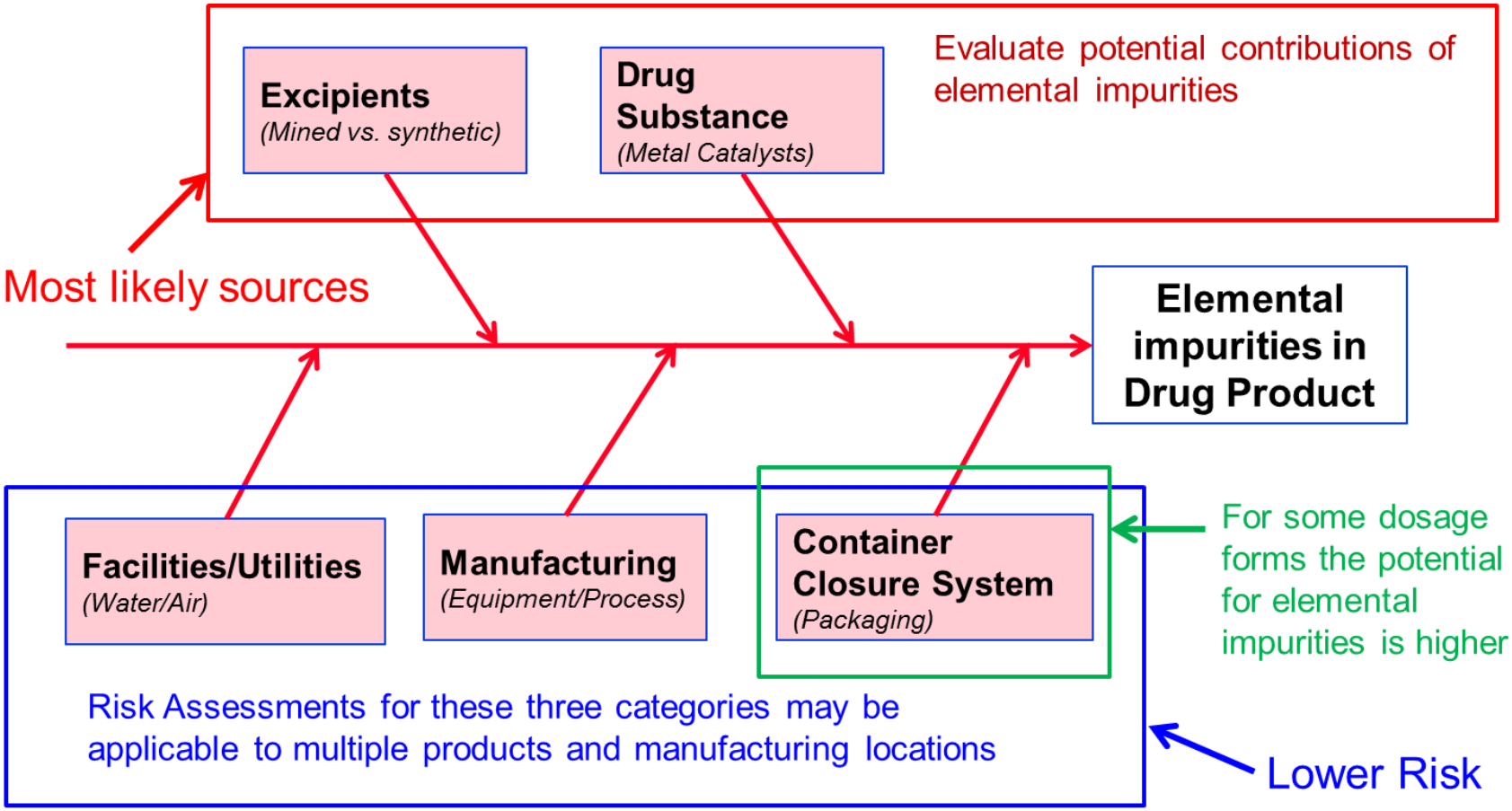
Comparison of Observed Levels with PDE

- LOQ ≤ Elemental Impurity Level ≤ Control Threshold – no additional controls required
- Control Threshold ≤ Elemental Impurity Level ≤ PDE
  - Current controls may be adequate
  - Need to assess variability and the controls currently in place
  - May require incoming material, drug substance or drug product specification
- PDE ≤ Elemental Impurity Level
  - Additional controls are needed (if daily, chronic dosing)
  - May need to identify source(s) of elemental impurities

If the drug is intended for less than daily, chronic administration or uses a route of administration that does not result in systemic exposure, higher levels may be acceptable. A justification for the higher levels will need to be developed following the principles described in ICH Q3D.

Product Assessment – Component Approach

Product Assessment - Component approach



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Lower risk sources of elemental impurities – Facilities and Utilities

- In general GMP policies, processes and procedures ensure that the contribution of elemental impurities drug products is low.
  - Facility & utility design and qualification
  - Facility & utility maintenance procedures
  - Water quality – internal quality standards and monitoring program
- Water in most cases has the higher potential to be a source of elemental impurities; however, GMP controls also ensure that the contribution of elemental impurities 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 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 to levels significantly below the limits specified in ICH Q3D

Lower risk sources of elemental impurities – Manufacturing Equipment

- 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
  - Cleaning validation/verification/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 more chemically aggressive than drug product processes.
  - Monitoring of drug substance for potential components of 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 – Container closure systems

- While certain materials used to prepare container closure systems (CCS) may contain elemental impurity residues, predominantly associated with deliberate use (e.g. metal catalysts in producing specific product or components or metals used in the components themselves), the probability of the occurrence of elemental impurity levels is low and further reduced by the generally low probability of transferring any elemental impurities present into the drug product.
- In order for potential elemental impurities to be transferred from the CCS to the drug product, there must be a mechanism to facilitate that transfer
- Recent publication (*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
  - Empirical results confirmed low potential of introduction of elemental impurities to the drug product from the CCS
- Potential risk may be further explored by conducting an appropriate leachables study.
- Not all drug product forms have the same potential for interactions with the CCS.

Summary table

Product risk assessment – Excipient contribution

- One of the principal potential sources of elemental impurities
  - related to compounds that are co-isolated or that occur coincident with the desired excipient
- 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 excipients show variations in the observed level based on mine location as well as variation within the same mine

Product risk assessment – Drug substance

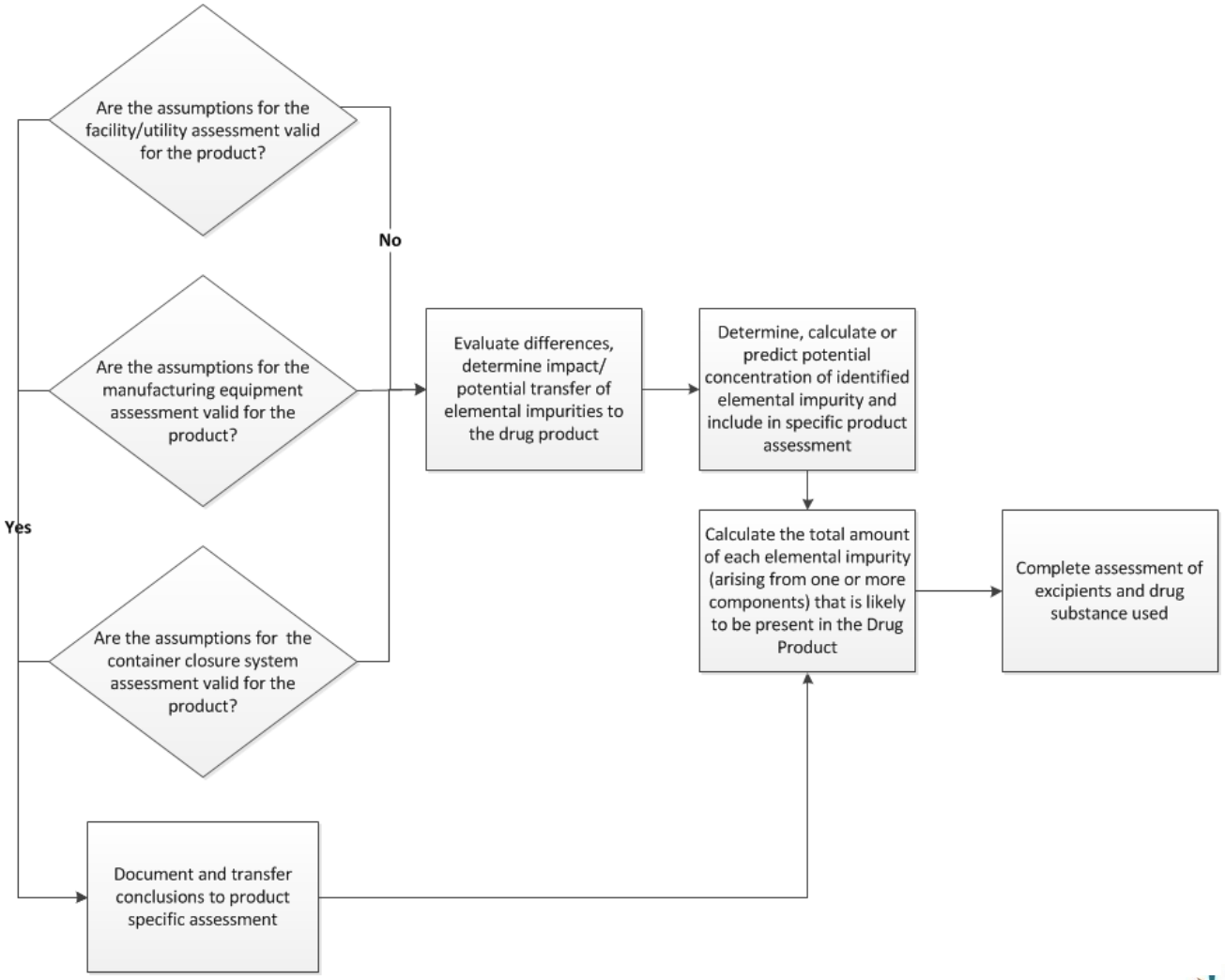
- The starting point for evaluating potential elemental impurities is the isolated drug substance
  - Evaluation of some potential sources of elemental impurities in earlier steps of the synthetic route may be of benefit
- For chemically derived drug substances, the most predominant source of elemental impurities is often the use of catalysts in the latter stages of the synthesis

Evaluation

- Compile data for components of the drug product
  - Published information
  - Data generated by the applicant or suppler (in a limited number of cases)
  - 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 as a function of the percent composition of the formulation and the total daily dose of the drug.

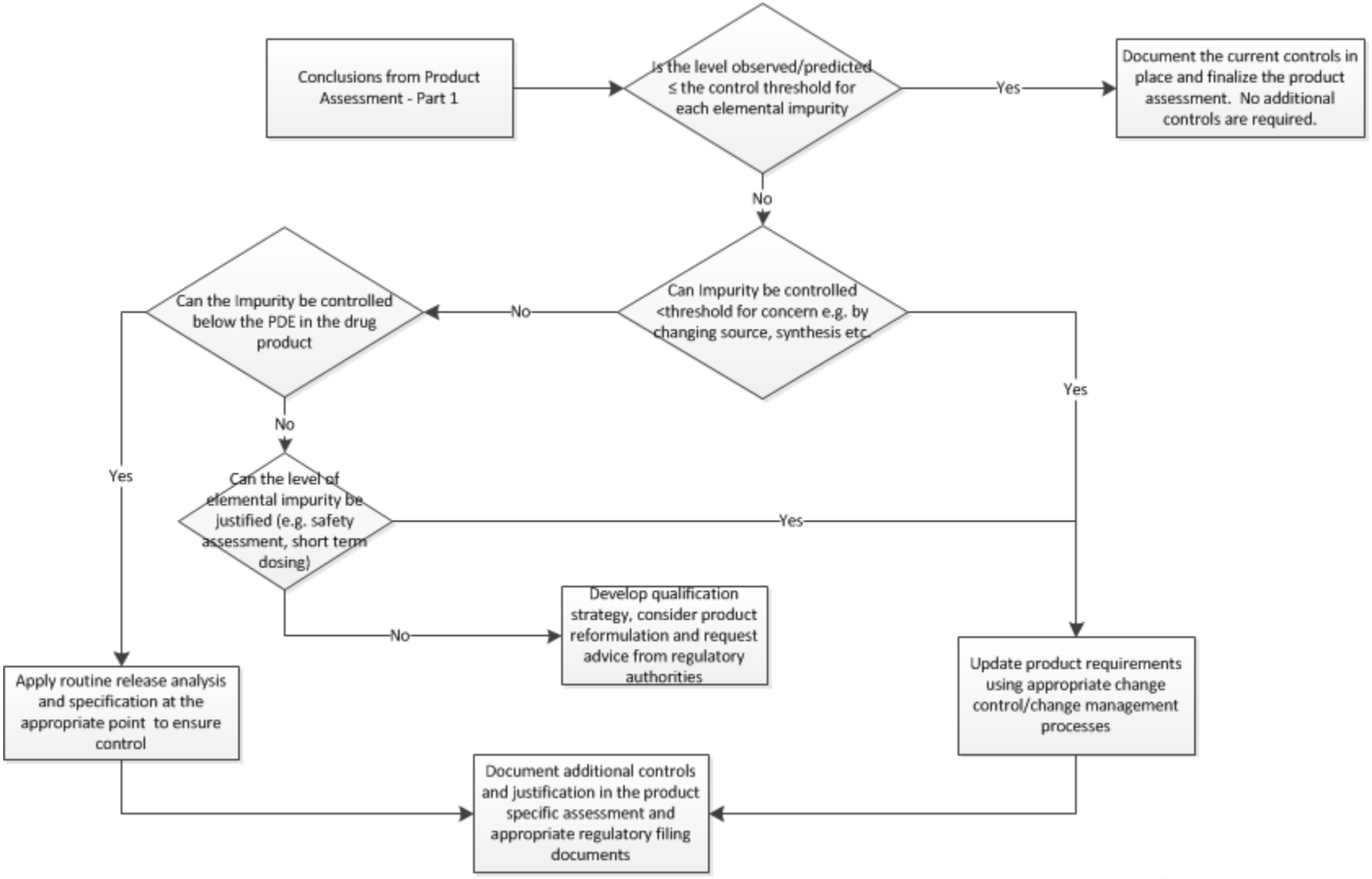
  Daily amount of elemental impurity = (impurity conc.,(µg)/g)×(mass of drug µg/day)
- The level of each elemental impurity should be determined by summing the contribution from each component to determine the final amount in the drug product
- Compare the total daily amount of each elemental impurity with the established Permitted Daily Exposure value (PDE).

Product Assessment – Component approach process flowchart – Part 1



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Product Assessment – Component approach process flowchart – Part 2



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Comparison of Observed Levels with PDE

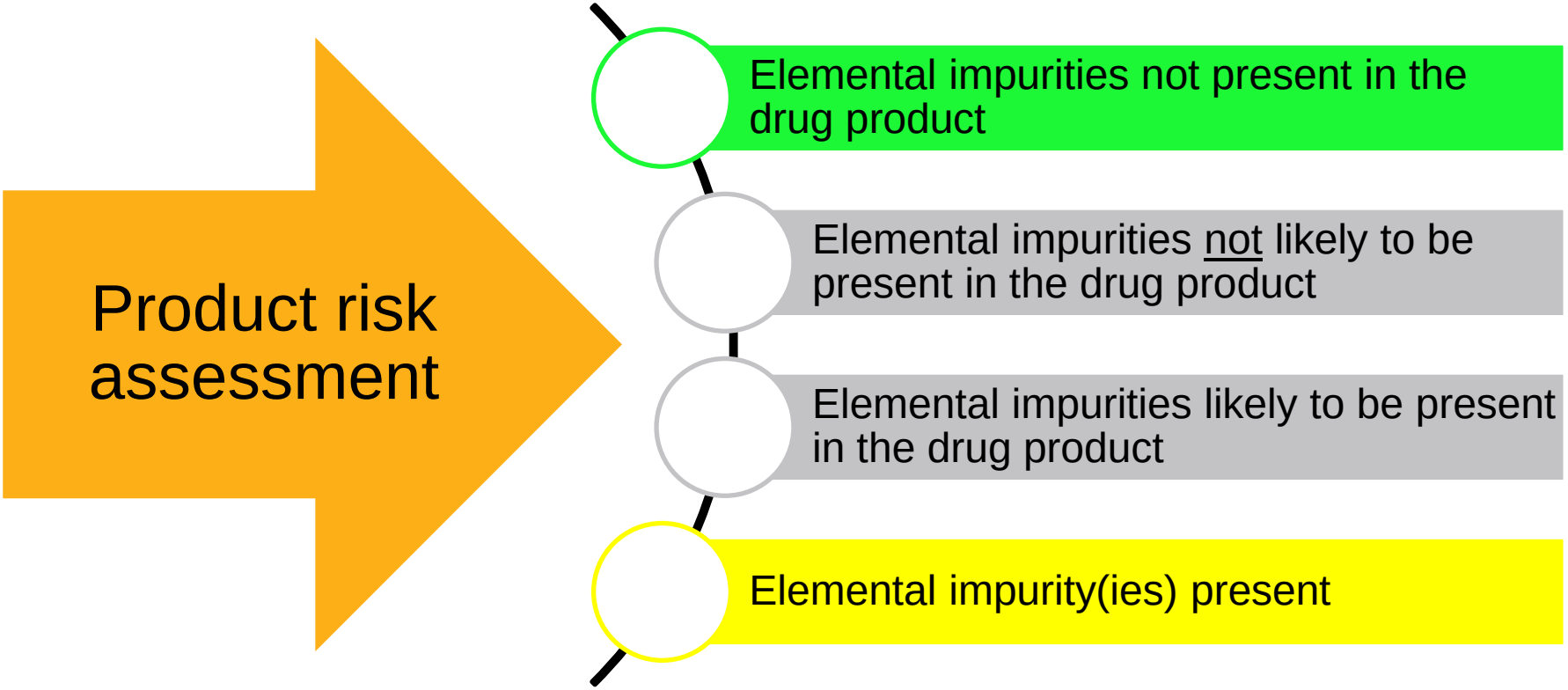
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Documentation and Conclusions of Risk Assessment

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Product Risk Assessment Output



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Documentation of Product Risk Assessments

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

Documentation

Preliminary thoughts on documentation

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

Acknowledgements

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Thank You!

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