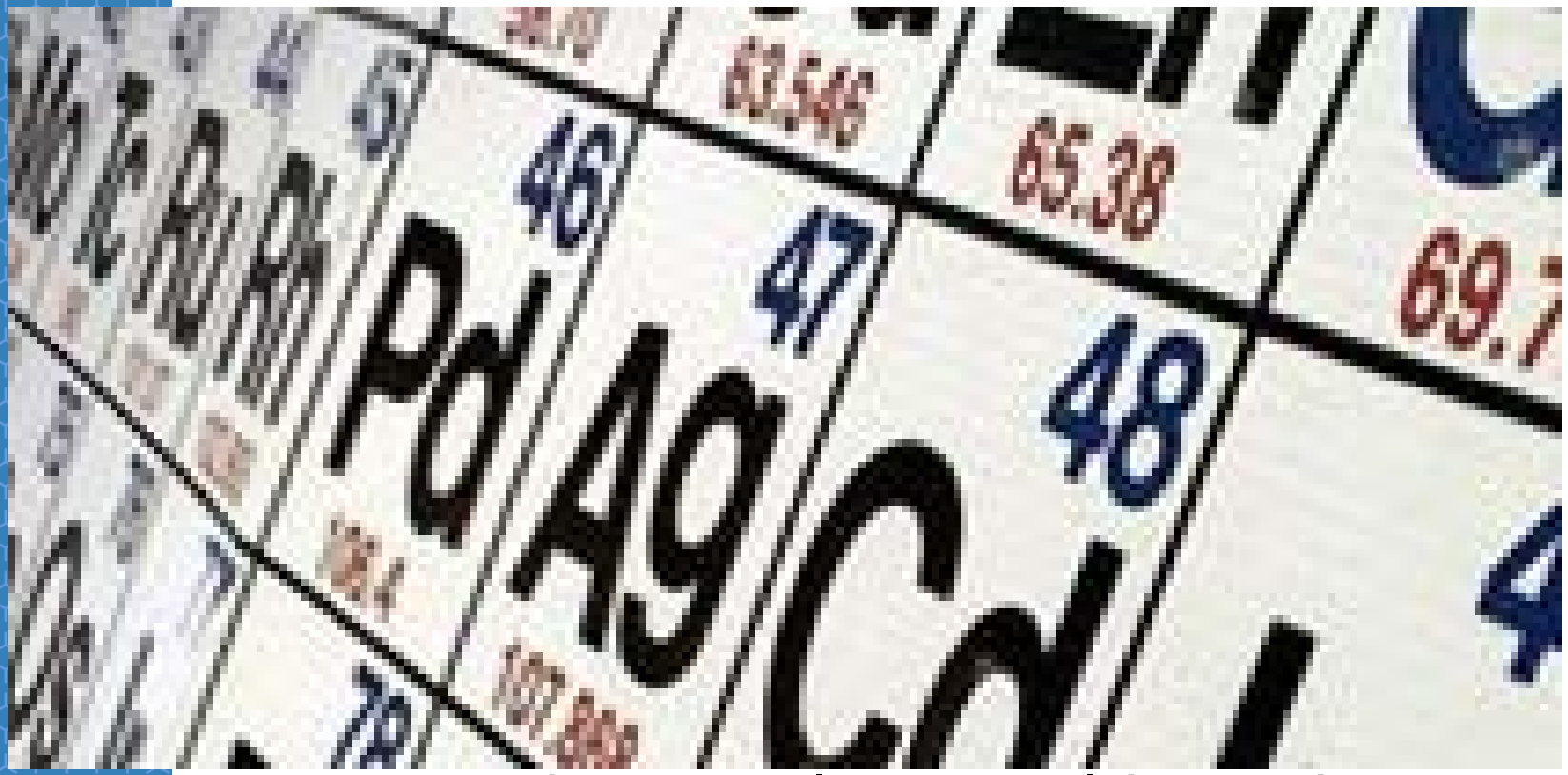

Approaches to elemental impurity product risk assessments with limited supplier information

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General expectations of EI product risk assessments

- The risk assessment should be based on scientific knowledge and principles.
- It should link to safety considerations for patients with an understanding of the product and its manufacturing process
- The product risk assessment should be focused on assessing the levels of elemental impurities in a drug product in relation to the established PDEs
- Information for this risk assessment includes but is not limited to: data generated by the applicant, information supplied by drug substance and/or excipient manufacturers and/or data available in published literature.

ICH Q3D commentary on sources of information

The applicant's risk assessment can be facilitated with information about the potential elemental impurities provided by suppliers of drug substances, excipients, container closure systems, and manufacturing equipment. The data that support this risk assessment can come from a number of sources that include, but are not limited to:

- Prior knowledge;
- Published literature;
- Data generated from similar processes;
- Supplier information or data;
- Testing of the components of the drug product;
- Testing of the drug product.

ICH Q3D – other considerations

During the risk assessment, a number of factors that can influence the level of the potential impurity in the drug product and should also have been considered in the risk assessment. These include but are not limited to:

- Efficiency of removal of elemental impurities during further processing;
- Natural abundance of elements (especially important for the categories of elements which are not intentionally added);
- Prior knowledge of elemental impurity concentration ranges from specific sources;
- The composition of the drug product.

ICH Q3D: Guidance on where to start the product assessment

- Starting point for all components – limits the elements of potential concern early in the assessment process

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

Alternative sources of EI data

- Published data
  - Li et al., **J. Pharm. Sci.** 104:4197–4206, 2015
    - Data on 31 excipients and 8 drug substances
  - Elemental Impurities Data Sharing consortium elemental impurities database (Lhasa Vitic)
- Literature/patent survey for product and process knowledge
  - Routes of synthesis/isolation/preparation
- Data/information on related materials or analogs
- Evaluation of additional controls in place relative to the amount of the excipient in the formulation

Recent experiences with availability of vendor information

- No statement/no information provided
- Limited statements of compliance with ICH Q3D/USP <232> limits
- Certificates of analysis containing EI data for representative lot(s) of the excipient/drug substance
- Certificates of analysis containing EI data for every specific lot provided.
- Comprehensive elemental impurity assessment

EI Product risk assessment

- Product/component knowledge
- Process knowledge
- Data

Data does not have to be EI data to be of value

EI product risk assessment – starting point

- Define what you know and what you do not know

Material Name	Maximum daily intake, g	Supplier statement/ data available?	Has data been generated?	Data from available from external sources	Data sufficient for assessment?	Preliminary risk (low, medium, high)	Is additional data needed? Follow up actions?
drug substance	0.020	no	no	no	no	medium	yes
Exc. 1	0.225	yes	no	no	yes	low	no
Exc. 2	0.100	no	no	yes	yes	low	no
Exc. 3	0.050	yes	no	yes	yes	low	no
Exc. 4	0.005	no	no	no	No	low	yes

Case study – additional evaluation

Drug substance

Additional information to be considered	How this helps	Example
DS synthetic route • Are any relevant elements intentionally added (relevant based on route of administration and cross-reference to ICH Q3D Table 5.1	If no relevant elements are intentionally added, there is a low probability that there will be a significant EI contribution to the drug product	No catalysts are used in the synthesis. The DS is used in a solid oral dosage form
Review the specification for the DS/COA provided	Typical limits 98-102% account for a minimum of 98% of the mass of the DS. Mass balance of the assay + related substances reduces the amount of material that could potentially be elemental impurities.	Assay limits 98.0-102.0 observed = 99.0% Impurities: total 0.5%
Evaluate information from alternative suppliers providing the same DS (if available)	While the synthetics routes may be different, there are also likely to be significant similarities that can help predict any potential elemental impurities of concern.	Three different routes identified – no catalysts used
Review compendial monographs for the drug substance, if available	Supporting evidence that EI may not be a concern if for example there has been no test for heavy metals or specific metal impurity tests.	Heavy metals test in original monographs

Case study summary/next steps

Drug substance

- Using the information in the example
  - no intentionally added EI of relevance
  - The estimated maximum contribution of EI (based on the daily dose of 0.020 g) = 0.0001 g (0.020 g x 99.5% = 0.0001 g (100 µg)
  - If entire residual amount, 100 µg, all translated to class 1 EI, the PDE would be exceeded in the drug product
- Additional information or justification is needed to further reduce the perceived risk of EI inclusion in the drug product
- If the potential for inclusion of elemental impurities cannot be further reconciled, It is always an option to select 3 lots of commercial material and analyze each lot for the presence of any potential elemental impurities.

Conclusions

- The availability of data in some form is needed to support the EI product risk assessment
- Supplier information can play a key role in providing strong support for a drug product EI product risk assessment
- The knowledge base of EI profiles is increasing across the industry
- Open access information on EI profiles for drug substances is limited
- Alternative data and information sources can reduce the reliance on the generation of EI data but in some cases a complete assessment may not be possible without the generation of additional data

Questions?

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Thank you

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