Review Article

Risk Assessment, Screening and Control of Elemental Impurities in Pharmaceutical Drug Products: A Review

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Running title: Risk Assessment, Screening and Control of Elemental Impurities

ABSTRACT

The scope of this article is to review and describe the steps involved in risk assessment of elemental impurities in drug products based on the permitted daily exposure limits for the twenty-four (24) elements that are considered as potential elemental impurities. Screening and estimation of elemental impurities in drug substances, excipients and drug products by Inductively Coupled Plasma Mass Spectrometry or Inductively Coupled Plasma Optical Emission Spectrometry and their controls involved as referred in the general chapters <232> & <233> of the United States Pharmacopoeia, Q3D guideline for Elemental Impurities as per International Conference on Harmonization and Q3D Elemental Impurities: guidance for Industry as per U. S., Food and Drug Administration US-FDA.

Keywords: Risk assessment, Elemental impurities (EIs), International Conference on Harmonization (ICH) Q3D guideline, United States Pharmacopoeia (USP) General Chapter <232> & <233>.

INTRODUCTION

EIs in pharmaceutical drug products have no therapeutic effect and may be harmful hence should be bring down to the safety levels if any. EIs in drug products could be contributed either from drug substances, excipients as natural, artificial colors, flavoring agents, manufacturing process, manufacturing equipments, instruments, water, solvents, containers, closures, and many other sources. These EIs from various sources combined together can be potentially hazardous to human health[1-4].

To control these impurities, the non-selective visual limit test specified under USP General Chapter <231>[5] is being replaced by specific, selective and quantitative instrumental technique in accordance with USP General Chapters <232> & <233>[6-7] and ICH Q3D guideline[8]. In USP General Chapter <232> (Elemental Impurity Limits) & <233> (Elemental Impurity Procedures) concentration limits are set for fifteen (15) elements in pharmaceutical drug products and two procedures are established for determination by ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometry) and ICP-MS (Inductively Coupled Plasma Mass Spectrometry)[6-7]. Whereas under ICH-Q3D guideline it has

permitted for daily exposure of twenty-four (24) elements. EIs testing is now become mandatory from January 2018 for new approvals and existing approvals[9].

RISK ASSESSMENT OF ELEMENTAL IMPURITIES IN DRUG PRODUCT

The ICH Q3D guideline established the threshold values for 24 different elements based on toxicological data for various exposure paths. These EIs are classified, based on their toxicity permitted daily exposure (PDE) and likelihood of occurrence in the drug products, into three classes[10-12].

Class 1: These elements are human toxicants that have limited or no use in manufacture of pharmaceuticals (Hg, Pb, As and Cd).

Class 2: These elements are considered as route-dependent human toxicants and further divided into sub-classes 2a and 2b based on their relative likelihood of occurrence in the drug product.

Class 2A: These elements have relatively high probability of occurrence in the drug product and are thus considered for risk assessment (Co, Ni and V).

Class 2B: These elements have a reduced probability of occurrence in the drug product related to their low abundance and low potential to be co-isolated with the other materials (Os, Ag, Ir, Au, Pd, Pt, Ru, Rh, Tl and Se).

Class 3: These elements have relatively low toxicity by oral route of administration, unless these elements are intentionally added (Ba, Cr, Sn, Li, Mo, Sb and Cu).

The likelihood of occurrence is derived from several factors including the probability of use in pharmaceutical processes, probability of being a co-isolated impurity with other EIs in materials used in pharmaceutical processes.

Some EIs for which PDEs have not been established due to their low inherent toxicity and/or differences in regional regulations are not included in ICH Q3D guideline. If any other EIs are present or included in the drug product they have to be addressed. Some of these elements considered as

aluminium (Al), boron (B), calcium (Ca), iron (Fe), potassium (K), magnesium (Mg), manganese (Mn), sodium (Na), tungsten (W), and zinc (Zn)[10, 13].

EIs specifications and EIs screening results from vendor/supplier of each individual component of drug products (drug substances, excipients, container closure systems, and manufacturing equipment etc.) are used for maximum daily exposure (MDE) calculation purposes. MDEs are compared with ICH Q3D guideline for EIs with their PDEs to demonstrate compliance[14-17].

MDE of each elemental impurity (EI) is determined by two methods[10, 18]: (i) based on vendor/supplier statements and (ii) individual component EI screening results. The calculated MDE of each individual EI is compared with the PDE limits for the EI as established in ICH Q3D to check the compliance for the particular route of administration. In many cases, the steps are considered simultaneously. The final approach should be developed to ensure the EIs do not exceeds the PDE, based on the outcome of risk assessment results[19-20].

In method (i) MDE for each EI in a formulation is calculated as follows using the available vendor/supplier statements as follows:

1. Calculate each ingredient's quantity (per unit dose) to obtain total daily intake (TDI) in grams (g) for that ingredient based on MDD (maximum daily dose) of the drug product.

2. Multiply the weight (grams) of each component of TDI with the EI's specification (µg/g) value (maximum specification value is taken for calculation) from the vendor's certificate of analysis/statement. This gives the µg per day of the EI for that ingredient.

3. To determine the MDI (total µg) of each EI per day sum the individual quantities (the µg/day) obtained for each component of the drug product in Step 2.

4. Repeat the above MDI calculation for each EI of concern and compare with the EI permissible daily exposure established in ICH Q3D.

The method (ii) MDI for each EI in a formulation is calculated as follows using the analytical data generated:

1. Convert each product EI level in µg/g to total daily intake in µg as MDI. Multiply the EI (µg/g) value with the weight of product (in g per day) to get the maximum daily intake (µg per day) of the EI for the product.

2. Repeat the above MDI calculation for each EI of concern and compare with the EI PDE established in ICH Q3D.

If EIs listed in Table 1 are added intentionally as a catalyst/inorganic reagent or potential EI that may be present in drug substances and/or excipients or potential EI derived from manufacturing equipment and process or leached from container closure systems, the possibility for inclusion of these elements in the drug product should be reflected in the risk assessment[10, 21-22]. The elements Cobalt (Co), Thallium (Tl), Gold (Au), Selenium (Se), Silver (Ag), Lithium (Li), Antimony (Sb), Barium (Ba), Tin (Sn) are not considered in USP general chapter <232>[6].

If the risk assessment process does not identify any potential EI then it is considered that the potential EI assessment process is concluded. The conclusion of the risk assessment, supporting information and data should be documented. For any EI identified in the process, the risk assessment should consider there sources of the identified EI or impurities and also document the conclusion of the assessment with supporting information.

The summery of risk assessment is derived by reviewing drug product data combined with information and knowledge to identify the significant probable EI that may be observed in the drug product.

The summary should consider the significance of the observed or predicted level of the EI relative to the PDE of the EI. For the observed significant EI level, a control threshold should be defined as a level that is 30 percent of the established PDE in the drug product. If the total EI level from all sources in the drug product is expected to be consistently less than 30 percent of the PDE, then additional controls

may be not required, provided that the data is assessed appropriately and demonstrated adequate controls on EI. If the risk assessment fails to demonstrate that an EI level is consistently less than the control threshold, controls should be established to ensure that the EI level does not exceed the PDE in the drug product.

The PDE of each of EI that may be contained in the maximum daily intake of a drug product are reported in micrograms per day (μg/day). Because the PDE reflects only total exposure from the drug product, it is useful to convert the PDE into concentrations as a tool in evaluating EI in drug products or their components.

The options listed below describe some acceptable approaches to establishing concentrations of EI in drug products or components that would assure that the drug product does not exceed the PDEs[10-11].

Option 1: When the daily intake of drug product is not more than 10 grams[23]

The option assumes that the daily intake (amount) of the drug product is 10 grams or less, and that EI identified in the risk assessment (the target elements) are present in all components of the drug product. Using Equation 1 below, and a daily intake of 10 grams of drug product, this option calculates a common permissible target elemental concentration for each component in the drug. This approach, for each target element, allows determination of a fixed common maximum concentration in micrograms per gram in each component.

$$\text{Concentrations}\left(\frac{\mu g}{g}\right) = \frac{\text{gPDE}\left(\frac{\mu g}{g}\right)}{\text{Daily amount of drug product}\left(\frac{g}{day}\right)}$$

If all the components in a drug product do not exceed the option 1 concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product.

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 using Equation 1 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.

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

This option should be supported with additional information that may be assembling regarding the potential for specific EI to be present in specific drug product components. For each element identified as potentially present in the components of the drug product, the maximum expected mass of the EI in the final drug product can be calculated by multiplying the mass of each component material times the permitted concentration established in each material and summing over all components in the drug product. The total mass of the EI in the drug product should comply with the PDEs. If the risk assessment has determined that a specific element is not a potential impurity in a specific component, there is no need to establish a quantitative result for that element in that component. 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

The concentration of each element may be measured in the final drug product. Equation 1 may be used with the maximum total daily dose of the drug product to calculate a maximum permitted concentration of the EI.

SCREENING OF ELEMENTAL IMPURITIES, ANALYTICAL PROCEDURES AND VALIDATION

The determination of EI should be conducted using appropriate procedures suitable for their intended purposes. Unless otherwise justified, the test should be specific for each EI identified for control during the risk assessment. Pharmacopoeial procedures or suitable alternative procedures for determining levels of EI should be used[24-26].

USP general chapter <233>[7] describes two analytical procedures (Procedures 1 and 2) for the determination of the EI and acceptance criteria for alternative procedures that meet the validation requirements[27].

Procedure 1 can be used for determination of EI by ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometry) and procedure 2 by ICP-MS (Inductively Coupled Plasma Mass Spectrometry). For both the procedures sample preparations should be optimized based on the sample nature and recoveries of the EI. Generally sample preparation can be done direct aqueous or organic solutions when a material is soluble. When a material is not directly soluble in aqueous or organic solvents, indirect solution can be obtained by digesting the sample using the "Closed vessel digestion" procedure with a suitable concentrated acid[28-30].

Based on the number of elements to be determined in the drug product, single or multiple methods the sample preparations can be adopted to get the desired signal intensity for the target elements and acceptable recoveries of elements[31-32].

If the specified compendial procedures do not meet the needs of a specific application, an alternative procedure may be developed. Alternative procedures must be validated and shown to be acceptable, in accordance with the validation requirements for alternative procedures[33]. The level of validation necessary to ensure that an alternative procedure is acceptable depends on whether a limit test or a quantitative determination. Validation parameters like accuracy, precision, specificity, linearity, limit of quantification, range and solution stability[34] should be demonstrated as per the acceptance criteria specified in USP general chapter <233>.

CONTROLS[35-37]

Control of EI in drug product is to assure that EI do not exceed the PDEs. When the EI in risk assessment and screening (analysis) in the drug product shows the level is 30 percent or less of the established PDE in the drug product then no further controls are required and acceptable, if the process, drug substances and excipients vendors are not to be changed in future. When the EI in risk assessment and screening (analysis) in the drug product shows the level is more than 30 percent and less than the established PDE in the drug product then further controls are required and testing may be applied to EI according to the principles described in ICH Q6A, which should be a part of specification[38].

When the level of EI exceeds the established PDEs (control threshold), additional measures should be implemented to assure that the level does not exceed the PDE. The following approaches can be used to control the EI level[39-41] by:

- Selection of drug substance and excipients vendors, who periodically monitors and controls the levels of EI and establishment of specification for drug substance and excipients.
- Selection of manufacturing equipments, container closure systems, water source which meets the compendia requirements and following the Good Manufacturing Practice (GMP).

- Understanding, modification of the steps in the manufacturing process and implementation of in-process controls that result in the reduction of EI below the control threshold in the drug product.

CONCLUSION

Risk assessment of EI in drug product is must as it gives necessary information about the presence of each individual EI which helps in selection of process, make and grade of excipients, manufacturing equipments and container and closure systems. The information of EI is also required to keep necessary controls by means of screening which is a regulatory requirement and a part of drug product filling.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1: Elements to be considered in the risk assessment as per ICH Q3D guideline

Element	Class	If intentionally added (all routes)*	Oral, PDE µg/day*		Parenteral, PDE µg/day*		Inhalation, PDE µg/day*	
Cadmium (Cd)	1	yes	yes	5	yes	2	yes	2
Lead (Pb)	1	yes	yes	5	yes	5	yes	5
Arsenic (As)	1	yes	yes	15	yes	15	yes	2
Mercury (Hg)	1	yes	yes	30	yes	3	yes	1
Cobalt (Co)	2A	yes	yes	50	yes	5	yes	3
Vanadium (V)	2A	yes	yes	100	yes	10	yes	1
Nickel (Ni)	2A	yes	yes	200	yes	20	yes	5
Thallium (Tl)	2B	yes	no	8	no	8	no	8
Gold (Au)	2B	yes	no	100	no	100	no	1
Palladium (Pd)	2B	yes	no	100	no	10	no	1
Iridium (Ir)	2B	yes	no	100	no	10	no	1
Osmium (Os)	2B	yes	no	100	no	10	no	1
Rhodium (Rh)	2B	yes	no	100	no	10	no	1
Ruthenium (Ru)	2B	yes	no	100	no	10	no	1
Selenium (Se)	2B	yes	no	150	no	80	no	130
Silver (Ag)	2B	yes	no	150	no	10	no	7
Platinum (Pt)	2B	yes	no	100	no	10	no	1
Lithium (Li)	3	yes	no	550	yes	250	yes	25
Antimony (Sb)	3	yes	no	1200	yes	90	yes	20
Barium (Ba)	3	yes	no	1400	no	700	yes	300
Molybdenum (Mo)	3	yes	no	3000	no	1500	yes	10
Copper (Cu)	3	yes	no	3000	yes	300	yes	30
Tin (Sn)	3	yes	no	6000	no	600	yes	60
Chromium (Cr)	3	yes	no	11000	no	1100	yes	3

* If elements added intentionally, then those elements should be considered for risk assessment or the elements indicated in the Table 1 should be considered based on the route of administration.
µg/day = micro gram per day.