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Risk based approach to evaluate the safety, risk and control of Elemental Impurities in Pharmaceutical Drug Products

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ABSTRACT: Elemental impurities (EI) are traces of metals, found in finished drug products of pharmaceutical formulations, which can come from catalysts, formulation ingredients and process vessels. They can interfere with drug efficacy or elicit toxic effect on the patient. Heavy metal EI possesses serious risks to patients. Modern methods provide better analytical tests to detect EI, which in turn, will help protect patients by ensuring approved products, have safe levels of these impurities. The ICH guidelines and USP General Chapters 232 EI (GC 232 EI)—Limits are focused on establishing Permitted Daily Exposures for EI in drug products. USP GC 233 IE—Procedures describes analytical approaches for the detection of EI. The analytical approaches described in USP GC 233 are based on modern analytical capabilities, replace.the outdated tests in the deleted USP GC 231 Heavy Metals, and allow us to more precisely measure impurities to ensure safe levels.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. EI 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 (By interactions with processing equipment and the container closure system). When EI 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.

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INTRODUCTIONS:

FDA, 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 [1]. The

specification guidance applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products containing existing drug substances. 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 New Drug Application (NDAs) and Abbreviated New Drug Application (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 EI guideline [1,2].

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 [3].

Table 1. Different classes of elemental impurities.

Class	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

REGULATORY CHALLENGES:

Risk Assessment should be performed as a part of risk mitigation plan, documented and be kept available. 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 [4].

Submission of a summary of a risk assessment/ management for elemental impurities 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 (Certificate of Suitability) assessor. The internal reports and the data generated on which the summary risk assessment/management is based on should be available for GMP inspections [5]. No risk assessment/management is performed by the drug substance manufacturer. 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 (Active Substance Master Files) ASMF/CEP assessment report, as this will be done in the context of the assessment of the drug product [6,7].

Table 2. Detail scenario of elemental impurities contaminating drugs.

Elements		Class	If intentionally added (All routes)	If intentionally not added		
				Oral	Parenteral	Inhalation
Arsenic (inorganic)	As	1	Yes	Yes	Yes	Yes
Cadmium	Cd	1	Yes	Yes	Yes	Yes
Mercury (inorganic)	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
Molybenum	Mo	3	Yes	No	No	Yes
Antimony	Sb	3	Yes	No	Yes	Yes
Tin	Sn	3	Yes	No	No	Yes

ELEMENT CLASSIFICATION:

The elements are in three classes based on their toxicity that is Permitted Daily Exposures (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 [8].

Table 3. Permitted daily exposures (PDE) for elemental impurities of class 1, 2A and 2B.

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

Class 1 elemental impurities are significantly toxic across all routes of administration and require consideration during risk assessment across all potential elemental impurity sources. Class 2A 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 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 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: This category includes elemental impurities that have been evaluated, but for which a PDE has not been established due to their low inherent toxicity and are addressed by other guidelines and regional regulations [9,10].

RISK ASSESSMENT PROCESS:

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. 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 [11].

Table 4. Permitted daily exposures (PDE) for elemental impurities of class 2B and 3.

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

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 [12].

VARIOUS POTENTIAL SOURCES OF ELEMENTAL IMPURITIES [13-17]:

- 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 drug substance is a key component that can contribute elemental impurities to the finished drug product. 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.

Table 5. Permitted concentration of elemental impurities for Option 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)	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

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 [13].

Metal catalysts:

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 [14].

Excipients:

One of the greatest challenges to performing an elemental impurity risk assessment for a drug product is to understand the potential contribution of elemental impurities from excipients. 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) [15].

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:

An essential consideration in determining the risk contribution for elemental impurities from an excipient is the proportion of the excipient used in the formulation [16].

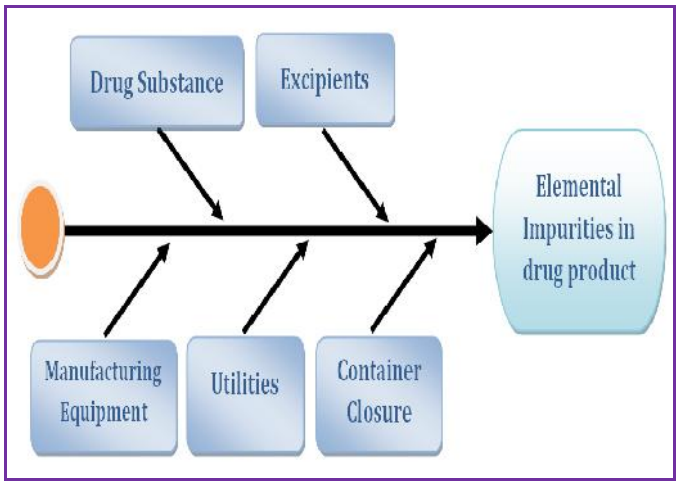

Fig 1. Assessment of the sources through Ishikawa (Fish Bone) diagram.

Manufacturing equipment:

Equipment compatibility assessment and qualification are sufficient to ensure that significant levels of elemental impurities are not leached from manufacturing equipment into the drug substance. 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. Contributions of elemental impurities from drug product processing equipment would be expected to be lower than contributions observed for the drug substance. However, when this is not the case based on process knowledge or understanding, the applicant should consider the potential for incorporation of elemental impurities from the drug product manufacturing equipment in the risk assessment [17].

Utilities:

Water used in the manufacture of both drug substances and formulated drug products is a potential source of elemental impurities.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 roducts using option 1 control strategy defined in ICH Q3D.As part of standard GMP, water quality should be routinely monitored and the purification system and storage of the water should not re-introduce 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 [17].

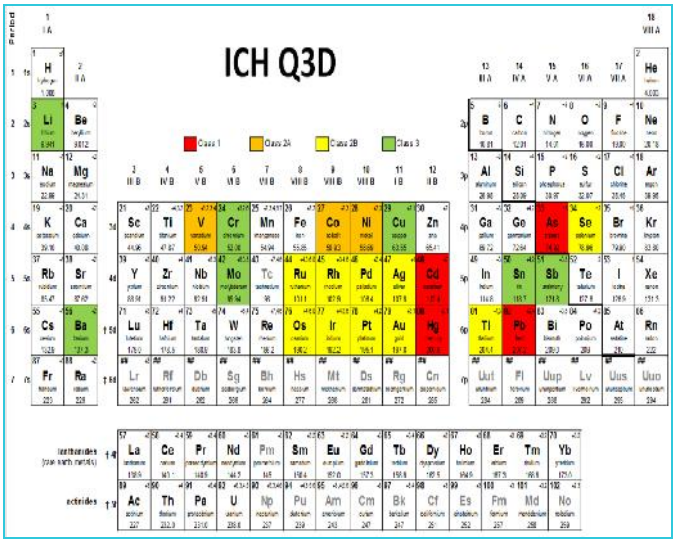

Fig 2. Various lethal elemental imurities shown in periodic table as per ICH Q3D.

Container closure system:

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 [16,17].

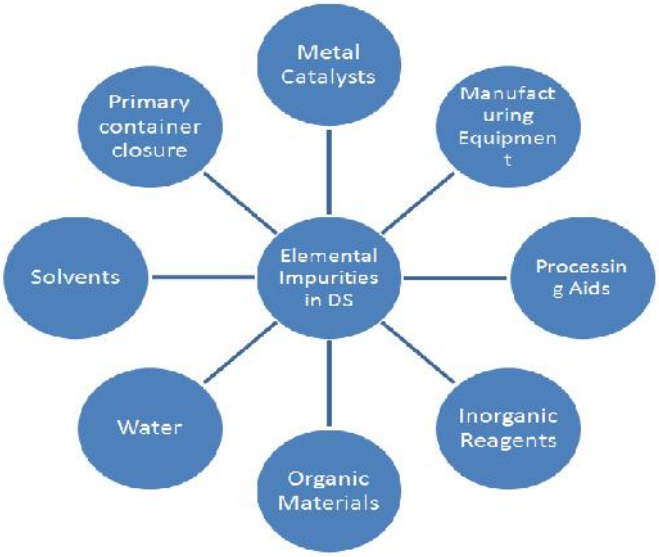

Fig 3. Various sources of Elemental Impurities in DS.

RECOMMENDATIONS FOR ELEMENTS TO BE CONSIDERED FOR RISK ASSESSMENT [18-20]:

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.

Approach of risk assessment:

A total of twenty four elemental impurities (Cd, Pb, As, Hg, Co, V, Ni, Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt, Li, Sb, Ba, Mo, Cu, Sn, and Cr) are specified with their toxicity limits, defined as maximum permitted daily exposure (PDE) levels in µg/day for the four major drug delivery categories.

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 identified in the risk assessment (the target elements) are present in all components of the drug product.

Conc. (µg/g) = PDE/ Daily amount of drug product ….. (1)

The PDE and daily amount of drug products are represented per day. 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 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.

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.

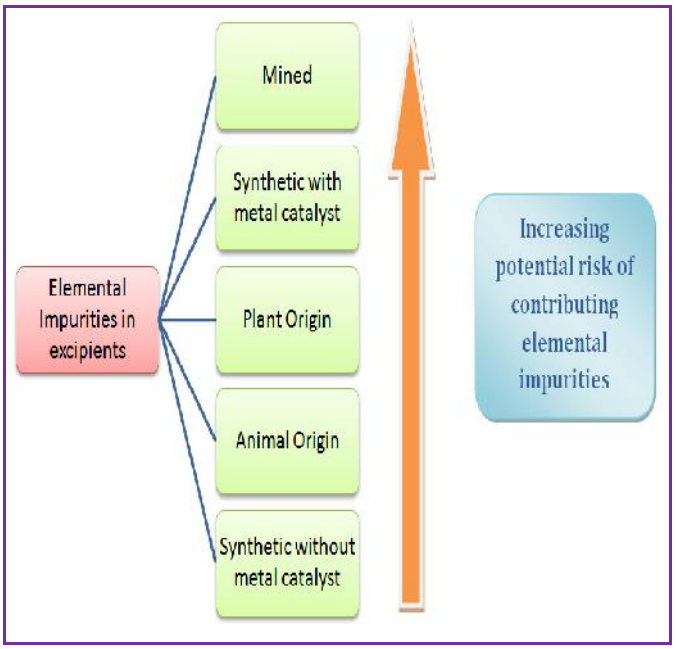

Fig 4. Elemental impurities of concern for excipients from various origins.

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: Finished Product Analysis:

Analytical testing:

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. Thus, a flexible approach may be adopted in terms of the analytical procedure, provided the method concerned meets the required acceptance criteria.

The analytical procedures will be based on some of these methods: Procedure 1: ICP-AES/OES. Procedure 2: Inductively coupled plasma mass spectrometry (ICP-MS) and Alternative procedure: e.g. Flame – Atomic Absorption (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.

EVALUATION [020,21]:

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.

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.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.

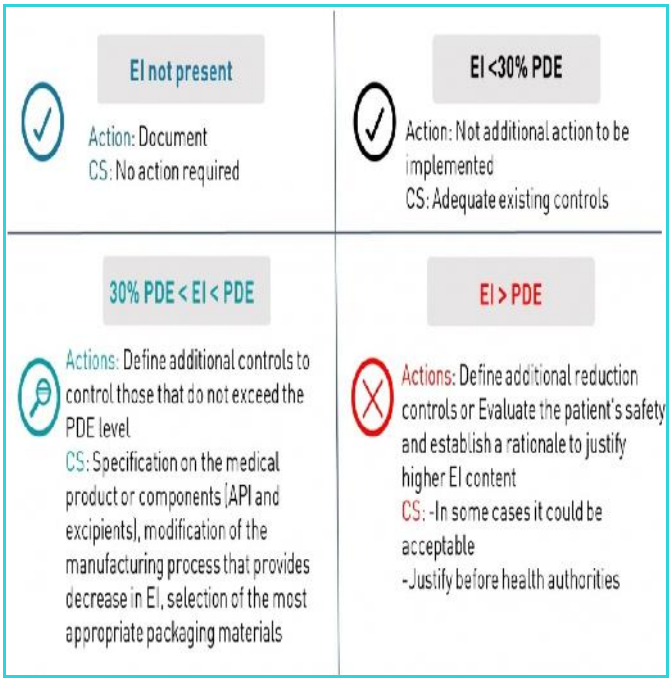

Fig 5. Documentary report on elemental impurities analysis.

Control strategy:

In the case of the presence of any elemental impurity, its significance is considered on the basis of its determined or predicted value and compared with its PDE value. ICH Q3D establishes a control limit of 30% of the PDE value for each elemental impurity.

CONCLUSION:

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.

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