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Elemental impurities in drug product

***Dr. Anup Sharma, Sanjay Kumar Jain**

Senior Manager, Teva Pharmaceuticals Ltd., Mumbai, Maharashtra, India

Abstract
An elemental impurity in drug product arises from several sources; they may be added intentionally in the synthesis of drug product component (e.g. Catalysts) or may be present as a contamination and subsequently detected in drug product. Elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. This article discusses the assessment process to ensure that elemental impurities are consistently maintained below the most stringent PDE limits between USP and ICHQ3D.

Keywords: Elemental impurities, USP, ICHQ3D

1. Introduction

An elemental impurity in drug product arises from several sources; they may be added intentionally in the synthesis of drug product component (e.g. Catalysts) or may be present as a contamination and subsequently detected in drug product. Elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits.

The process to assess and control elemental impurities in the drug product contains the following stages.

1. Information from external and internal source
2. Analyzing the data to generate the list of potential elemental impurities.
3. Evaluate the potential risk of elemental impurities to be present in the finished drug product and determine the control strategy.

1.1 Element Classification

The elements included in this guideline have been placed into three classes based on their toxicity (PDE) and likelihood of occurrence in the drug product. The likelihood of occurrence is derived from several factors including: probability of use in pharmaceutical processes, probability of being a co-isolated impurity with other elemental impurities in materials used in pharmaceutical processes, and the observed natural abundance and environmental distribution of the element. For the purposes of this guideline, an element with low natural abundance refers to an element with a reported natural abundance of < 1 atom/106 atoms of silicon. The classification scheme is intended to focus the risk assessment on those elements that are the most toxic but also have a reasonable probability of inclusion in the drug product. The elemental impurity classes are:

Class 1: The elements, As, Cd, Hg, and Pb, are human toxicants that have limited or no use in the manufacture of pharmaceuticals. Their presence in drug products typically comes from commonly used materials (e.g., mined excipients). Because of their unique nature, these four elements require evaluation during the risk assessment, across all potential sources of elemental impurities and routes of administration. The outcome of the risk assessment will determine those components that may require additional controls which may in some cases include testing for Class 1 elements. It is not expected that all components will require testing for Class 1 elemental impurities; testing should only be applied when the risk assessment identifies it as the appropriate control to ensure that the PDE will be met.

Class 2: Elements in this class are generally considered as route-dependent human toxicants. Class 2 elements are further divided in sub-classes 2A and 2B based on their relative likelihood of occurrence in the drug product.

- **Class 2A** elements have relatively high probability of occurrence in the drug product and thus require risk assessment across all potential sources of elemental impurities and routes of administration (as indicated). The class 2A elements are: Co, Ni and V.
- **Class 2B** elements have a reduced probability of occurrence in the drug product related to their low abundance and low potential to be co-isolated with other materials. As a result, they may be excluded from the risk assessment unless they are intentionally added during the manufacture of drug substances, excipients or other components of the drug product. The elemental impurities in class 2B include: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl.

Class 3: The elements in this class have relatively low toxicities by the oral route of administration (high PDEs, generally > 500 µg/day) but may require consideration in the risk assessment for inhalation and parenteral routes. For oral routes of administration, unless these elements are intentionally added, they do not need to be considered during the risk assessment. For parenteral and inhalation products, the potential for inclusion of these elemental impurities should be evaluated during the risk assessment, unless the route specific PDE is above 500 µg/day. The elements in this class include: Ba, Cr, Cu, Li, Mo, Sb, and Sn.

Other elements: Some elemental impurities for which PDEs have not been established due to their low inherent toxicity and/or differences in regional regulations are not addressed in this guideline. If these elemental impurities are present or

included in the drug product they are addressed by other guidelines and/or regional regulations and practices that may be applicable for particular elements (e.g. Al for compromised renal function; Mn and Zn for patients with compromised hepatic function), or quality considerations (e.g., presence of W impurities in therapeutic proteins) for the final drug product. Some of the elements considered are: Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn.

1.2 GMP impact of elemental impurities

21 US Code 351 (a) (2) (B) (based on which FD&C 501(a) (2)(B) was enacted)

- A drug or device shall be deemed to be adulterated—if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics

21 CFR 211.65

- Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements

1.3 FDA Guidance on Process Validation

- For stage 2 process validation "selecting utilities and equipment construction materials, operation principles, and performance characteristics based on whether they are appropriate for their specific uses"
- Qualification (of equipment) refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. These activities necessarily precede manufacturing products at the commercial scale.

1.4 ICH Q7 5.1

- Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications

1.5 Risk assessment methodology

In developing controls for elemental impurities in drug products, the principles of quality risk management, described in ICH Q9, should be considered. 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 (ICH Q8 and Q11). 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

1.6 Risk Assessment

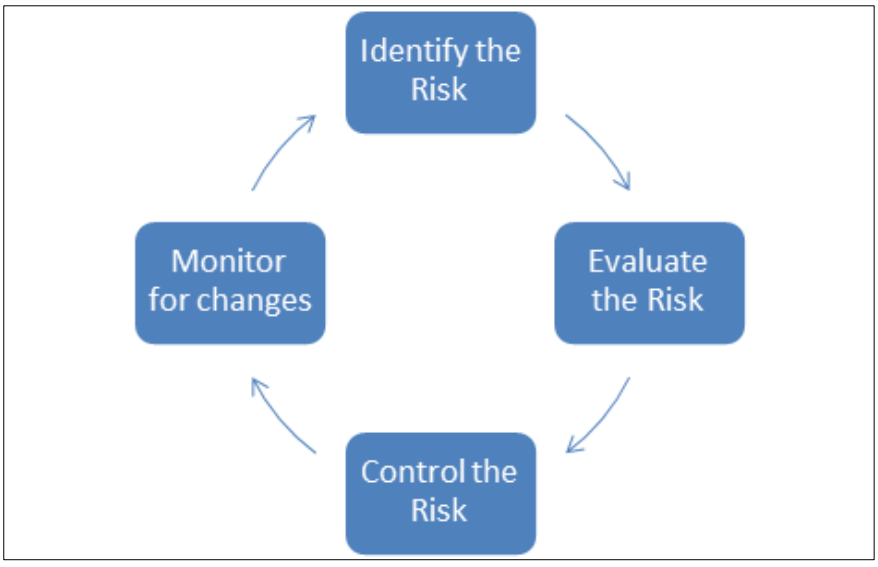
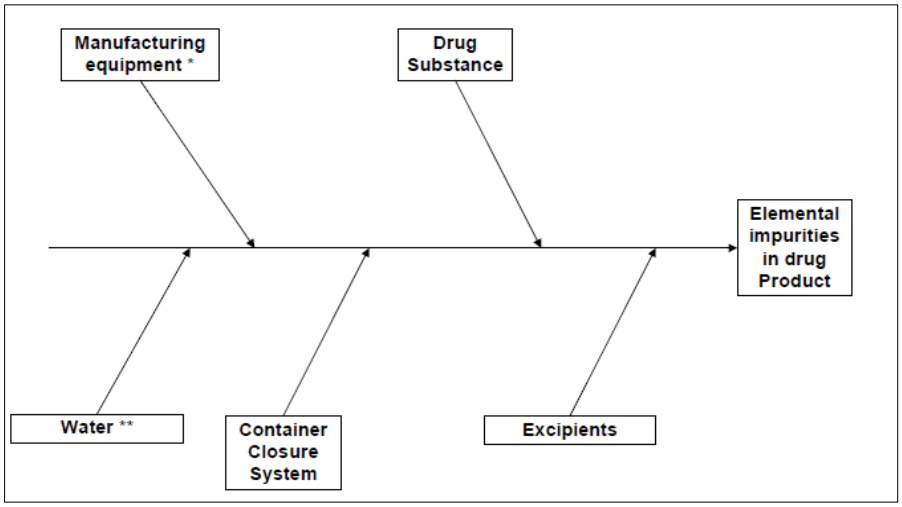


Fig 1

The following diagram shows an example of typical materials, equipment and components used in the production of a drug product. Each of these sources may contribute elemental impurities to the drug product, through any individual or any combination of the potential sources listed below during the risk assessment, the potential contributions from each of these sources should be considered to determine the overall contribution of elemental impurities to the drug product.



***Source*:** ICH Q3D page No. 6

Fig 2

* The risk of inclusion of elemental impurities can be reduced through process understanding, equipment selection, equipment qualification and Good Manufacturing Practice (GMP) processes.

** The risk of inclusion of elemental impurities from water can be reduced by complying with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US Pharmacopeial Convention) water quality requirements, if purified water or water for injection is used in the manufacturing process (es).

1.7 Risk Identification

The information shall be collected regarding elemental impurities contamination from component vendors. The sources of elemental impurities are: elements intentionally added to the reactions or processed leading up to the preparations of APIs and excipients (components), the pharmaceutical manufacturing process and primary packaging materials. While not intentionally added, some elemental impurities may be present in some drug substances and/or excipients. The possibility for inclusion of these elements in the drug product should be reflected in the risk assessment.

For the oral route of administration, the risk assessment should evaluate the possibility for inclusion of Class 1 and Class 2A elemental impurities in the drug product. For parenteral and inhalation routes of administration, the risk assessment should evaluate the possibility for inclusion of the Class 1, Class 2A and Class 3 elemental impurities as shown in Table 1

The main risk of elemental impurities contamination is in the Drug substance and excipients. Required information shall be gathered from the component vendors to assess the risk.

The probability of leaching from container closure in solid dosage form is minimal and do not require further assessment. For liquid and semi solid form there is high probability that elemental impurity can leach from container closure system into the drug product during shelf life of product. Data for leaching and elemental impurities shall be collected from container closure system vendor.

The contribution of elemental impurities from this manufacturing equipment may be limited and the subset of elemental impurities that should be considered in the risk assessment will depend on the manufacturing equipment used in the production of the drug product. Application of process knowledge, selection of equipment, equipment qualification and GMP controls ensure a low contribution from manufacturing equipment. The specific elemental impurities of concern should be assessed based on knowledge of the composition of the components of the manufacturing equipment that come in contact with components of the drug product. The risk assessment of this source of elemental impurities is one that can potentially be utilized for many drug products using similar process trains and processes.

1.8 Risk Evaluation

The gathered information needs to be evaluated for each product. As the potential elemental impurity identification process is concluded, there are two possible outcomes:

1) The risk assessment process does not identify any potential elemental impurities. The conclusion of the risk assessment and supporting information and data should be documented.
2) The risk assessment process identifies one or more potential elemental impurities. For any elemental impurities identified in the process, the risk assessment should consider if there are multiple sources of the identified elemental impurity or impurities and document the conclusion of the assessment and supporting 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.

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.

1.9 Sources of elemental impurities

Following can be the potential sources of elemental impurity getting introduced through the manufacturing process -

- ASTM 316/316/L stainless steel equipment
- Glass-lined vessels
- Polymeric materials used in gaskets, valves, tubing, filters, etc.:
  - elemental impurities from petroleum raw material, catalysts, reagents used during polymerization and fabrication
- Processing solvents
  - Water
  - Petro based solvents
- Cross contamination during manufacturing

1.10 Contributions from Utilities

- 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

1.11 Control of elemental impurities

Control of elemental impurities is one part of the overall control strategy for a drug product that assures that elemental impurities do not exceed the PDEs. When the level of an elemental impurity may exceed the control threshold, additional measures should be implemented to assure that the level does not exceed the PDE. Approaches that an applicant can pursue include but are not limited to:

- Modification of the steps in the manufacturing process that result in the reduction of elemental impurities below the control threshold through specific or non-specific purification steps;
- Implementation of in-process or upstream controls, designed to limit the concentration of the elemental impurity below the control threshold in the drug product;
- Establishment of specification limits for excipients or materials (e.g., synthetic intermediates);
- Establishment of specification limits for the drug substance;
- Establishment of specification limits for the drug product;
- Selection of appropriate container closure systems.

Periodic testing may be applied to elemental impurities according to the principles described in ICH Q6A.

1.12 Points to be considered in the risk assessment

1. Review of GMP policies, processes and procedures: Adequate GMP policies 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
- Qualification, usage, maintenance, cleaning of equipment, change control
- Quality agreement with vendors including auditing

2. Product and process specific understanding

- Equipment understanding: construction material, operation principles and compatibility
- Product understanding: formulation, physical and chemical characteristics
- Process understanding: impact on the equipment and quality of the drug product
- Drug usage understanding: indication, maximum daily dose, route of administration, duration

3. 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

4. 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 1

The following table 1 provides recommendations for inclusion of elemental impurities in the risk assessment. This table can be applied to all sources of elemental impurities in the drug product.

Table 1: Elements to be considered in 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

Source: ICH Q3D Table No. 5.1 Page No. 7&8

1.13 A five step risk assessment process

1. Identify known and potential sources of elemental impurities

- Elemental impurities coming from catalysts and reagents used in the manufacture of APIs, excipients, and drug products;
- Potentially present in API, water, and excipients;
- Leachates from manufacturing equipment, transfer tubing, valves, filters, gaskets, used in the manufacture of APIs, excipients, and drug products; and
- Container closure systems used for packaging and storage.

2. Data gathering

- Information from API and excipient vendors
- Prior knowledge on the elemental impurities within Amneal
- Data available from published literature
- Analytical data on elemental impurities generated by Amneal on components of the drug product and drug product itself

3. PDE calculations: ICH Q3D and USP<232>

- Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily intake of NMT 10 grams
- Option 2a: Common permitted concentration limits across drug product components for a drug product with a specified daily intake
- Option 2b: Permitted concentration limits of elements in individual components of a product with a specified daily intake.
- Option 3: Finished product analysis

4. Batch analysis data for APIs, Excipients, Drug Products

- Data from three representative production scale lots or six representative pilot scale lots of the components or drug product may be needed to establish the level and variability of each elemental impurity in the absence of other justification.

5. Control strategy

- Clearly define the control strategy and justify
- Define a control threshold for each impurity at a level that is 30% of the established PDE in the drug product
- If it is expected to be consistently less than 30% of the PDE, then additional controls are not required
- If this cannot be demonstrated, then additional controls will be required tighter limits in vendors' CoAs our own acceptance tests for APIs/excipients in-process tests finished product tests as appropriate

1.14 Example of Risk Assessment performed based on component and Drug Product approach

Let us consider there is a solid oral drug product that has daily intake of 5 gm, containing 9 components (1 drug substance and 8 excipients)

Table 2: Example Drug Product composition

Product- ABC	Strength	2.5 mg	5 mg
Components	**MDI g/day**	**Component Composition, g/tablet**	
Drug Substance	NA	0.200	0.400
Microcrystalline Cellulose (MCC)	NA	1.100	2.200
Lactose	NA	0.450	0.900
Ca Phosphate	NA	0.350	0.700
Crospovidone	NA	0.265	0.530
Mg Stearate	NA	0.035	0.070
HPMC	NA	0.060	0.120
Titanium Dioxide	NA	0.025	0.050
Iron Oxide	NA	0.015	0.030
Drug Product	5.0	2.500	5.000

Risk assessment shall be performed on one of the strengths for drug product having multiple strengths provided the strength are proportionally similar in composition as shown in above example.

1.15 Approaches for elemental impurities assessment

2 approaches are taken here for the assessment of Elemental impurities

1. **Component assessment approach:-** Component assessment approach is chosen if the information's from the component suppliers, literature survey, drug product manufacturing process and drug product container closure is available
2. **Drug product assessment approach:-** Drug product assessment approach is chosen if the information's from the component suppliers, literature survey, drug product manufacturing process and drug product container closure is not available.

1.16 Component assessment approach

Information's from the component suppliers, literature survey, drug product manufacturing process and drug product container closure is available and mentioned below

Table 3: Elemental Impurities Identification

Product	ABC				
Strength	400 mg/tablet				
MDD	5 g				
Drug product Components	Intentionally added (Information received from Vendor)	Known to be present from other sources through literature reference	Drug product Manufacturing process through machine equipment	Drug product container closure system	Water
Drug Substance	Pd, Ni	Pb, As, Cd, Hg	Mn,Cr,Ni,Mo	None	Meets requirements for purified water
Microcrystalline Cellulose (MCC)	NA	Pb, As, Cd, Hg			
Lactose	NA	Pb, As, Cd, Hg			
Ca Phosphate	NA	Pb, As, Cd, Hg			
Crospovidone	NA	Pb, As, Cd, Hg			
Mg Stearate	NA	Pb, As, Cd, Hg			
HPMC	NA	Pb, As, Cd, Hg			
Titanium Dioxide	NA	Pb, As, Cd, Hg			
Iron Oxide	NA	Pb, As, Cd, Hg			

1.17 Elemental Impurities Identification for above example

Collect the information from the component suppliers for the elements which are added intentionally and present in the components (Analytical results from suppliers needed) or possible elements which may be present in the component as identified through literature references in the above table 3. Assess the Process equipment, container – closure system and water used during the process of the components.

Table 4: Elemental Impurities Assessment- Total Daily Elemental Impurities Intake Calculation

Components	**Component %**	**MDI g/day (A)***	**Measured or reported concentration (µg/g) (B)****									**Total Daily Mass of elemental impurities µg (C=A x B)*****								
			Cd	pb	As	Pd	Ni	Hg	Mn	Cr	Mo	Cd	pb	As	Pd	Ni	Hg	Mn	Cr	Mo
Drug Substance	8	0.400				38									15					

Microcrystalline Cellulose (MCC)	44	2.200			1								2.2						
Lactose	18	0.900		0.8								0.72							
Ca Phosphate	14	0.700																	
Crospovidone	10.6	0.530																	
Mg Stearate	1.4	0.070					< 1								<0.07				
HPMC	2.4	0.120																	
Titanium Dioxide	1	0.050		< 1	< 1							<0.05	<0.05						
Iron Oxide	0.6	0.030																	
Manufacturing process	100	5					32								160				
Container closure system	100	5																	
Water	100	5																	
Drug Product	100	5																	
Total Daily elemental impurities intake by option 2b 5g/day												0.73	2.25	15	161				
Oral PDE as per ICH												5	15	100	200				
Control threshold 30% of PDE												1.5	4.5	30	60				
Control threshold Assessment-is total Daily intake ≥control threshold												No	No	No	Yes				

* MDI data is received from the tablet formulation based on the Maximum Daily intake

**Measured or reported concentration data is received from the Excipient vendor or measured by drug product manufacturer by validated method as part of risk assessment.

*** Total Daily Mass of elemental impurities is MDI x Measured or reported concentration.

Oral PDE in the above table is taken from ICH Q3D Table A.2.1: Permitted Daily Exposures for Elemental Impurities.

Table 5

If Total Daily Elemental impurities Intake	Action
Less Than 30% of PDE	No Further Control required
Greater Than 30% of PDE	Identify and Develop process to reduce the source of Elemental impurities and establish control to ensure that PDE is not exceeded

Inference from above table: - As per assessment pb,As, pd are below the control threshold and no further actions are needed. Ni is above the control threshold and control need to be build inline with the discussion above in the paper "Control of elemental impurities".

1.18 Drug product assessment approach

Information's from the component suppliers, literature survey, drug product manufacturing process and drug product container closure is not available. Drug substance Supplier has declared that Pd, Ni are intentionally added. Analytical results for none of the components are available. Screening of drug product is performed and details are as below.

Table 6: Elemental impurities assessment of Example Drug Product

Product	**ABC**					
Strength	**400 mg/tablet**					
MDD	**5 g**					
Drug product Components	Intentionally added	Known to be present from other sources	Drug product Manufacturing process	Drug product container closure system	Water	Potential Impurities identified from Drug product screening
Drug Substance	Pd, Ni	NA	NA	None	Meets requirements for purified water	NA
Microcrystalline Cellulose (MCC)	NA	NA				NA
Lactose	NA	NA				NA
Ca Phosphate	NA	NA				NA
Crospovidone	NA	NA				NA

Mg Stearate	NA	NA				NA
HPMC	NA	NA				NA
Titanium Dioxide	NA	NA				NA
Iron Oxide	NA	NA				NA
Drug Product Screening	Pd, Ni	NA	NA	NA	NA	Pb, As, Pd,Ni

Table 7: Elemental Impurities Assessment- Total Daily Elemental Impurities Intake Calculation

Components	**Component %**	**MDI g/day (A)***	**Measured or reported concentration (µg /g) (B)****				**Total Daily Mass of elemental impurities µg (C=A x B)*****			
			pb	As	Pd	Ni	pb	As	Pd	Ni
Drug Product	100	5	<LOQ 0.15ppm	<LOQ 0.45ppm	<LOQ 3ppm	32	0.75	2.25	15	160
Oral PDE							5	15	100	200
Control threshold 30% of PDE							1.5	4.5	30	60
Control threshold Assessment-is total Daily intake ≥control threshold							No	No	No	Yes

Oral PDE in the above table is taken from ICH Q3D Table A.2.1: Permitted Daily Exposures for Elemental Impurities.
* MDI data is received from the tablet formulation based on the Maximum Daily intake
**Measured or reported concentration data is received from the Excipient vendor or measured by drug product manufacturer by Validated method as part of risk assessment.
*** Total Daily Mass of elemental impurities is MDI x Measured or reported concentration.
In above table the results for finished drug product assessment observed <LOQ hence the LOQ value from the method validation is used to calculate total daily mass of elemental impurities.

Table 8

If Total Daily Elemental impurities Intake	**Action**
Less Than 30% of PDE	No Further Control required
Greater Than 30% of PDE	Identify and Develop process to reduce the source of Elemental impurities and establish control to ensure that PDE is not exceeded

Inference from above table:- As per assessment pb,As, pd are below the control threshold and no further actions are needed. Ni is above the control threshold and control need to be build inline with the discussion above in the paper "Control of elemental impurities".

2. Conclusion

The implementation of the ICH Q3D guideline for elemental impurities needs to be implemented using an appropriate risk-based process. A risk assessment should be performed to identify any elemental impurities that may potentially be present at significant levels in the drug product. Such an assessment is then used to define an appropriate control strategy. ICH Q3D allows the option that the scope and extent of quality control testing may be reduced, or even eliminated provided there is adequate control. Appropriate control strategy for the Potential elemental impurities present more than 30% of PDE should be established and shall be monitored.

3. References

1. International Conference on Harmonization (ICH) Harmonized Tripartite Q3D Step 4 Guideline, "Guideline for Elemental Impurities, Q3D"
2. United States Pharmacopeia (USP), Elemental Impurities General Chapters <232> Limits and <233> Procedures.
3. Training Materials of ICH Q3D
4. International Conference on Harmonization (ICH) Harmonized Tripartite Q9, Quality Risk Management.