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Review Article

The recent challenge for the pharmaceutical industries – ICH Q3D Elemental Impurities

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Abstract

The new guidelines relating to elemental impurities from the international council on harmonization (ICH) Q3D guidelines for Elemental impurities have presented the pharmaceutical industry with new challenges. These challenges include the complexity of introducing new analytical technology techniques replacing the wet chemical limit tests like Heavy metals. At present ICH Q3D advocates the use of a risk based approach to assessing the potential aspects of pharmaceutical development, application to elemental impurities in drug products. Specific challenges include determining how to assess or quantify the risks associated with factors such as water, container closure systems and excipients. Defining where in the assessment process data may be required and identifying where risks can be negligible through a through scientific theoretical risk assessment also present significant questions.

Elemental impurities in pharmaceutical formulations can come from catalysts, formulation ingredients and process vessels. They can interfere with drug efficacy or elicit a direct toxic effect on the patient. Heavy metal elemental impurities pose serious risks to patients without providing a benefit. Modern methods provide better analytical tests to detect elemental impurities, which in turn, will help protect patients by ensuring that the approved products have safe levels of these impurities.

The ICH guidelines and USP General Chapters <232> Elemental Impurities — Limits are focused on establishing Permitted Daily Exposures (PDEs) for elemental impurities in drug products. USP General Chapter <233> Elemental Impurities—Procedures describes analytical approaches for the detection of elemental impurities. The analytical approaches described in USP General chapter <233> are based on modern analytical capabilities. The outdated tests in the deleted USP General Chapter <231> and allow us to more precisely measure impurities to ensure safe levels. FDA, ICH, USP, and industry experts worked together to develop the new standards that are in alignment and help ensure high quality medicines.

Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container closure system). When elemental impurities are known to be present, have been added, or have the potential for introduction, assurance of compliance to the specified levels is required. A risk-based control strategy may be appropriate when analysts determine how to assure compliance with this standard.

Keywords: Implementation challenges for Elemental impurities, Elemental impurities risk assessment as per ICH Q3D, USP General Chapter <232>, New analytical techniques to determine Elemental impurities, Control strategies for ICH Q3D elemental impurities.

Introduction

Elemental impurities in drug products may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. Focus areas include 1) The evaluation of

the toxicity data for potential elemental impurities. 2) The establishment of a permitted daily exposure (PDE) for each element of toxicological concern. 3) Application of a risk-based approach to control elemental impurities in drug products.

Food and drug administration together with other organizations, such as the International Council for Harmonisation (ICH) and the U.S. Pharmacopeial Convention (USPC), have engaged in long-standing efforts to best protect patients from the risks posed by elemental impurities by developing limits for their amounts in drug products, and standardized approaches to use in determining the amount of elemental impurities in these products.

The drug products containing purified proteins and polypeptides (including proteins and polypeptides produced from recombinant or non-recombinant origins), their derivatives, and products of which they are components (e.g., conjugates) are within the scope of this guidance. All new and existing NDAs and ANDAs for drug products with an official USP monograph are required to meet the requirements in USP General Chapters <232> and <233> for the control of elemental impurities. Applicants submitting NDAs and ANDAs for drug products without a USP monograph are expected to follow the recommendations in the ICH Q3D Elemental Impurities guideline.

FDA, ICH, and USP have all engaged with brand and generic drug manufacturers to support implementation of these requirements. These requirements are the result of long-standing efforts, and both ICH and USP included industry participants on their expert panels that developed these standards.

Regulatory Challenges:

The requirements related to the implementation of ICH Q3D and the standards of assessment are the same between an ASMF and a CEP dossier. The route of synthesis of the drug substance must be described including information on all intentionally added catalysts and reagents. A summary of the drug substance risk assessment/risk management on the potential for intentionally added elemental impurities in the drug substance is to be included in the ASMF/CEP and made available to the drug product manufacturer allowing his overall risk management as well as the competent authority. This also includes any elemental impurity controls or mitigation steps necessary. It is also recommended that the ASMF/CEP dossier contains a summary of a risk assessment/management that also covers all other potential elemental impurities from other sources than the intentionally added elements to inform the drug product manufacturers overall risk assessment including any mitigation steps necessary.

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.

A summary of risk assessment for elemental impurities shall be submitted by the drug substance manufacturer. Such information would inform the drug product manufacturers overall risk management and would also be assessed by the quality assessor/CEP assessor. The internal reports and the data generated on which the summary risk assessment/ management is based on should be available for GMP inspections.

As per Union legislation it is mandatory to submit detailed information on the synthesis of the drug substance including information on any metal catalysts or reagents used. The quality assessor/CEP assessor will assess the use of such catalysts or reagents. If the level of an elemental impurity is routinely controlled by the drug substance manufacturer, the quality assessor will also assess the analytical procedure but not make a final conclusion on the compliance with ICH Q3D in the ASMF/CEP assessment report, as this will be done in the context of the assessment of the drug product.

Assessment of Safety:

The method used for establishing the PDE for each elemental impurity is discussed in detail in Appendix 1. Elements evaluated in this guidance were assessed by reviewing the publicly available data contained in scientific journals, government research reports and studies, international regulatory standards (applicable to drug products) and guidance, and regulatory authority research and assessment reports.

A summary safety assessment identifying the critical study for setting a PDE for each element is included in Appendix 3 of ICH Q3D. There are insufficient data to set PDEs by any route of administration for iridium, osmium, rhodium, and ruthenium. The PDEs for these elements were established on the basis of their similarity to palladium.

The factors considered in the safety assessment for establishing the PDE are listed below in approximate order of relevance:

1) The likely oxidation state of the element in the drug product.
2) Human exposure and safety data when it provided applicable information.
3) The most relevant animal study
4) Route of administration
5) The relevant endpoint(s)

Standards for daily intake for some of the elemental impurities discussed in this guidance exist for food, water, air, and occupational exposure. Where appropriate, these standards were considered in the safety assessment and establishment of the PDEs. The longest duration animal study was generally used to establish the PDE. When a shorter duration animal study was considered the most relevant, the rationale is provided in the individual

For Oral route of administration, an assessment may either increase or decrease an established PDE. The process of derivation of the PDE for another route of administration may include the following:

Assess if the elemental impurity is expected to have local effects when administered by the intended route of administration:

If local effects are expected, assess whether a modification to an established PDE is necessary. Consider the doses/exposures at which these effects can be expected relative to the adverse effect that was used to set an established PDE. If local effects are not expected, no adjustment to an established PDE is necessary.

If data are 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:

When a difference is observed, a correction factor may be applied to an established PDE. For example, when no local effects are expected, if the oral bioavailability of an element is 50 percent and the bioavailability of an element by the intended route is 10 percent, a correction factor of 5 may be applied.

Classification of Element:

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 likelihood of occurrence is derived from several factors including:

1. Probability of use in pharmaceutical processes.
2. 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 elements.

The elemental impurities are classified as follows as per ICH Q3D:

Table-1: Classification of Elemental Impurities

Class 1	Cd, Pb, As, Hg
Class 2A	Co, V, Ni
Class 2B	Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, Tl
Class 3	Ba, Cr, Cu, Li, Mo, Sb, Sn

Class 1 These elemental impurities are significantly toxic across all routes of administration and require consideration during risk assessment across all potential elemental impurity sources.

Class 2A These elemental impurities possess enough toxicity to require assessment across all potential sources and routes of administration due to their higher relative natural abundance.

Class 2B These elemental impurities have more variable toxicities and require assessment across potential elemental impurity sources only if they are intentionally added to the processes used to generate the material under evaluation.

Class 3 These elemental impurities have relatively low toxicity via the oral administration route but require consideration in the risk assessment for other routes of administration (e.g., inhalation and parenteral routes).

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. Some of the elements considered include: Al, B, Ca, Fe, K, Mg, Mn, Na, W & Zn.

Risk Assessment Process:

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). In the case of elemental impurities, the product risk assessment would therefore be focused on assessing the levels of elemental impurities in a drug product in relation to the PDEs presented in this guidance. 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.

The risk assessment process can be described in three steps:

1) Identify known and potential sources of elemental impurities that may find their way into the drug product.
2) 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.
3) 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.

The use of informal risk management processes (using empirical tools and/or internal procedures) may also be considered acceptable. Risk assessment to evaluate the need to have a control strategy for the elemental impurities which are likely to be present in drug products, if required ensure the residues of metal catalysts or metal reagents that may be present in pharmaceutical substances or in drug products are within recommended maximum acceptable concentration limits as per guideline ICH Q3D (Figure-1).

Various Potential sources of Elemental Impurities:

- Residual impurities resulting from elements intentionally added (e.g., catalysts) in the formation of the drug substance, excipients or other drug product components. The risk assessment of the
- drug substance should address the potential for inclusion of elemental impurities in the drug product.
- Elemental impurities that are not intentionally added and are potentially present in the drug substance, water or excipients used in the preparation of the drug product.
- Elemental impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment.
- Elemental impurities that have the potential to be leached into the drug substance and drug product from container closure systems.

Drug Substances:

The risk of inclusion of elemental impurities from a drug substance, therefore, needs to be considered when conducting a drug product risk assessment.

Control of the elemental impurity content of a drug substance can be assured through a thorough understanding of the manufacturing process including equipment selection, equipment qualification, GMP processes, packaging components, and the selection and application of appropriate control strategies.

Potential sources of elemental impurities in the drug substance manufacturing process:

Of the sources highlighted, the greatest risk comes from intentionally added metals (e.g., metal catalysts used in the process). Manufacturing equipment, processing aids, inorganic reagents, water, solvents, and other organic materials are less likely to serve as major contributors of elemental impurities in the finished drug substance, but do require consideration.Metal catalysts such as palladium and platinum are often used in the drug-substance manufacturing process and can therefore be present at low levels in the finished drug substance.

Figure-1:Elemental Impurities as per ICH Q3D

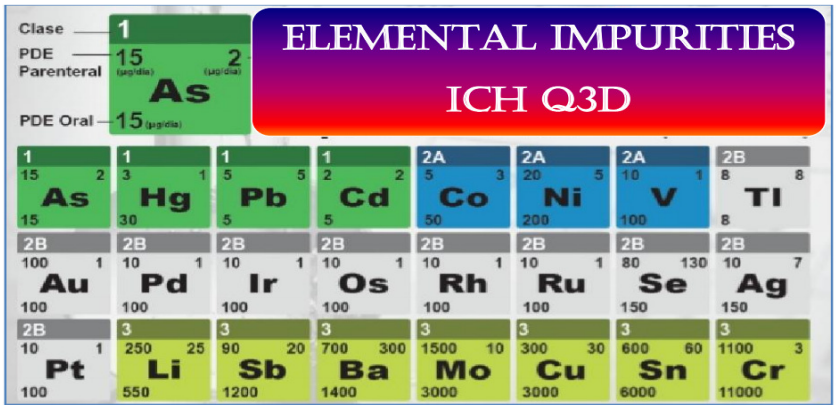
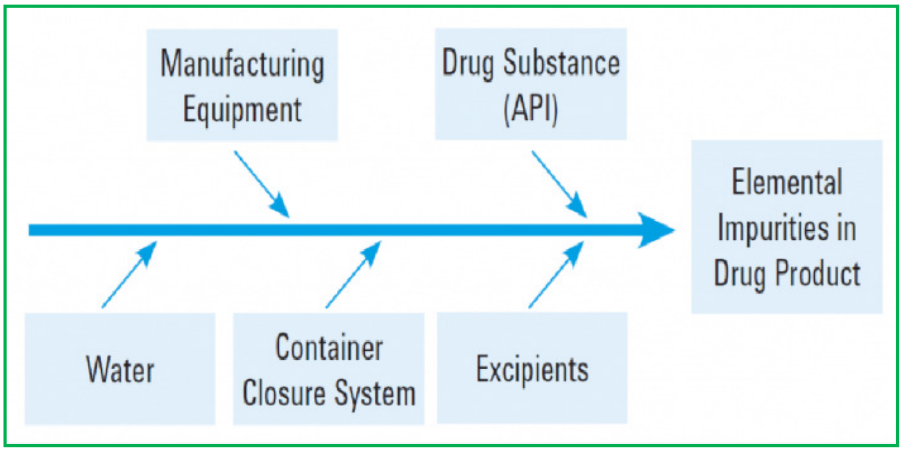


Figure-2: Assessment of the sources through Ishikawa (Fish Bone) tool



Excipients:

An essential consideration in determining the risk contribution for elemental impurities from an excipient is the proportion of the excipient used in the formulation.

Elemental impurities of concern for excipients would typically be:

- Class 1 and Class 2a elements potentially present at trace levels in the excipient based on environmental factors intentionally added catalysts or reagents for synthetic excipients.
- Class 3 elements from excipients that are targeted for a specific route of administration (e.g., inhaled).

Source of the excipient: The origin of an excipient can have a significant impact on the degree of risk associated with elemental impurities.

Proportion of formulation:

As a part of risk assessment, the different proportions of the possible factors to be considered for the risk assessment process.

Manufacturing equipment:

Stainless steel and glass are the most commonly used materials of construction for drug substance manufacturing equipment, due to their superior chemical resistance. Under extreme/corrosive reaction conditions, such as high temperature and low/high pH, these elements could have the potential to leach from manufacturing equipment. In such cases, it may be necessary to supplement standard GMP equipment compatibility assessments with specific studies to assess the elemental impurity-leaching propensity from manufacturing equipment due to corrosive reaction conditions.

Other potential sources include high-energy processes such as milling/micronization equipment. These are also generally considered to be low risk, but should be addressed via appropri-

ate GMP including cleaning records and visual inspection. Particle size reduction is discussed in the Drug Product Manufacture section.

Processing aids/inorganic reagents.

Processing aids such as charcoal, silica, celite, and darco, and inorganic reagents such as sodium chloride, magnesium sulfate, and sodium sulfate, are often used in drug-substance manufacturing processes and may be used in significant quantities. Depending on their specific composition, inorganic reagents should be considered within the risk assessment, especially when ICH Q3D elements are integral to the formula.

Solvents: Most solvents used in the manufacture of drug substances, particularly those listed in ICH Q3C, Impurities:

Guideline for Residual Solvents (2) Class 3, are unlikely to contribute elemental impurities to the finished drug substance. The majority of solvents are purified by distillation and few involve the direct use of metal catalysts in their manufacture; hence they are considered a low risk source of elemental impurities. In the event that solvents have not been purified by distillation, especially if a catalyst in used in their manufacture, further evaluation in the risk assessment should be considered.

Utilities:

As part of standard GMP, water quality should be routinely monitored and the purification system and storage of the water should not reintroduce elemental impurities. Air is not likely to present a substantive risk; furthermore, air quality can also be managed through proper GMPs via use of HEPA filtered air, etc. No specific assessment is therefore generally required.

The source water used in drug product manufacturing must meet the World Health Organization (WHO) standard for drinking water. When this source water is further purified in a contemporary plant to generate purified water (PW) and/or water-for-injection (WFI), the elemental impurity levels should be below acceptable concentrations allowed for drug products using option 1 control strategy defined in ICH Q3D.

Container closure system:

The identification of potential elemental impurities that may be introduced from container closure systems should be based on a scientific understanding of likely interactions between a particular drug product type and its packaging. When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional risk assessment needs to be performed. It is recognized that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment. For liquid and semi -solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system during the shelf-life of the product. Studies to understand potential leachables from the container closure system (after washing, sterilization, irradiation, etc.) should be performed. One of the potential sources of elemental impurities is product packaging, often referred to as container-closure system (CCS). In determining the risk posed by the CCS, there are a number of factors that need to be taken into consideration including nature of formulation--mechanism for contamination, Level of metals present in the CCS, Nature of risk: safety vs. quality risk, Duration of storage (liquids).

When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional risk assessment needs to be performed. It is recognized that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment.

Recommendations for elements to be considered for risk assessment:

ICH Q3D classifies 24 elements based on toxicity and likelihood of occurrence in final drug products. The elements included in each class, noting when risk assessment is required.

Risk assessment Approach of Elemental Impurities:

Class 1 and Class 2A elements shall be considered in all risk assessments. The control threshold helps determine which elements are at risk of exceeding the PDE. For elements consistently below the control threshold – 30% of the PDE – existing controls are considered adequate. Elements that surpass the control threshold need to be controlled, whether by upstream controls or by source purification. A rationale for higher levels of exposure (eg, short-term usage, a life-threatening disease) may justify surpassing the threshold.

Strategy to follow for Elemental Impurities:

Option 1, 2A and 2B represent the "component-based approach" for the risk assessment, whereas Option 3 represents the "finished-product-based approach"

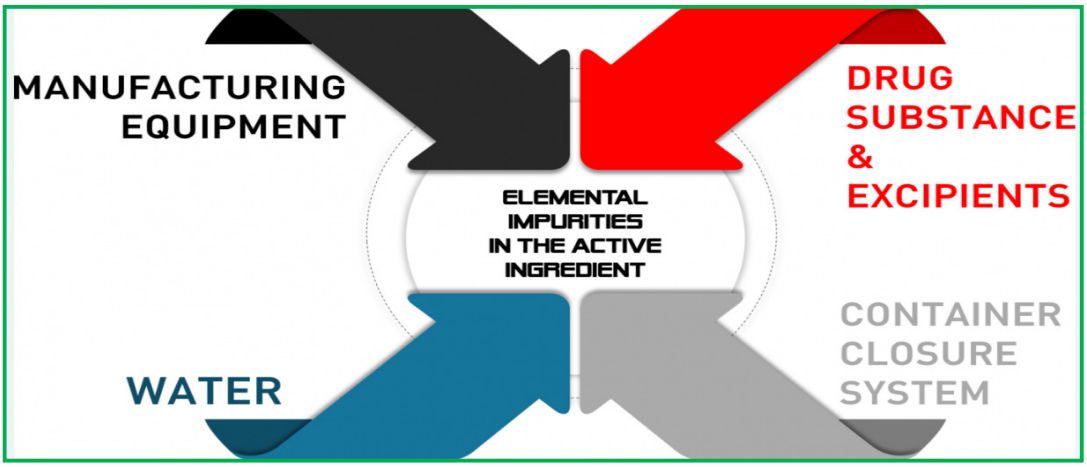
Option 1 considers that all the components could be used in any proportion and that the product intake is not more than 10 g/day. For each elemental impurity, the concentration limit (CL) is calculated by dividing the PDE by 10 g/day. Acceptance criteria: None of the components exceeds the calculated CL.

Option 2A considers that all the components could be used in any proportion and calculates the real maximum daily product intake (MDI). For each elemental impurity, the concentration limit (CL) is calculated by dividing the PDE by the MDI in grams. Acceptance criteria: None of the components exceeds the calculated CL.

Option 2B considers the real quantitative composition of the product and the real maximum daily product intake. Calculate, for each component, the level of all elemental impurities. Then, for each elemental impurity, calculate the total level (aggregated from all the components). Acceptance criteria: The total level does not exceed the PDE.

Option 3 consists in the finished product analysis. The levels of the elemental impurities should be individually determined by appropriate techniques (ICP-MS) by analyzing 3 representative batches (industrial scale) or 6 representative batches (pilot scale). The total exposition to the elemental impurities is calculated with the maximum daily intake of the product. Acceptance criteria: The total exposition does not exceed the PDE.

Figure-3: Elemental Impurities in Acitve Ingredients



Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily intakes of not more than 10 grams: This option is not intended to imply that all elements are present at the same concentration, but rather provides a simplified approach to the calculations. The option assumes the daily intake (amount) of the drug product is 10 grams or less, and that elemental impurities dentified in the risk assessment (the target elements) are present in all components of the drug product.

$$\text{Concentration } (\mu g/g) = \frac{\text{PDE } (\mu g/\text{Day})}{\text{Daily amount of drug product } (g/\text{day})}$$

Figure-4: Elemental Impurities in Excipients

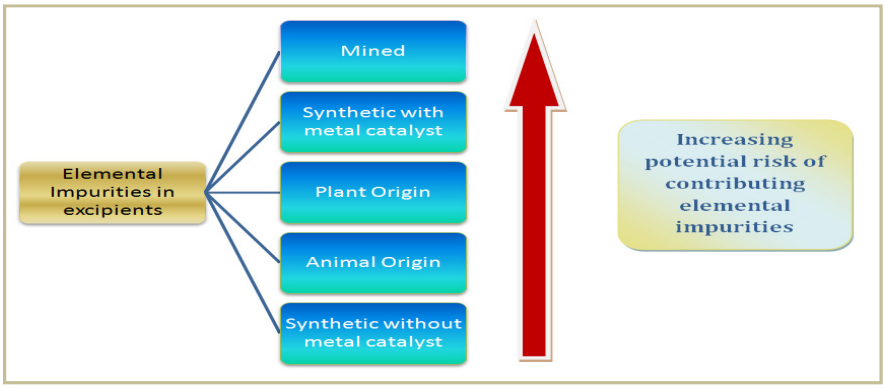


Table-2

Elements		Class	If intentionally added (All routes)	If intentionally not added		
				Oral	Parenteral	Inhalation
Arsenic (inor-ganic)	As	1	Yes	Yes	Yes	Yes
Cadmium	Cd	1	Yes	Yes	Yes	Yes
Mercury (in-organic)	Hg	1	Yes	Yes	Yes	Yes
Lead	Pb	1	Yes	Yes	Yes	Yes
Cobalt	Co	2A	Yes	Yes	Yes	Yes
Nickel	Ni	2A	Yes	Yes	Yes	Yes
Vanadium	V	2A	Yes	Yes	Yes	Yes
Silver	Ag	2B	Yes	No	No	No
Gold	Au	2B	Yes	No	No	No
Iridium	Ir	2B	Yes	No	No	No
Osmium	Os	2B	Yes	No	No	No
Palladium	Pd	2B	Yes	No	No	No
Platinum	Pt	2B	Yes	No	No	No
Rhodium	Rh	2B	Yes	No	No	No
Ruthenium	Ru	2B	Yes	No	No	No
Selenium	Se	2B	Yes	No	No	No
Thallium	Tl	2B	Yes	No	No	No
Barium	Ba	3	Yes	No	No	Yes
Chromium	Cr	3	Yes	No	No	Yes
Copper	Cu	3	Yes	No	Yes	Yes
Lithium	Li	3	Yes	No	Yes	Yes
Molybdenum	Mo	3	Yes	No	No	Yes
Antimony	Sb	3	Yes	No	Yes	Yes
Tin	Sn	3	Yes	No	No	Yes

Table-3: Permitted daily exposures (PDE) for elemental impurities

Element	Cd	Pb	As	Hg	Co	V	Ni	Tl	Au	Pd	Ir	Os
Class	1	1	1	1	2A	2A	2A	2B	2B	2B	2B	2B
Oral PDE (µg/day)	5	5	15	30	50	100	200	8	100	100	100	100
Parenteral PDE (µg/day)	2	5	15	3	5	10	20	8	100	10	10	10
Inhalation PDE (µg/day)	2	5	2	1	3	1	5	8	1	1	1	1

Element	Rh	Ru	Se	Ag	Pt	Li	Sb	Ba	Mo	Cu	Sn	Cr
Class	2B	2B	2B	2B	2B	3	3	3	3	3	3	3
Oral PDE (µg/day)	100	100	150	150	100	550	1200	1400	3000	3000	6000	11000
Parenteral PDE (µg/day)	10	10	80	10	10	250	90	700	1500	300	600	1100
Inhalation PDE (µg/day)	1	1	130	7	1	25	20	300	10	30	60	3

Table-4: Permitted concentration of elemental impurities for Option 1 as per ICH Q3D

Element	Rh	Ru	Se	Ag	Pt	Li	Sb	Ba	Mo	Cu	Sn	Cr
Class	2B	2B	2B	2B	2B	3	3	3	3	3	3	3
Oral PDE (µg/day)	0.5	0.5	1.5	3	5	10	20	0.8	10	10	10	10
Parenteral PDE (µg/day)	0.2	0.5	1.5	0.3	0.5	1	2	0.8	10	1	1	1
Inhalation PDE (µg/day)	0.2	0.5	0.2	0.1	0.3	0.1	0.5	0.8	0.1	0.1	0.1	0.1

Element	Rh	Ru	Se	Ag	Pt	Li	Sb	Ba	Mo	Cu	Sn	Cr
Class	2B	2B	2B	2B	2B	3	3	3	3	3	3	3
Oral PDE (µg/day)	10	10	15	15	10	55	120	140	300	300	300	1100
Parenteral PDE (µg/day)	1	1	8	1	1	25	9	70	150	30	60	110
Inhalation PDE (µg/day)	0.1	0.1	13	0.7	0.1	2.5	2	30	1	3	6	0.3

The values presented in this table represent permitted concentrations in micrograms per gram for elemental impurities in drug products, drug substances and excipients. These concentration limits are intended to be used when Option 1 is selected to assess the elemental impurity content in drug products with daily doses of not more than 10 grams per day.

Option 2a: Common permitted concentration limits across drug product components for a drug product with a specified daily intake

This approach, for each target element, allows determination of a fixed common maximum concentration in micrograms per gram in each component based on the actual daily intake provided. If all components in a drug product do not exceed the Option 2a concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product. This option is similar to Option 1, except that the drug daily intake is not assumed to be 10 grams. The common permitted concentration of each element is

determined and the actual maximum daily intake.

Option 2b: Permitted concentration limits of elements in individual components of a product with a specified daily intake:

This approach allows that the maximum permitted concentration of an element in certain components of the drug product may be higher than the Option 1 or Option 2a limit, but this should then be compensated by lower allowable concentrations in the other components of the drug product.

Option 3: Product Analysis:

Analytical testing:

The determination of elemental impurities should be conducted using appropriate procedures suitable for their intended purposes. Unless otherwise justified, the test should be specific for each elemental impurity identified for control during the risk assessment.

The analytical procedures will be based on some of these methods:

Procedure 1: ICP-AES/OES

Procedure 2: ICP-MS

Alternative procedure: e.g. Flame - AA, Graphite - AA, Cold Vapor Atomic Absorption Spectroscopy (CVAAS) - Hg, may be used provided that they are validated.

The analytical plan allows to define what elements we have to analyse, how many samples we need and which volume of it, what analytical technique is the most appropriate etc. When testing, the ICH Q3D requires that the screening is performed in at least 3 representative batches produced in an industrial scale or at least 6 representative batches produced in a pilot scale. Costs can be reduced through an appropriate selection of the elemental impurities to be tested as well as the analytical methodology to apply. Analytical testing for elemental impurities is clearly an important aspect of the assessment of elemental impurities. It is not, however, within the scope of ICH Q3D. The guideline states that "Pharmacopoeial procedures or suitable validated alternative procedures for determining levels of elemental impurities should be used, where feasible."

USP has developed General Chapter <233> "Elemental Impurities—Procedures" (11), and the European Pharmacopoeia (Ph.Eur.) has recently published general chapter 2.4.20 "Determination of Metal Catalyst or Metal Reagent Residues" covering analytical testing (12). USP <233> describes two specific procedures for the evaluation of the levels of metal impurities. Importantly, it also describes criteria for the use of alternative procedures.

Evaluation:

The 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;

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. 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. 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.

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.

Lifecycle management:

Product and/or process changes have the potential to change the elemental impurity content of the final drug product. Therefore, their impact on the overall risk assessment, including established controls should be evaluated. Such changes could include, but are not limited to,

changes in synthetic routes, excipient suppliers, raw materials, processes, equipment, container closure systems, or facilities.

If changes to the drug product or components have the potential to change the elemental impurity content of the drug product, the risk assessment, including established controls for elemental impurities, should be re-evaluated. Such changes could include, but are not limited to: changes in synthetic routes, excipient suppliers, raw materials, processes, equipment, container closure systems or facilities. All changes are subject to internal change management process (ICH Q10) and if needed appropriate regional regulatory requirements.

Control strategy:
ICH Q3D provides PDE limits in µg/day for elemental impurities. However, concentration limits in µg/g are more useful for evaluating sample impurity content.

The implementation of ICH Q3D is a living process. In the case of changes to the product and/or components which are potential sources of elemental impurities, it must be re-evaluated. These changes may be (but not limited to): changes to synthesis route, changes of manufacturers, changes in the processes, changes to the packaging materials, facilities. All of these changes will be subject to change controls and, if necessary, regulatory variation.

Table-5: Control Strategy

EI not present Action: Document CS: No action required	**EI <30% PDE** Action: Not additional action to be implemented CS: Adequate existing controls
30% PDE < EI < PDE Actions: Define additional controls to control those that do not exceed the PDE level CS: Specification on the medical product or components (API and excipients), modification of the manufacturing process that provides decrease in EI, selection of the most appropriate packaging materials	**EI > PDE** Actions: Define additional reduction controls or Evaluate the patient's safety and establish a rationale to justify higher EI content CS: -In some cases it could be acceptable -Justify before health authorities

Conclusion:

The component assessment approach allows drug product manufacturers to assess elemental impurity risk in compliance with ICH Q3D. For standardizing impurity limits across components, manufacturers and excipient suppliers may find the Option 1 limit useful as the default concentration limit. This approach permits manufacturers and suppliers to obtain crucial impurity information for components with indeterminate impurity limits, particularly excipients. The implementation of the ICH Q3D guideline can be adequately achieved through using an appropriate risk-based process combined with existing GMP standards. 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. The component assessment approach allows drug product manufacturers to assess elemental impurity risk in compliance with ICH Q3D. For standardizing impurity limits across components, manufacturers and excipient suppliers may find the Option 1 limit useful as the default concentration limit. This approach permits manufacturers and suppliers to obtain crucial impurity information for components with indeterminate impurity limits, particularly excipients.

Abbreviations:

CFR: Code of Federal Regulations. (USA)

CEP: Certificate of Suitability

IUPAC: International Union of Pure and Applied Chemistry.

ICP-OES: Inductively coupled plasma optical emission spectroscopy

ICP-MS: Inductively coupled plasma mass spectrometry

USP: United States of Pharmacopiea

EHC: Environmental health criteria

ICH: International council of harmonisation

LOQ: Limit of Quantitation

IPCS: International Programme for Chemical Safety.

GMP: Good manufacturing practices

PDE: Permitted daily exposure

NOAEL: No-Observed-Adverse-Effect Level

ASMF: Active Substance Master Files

NTP: National Toxicology Program

AA: atomic absorption

PEL: Permitted Exposure Limit

WHO: World Health Organization.

References:

1. ICH, Q3D Guideline for Elemental Impurities (2014).
2. IPCS. Principles and methods for the risk assessment of chemicals in food, chapter 5:dose-response assessment and derivation of health based guidance values. Environmental Health Criteria 240. International Programme on Chemical Safety. World Health Organization, Geneva. 2009; Table 5.5.
3. ICH Q9, Quality risk management.
4. EU regulatory perspective and expectations, Lakemedelsverket, Medical products agency.
5. Agilent Publication number: 5991-7674EN, Determining Elemental Impurities in Pharmaceutical Ingredients using USP/ICH Methodology and ICPMS, 2017.
6. T. S. A. Bevilacqua, "Stimuli to the Revision Process: Elemental Impurities in Pharmaceutical Waters," Pharmacopoeial Forum 39(1) (2013).
7. ICH. 2016. ICH Q3D Training Package Module 5.
8. NSF health sciences Pharma biotech journal issue 26, fall 2013
9. EMEA, Guideline on the Specification Limits for Residues of Metal Catalysts or MetalReagents,EMEA/CHMP/SWP/4446/2000 (2008).
10. USP General Chapter <233> "Elemental Impurities-Procedures".
11. EMA, EMA/CHMP/CVMP
12. Guidence for Industry, Q3D Elemental Impurities, September 2015.
13. USP General Chapter <232> "Elemental Impurities in Pharmaceutical Products — Limits".
14. /SWP/169430/ 2012, Guideline for setting health based exposure limits for use of risk identification.
15. EMA/CHMP/QWP/115498/2017, Implementation strategy of ICH Q3D guidelines.
16. Reichert U. Elemental impurities: ICH Q3D finalized. Pharm Ind. 2016;78(5):670-676.

17. IPEC Americas, PDE Calculator, http://ipecamericas.org/content/pde-calculator, accessed Feb. 17, 2015.
18. FDA, Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (Rockville, MD, May 1999).
19. ICH, Q10 Pharmaceutical Quality System (2008).
20. Implementation of ICH Q3D elemental impurities guideline: challenges and opportunities. Pharm Tech. 2015;39(3):36-49.
21. Validating the Agilent 7700x/7800 ICP-MS for the determination of elemental impurities in pharmaceutical ingredients according to draft USP general chapters <232>/<233>, 2015.
22. FDA perspective on standards and recommendations for control of elemental impuritiesin drug products, GPHA CMC work shop, 17 May 2016.
23. Ball D, Blanchard J, Jacobson-Kram D, McClellan R, McGovern T, Norwood DL et al.Development of safety qualification thresholds and their use in orally inhaled and nasal drug product evaluation. Toxicol Sci 2007;97(2):226-36.
24. Haxel GB, Hedrick JB, Orris GJ. Rare earth elements-critical resources for high technology. US Geological Survey 2005;Fact Sheet 087-02
25. Tvermoes BE, Unice KM, Paustenbach DJ, Finley BL, Otani JM, Galbraith DA. Effects and blood concentrations of cobalt after ingestion of 1 mg/d by human volunteers for 90 d. Am J Clin Nutr 2014;99:632-46.
26. US FDA, Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000), available at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm.