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GUIDELINES ON ELEMENTAL IMPURITIES

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ABSTRACT

Abstract is related to the elemental impurities it included identification, structural elucidation and quantitative determination of impurities. It included According to ICH guidelines, Impurities associated with APIs are classified into the categories. In elemental impurities Four-step process to assess and control elemental impurities in the drug product. Identification of impurities is done by variety of Chromatographic and Spectroscopic techniques, either alone or in combination with other techniques. These impurities are control with strategy.

INTRODUCTION OF ICH Q3D

The introduction of ICH Q3D is listed 24 elements that need to be evaluated by drug manufacturers, including mercury, lead, cadmium and arsenic. It included heavy metals in elemental impurities. Sources are elemental impurities are form residual catalysts added in synthesis, arising from processing equipment, presents in components of the drug product. Elemental classification is included four classes. The introduction of ICH Q3D (1) is one of the most complex changes in regulations pertaining to impurities seen by the pharmaceutical industry. While the guideline is ultimately intended to focus on final drug product quality, the actual risk assessment will touch all facets of the manufacture of a drug product. The guideline introduces toxicologically relevant permitted daily exposure (PDE) limits to individual elements replacing non-specific 19th century wet chemical "heavy metal" limit tests. ICH Q3D advocates the use of a risk-based approach to assessing the potential for presence of elemental impurities in drug products. The process of executing and documenting the risk assessment is a major challenge, primarily as a result of a limited global understanding about how to assess or quantify the risk associated with factors such as water, container-closure systems, and recipients[1].

SOURCES AND TYPES OF IMPURITIES:-

According to ICH guidelines, Impurities associated with APIs are classified into the following categories:

- Organic impurities (Process and Drug related)
- Inorganic impurities
- Reagents, ligands and catalysts
- Heavy metals
- Residual solvent

1) Organic impurities:

Organic impurities may arise during the manufacturing process and/or storage of the drug substance. They may be identified or unidentified, volatile or non-volatile including starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts. Starting materials or intermediates are the most common impurities found in every API unless a proper care is taken in every step involved in throughout the multi-step synthesis.

2) Inorganic impurities:

Inorganic impurities may also arrive from manufacturing processes used for bulk drugs. They are normally known and identified.

3) Reagents, ligands and catalysts-

The chances of presence of these impurities are rare. However, in some processes, these could create a problem unless the manufacturer takes proper care during production.

4) Heavy metals-

The main sources of heavy metals are the water used in the processes and the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place. These impurities of heavy metals can easily be avoided using demineralized water and glass-linked reactors.

5) Residual solvents [2]

Residual solvents are organic or inorganic liquids used during the manufacturing process. It is very difficult to remove these solvents completely by the workup process.

6) Environment related impurities:

Due to exposures to adverse temperatures (e.g. Vitamins as drug substances are very heat-sensitive and degradation frequently leads to loss of potency in vitamin products, especially in liquid formulations).

Due to exposure of light specially UV light (e.g. Ergometrine as well as methyl Ergometrine is unstable under tropical conditions such as light and heat).

Humidity (Humidity is considered Humidity (Humidity is considered detrimental for hygroscopic products e.g. Aspirin and Ranitidine).

ELEMENTAL CLASSIFICATION [3]

Classification	Description	Include in Risk Assessment
Class 1	Significantly toxic across all routes of administration	Yes
Class 2	Toxic to a greater or lesser extent based on route of Administration	Class 2A – Yes Class 2B – Yes only if intentionally added
Class 3	Impurities with relatively low toxicity (high PDEs) by the oral route of administration but require consideration in the risk assessment for other routes of administration	Dependent upon route of Administration
Class 4	Elemental impurities have been evaluated but for which a PDE has not been established due to their low inherent toxicity and/or regional regulations	No

Process to assess and control elemental impurities [4]:-

Four-step process to assess and control elemental impurities in the drug product

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

2. Analyze: Determine the probability of observance of a particular elemental impurity in the drug product.

3. Evaluate: Compare the observed or predicted levels of elemental impurities with the established PDE.

4. Control: Document and implement a control strategy to limit elemental impurities in the drug product.

SAFETY ASSESSMENT OF POTENTIAL ELEMENTAL IMPURITIES:-

1 Principles of the Safety Assessment of Elemental Impurities for Oral, Parenteral [5] and Inhalation Routes of Administration

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

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

In the absence of data and/or where data are available but not considered sufficient for a safety assessment for the parenteral and or inhalation route of administration, modifying factors based on oral bioavailability were used to derive the PDE from the oral PDE:

- Oral bioavailability <1%: divide by a modifying factor of 100;
- Oral bioavailability ≥ 1% and <50%: divide by a modifying factor of 10;
- Oral bioavailability ≥50% and <90%: divide by a modifying factor of 2; and
- Oral bioavailability ≥ 90%: divide by a modifying factor of 1.

Where oral bioavailability data or occupational inhalation exposure limits were not available, a calculated PDE was used based on the oral PDE divided by a modifying factor of 100.[6]

2. Other Routes of AdministrationPDEs were established for oral, parenteral and inhalation routes of administration:-

- Based on a scientific evaluation, the parenteral and inhalation PDEs may be a more appropriate starting point.

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

Guideline for Elemental Impurities:-

1. If local effects are expected, assess whether a modification to an established PDE is necessary.

2. Consider the doses/exposures at which these effects can be expected relative to the adverse effect that was used to set an established PDE.

3. If local effects are not expected, no adjustment to an established PDE is necessary.

4 If 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:

5. 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% and the bioavailability of an element by the intended route is 10%, a correction factor of 5 may be applied.

6.If a PDE proposed for the new route is increased relative to an established PDE, quality attributes may need to be considered.

Justification for Elemental Impurity [7, 8]:-

Levels of elemental impurities higher than an established PDE may be acceptable in certain cases. These cases could include, but are not limited to, the following situations:

- Intermittent dosing;
- Short term dosing (i.e., 30 days or less);
- Specific indications (e.g., life-threatening, unmet medical needs, rare diseases).

RISK ASSESSMENT

The evaluation of the potential risk posed by elemental impurities within a formulated drug product requires a holistic approach taking into account all potential sources of elemental impurities. **Figure 1** illustrates potential sources that should be considered in such an evaluation.

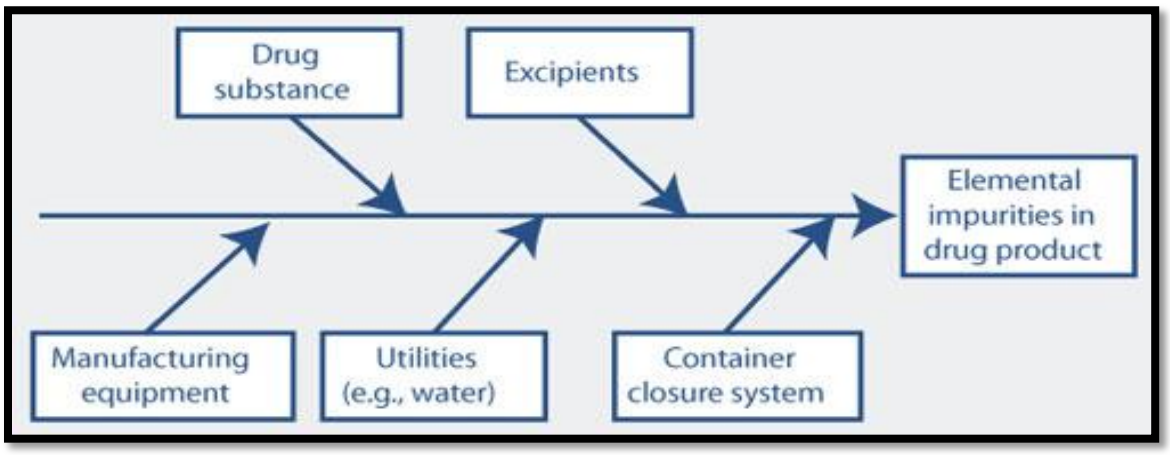

Figure 1: Sources of elemental impurities in finished drug products.

1) Drug substance

As presented in Figure 1, 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.

A principal responsibility for any drug-substance manufacturer is to develop a strategy to ensure effective control of the levels of elemental impurities in the finished drug substance. An approach based on assessing and controlling potential sources of elemental impurities, coupled with focused, limited testing, is preferable to exhaustive testing on the finished drug substance. A scientific, risk-based approach combined with knowledge and control of the key sources of elemental impurities in the drug-substance manufacturing process such as catalysts, provides an efficient and comprehensive elemental impurity control strategy for finished drug substances.

Figure 2 shows 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.

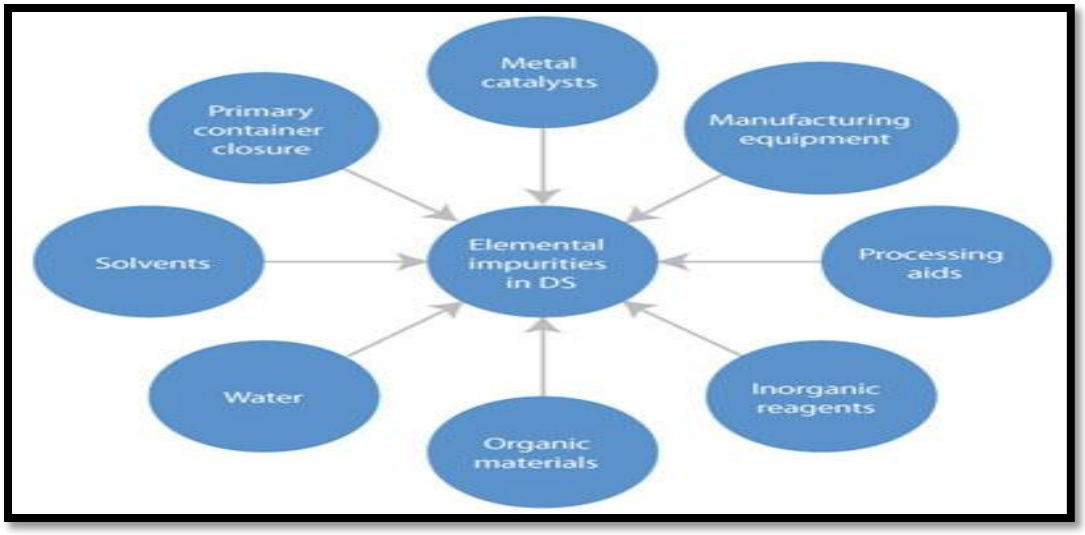

Figure 2: Primary sources of elemental impurities in drug substances.

2) Metal catalysts [9]

Metal catalysts such as palladium and platinum are often used in the drug substances Manufacturing Process and can therefore be present at low levels in the finished drug substance. The synthetic routeshould be reviewed for intentionally added metals, and data from purging Studies, including any supportive testing of appropriate isolated intermediates, should be used in the design of an appropriate control strategy. The ability to remove the catalyst (purge capacity) will be influenced bycatalystloadingand the nature of the catalyst used in the process Homogeneous vs.Heterogeneous catalysts .Heterogeneous catalysts, such as palladium on carbon, are often easilyRemoved from reaction mixtures by filtration, and therefore, the risk of carryover of elemental Impurities into the drug substance aretypically Low. Even in cases where metal catalysts are used in the final stages of the process, good historical data and/orunderstandingof carry-over may permit reduced testing schemes. When considering the other Potential sources highlighted in Figure 2, it is recommended to focus primarily on the manufacturing steps that occurs after the formationof the final intermediate. Washes, crystallizations, phase separations, Chromatography, distillations, and processing Aids scavengers aid in purging of elemental impurities and, therefore, reduce The risk ofcarryover into the finished drug substance from stages earlier in the upstream Process. Areas for further Consideration include manufacturing equipment, processing inorganic reagents, and packaging.

3) Manufacturing equipment.

In general, GMPs, including 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. Hastily, stainless steel, and glass are the most commonly used materials of construction for drug substance manufacturing equipment, due to their superior chemical resistance. Nickel, cobalt, vanadium, molybdenum, chromium, and copper are key elements in some hastelloy and stainless-steel alloys. 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.

Particle size reduction is discussed in the Drug Product Manufacture section.

4) Inorganic reagents.

Processing aids such as charcoal, silica, celite, and Draco, 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.

Therefore, the risk assessment should primarily focus on processing aids and inorganic reagents used late in the drug substance manufacturing process, and/or where aggressive reaction conditions exist (e.g., extreme pH/high temperatures for prolonged times).

5) Solvents [2].

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.

6) Packaging.

Packaging is discussed in the section Container-closure Systems (CSS) as a Potential Source of Elemental Impurities in Finished Drug Product.

7) Evaluation option limits.[10]

It must be recognized that, from a compliance perspective, the limits for elemental impurities in ICH Q3D apply only to the drug product. To ensure effective control of the level of elemental impurities in the drug substance a number of options are available:

- The ICH Q3D option 1 concentration limits assume a maximum daily drug product intake of 10 g/day. Drug substances that meet option 1 concentration limits can be used at any dose in the drug product.
- ICH Q3D option 2 concentration limits are calculated specifically based on the actual daily drug product intake (and composition) and may provide higher concentration limits than option 1 (if the maximum daily intake of drug product is <10g).

The acceptable level of elemental impurities in a drug substance may be defined and agreed upon in a suitable quality agreement between the drug substance manufacturer and the drug product manufacturer.

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.

 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.
- The information on the control of elemental impurities that is provided in a regulatory submission includes, but is not limited to, a summary of the risk assessment, appropriate data as necessary, and a description of the controls established to limit elemental impurities.

CONTROL STRATEGY:-

A drug-product risk assessment can use prior knowledge of the input materials to demonstrate that the risk of significant elemental impurity levels is low across multiple batches. When the risk assessment concludes that elemental impurities are below 30% PDE, it should be acceptable to rely on the quality system to maintain the control of the process and the existing use of standard cGMPs as a control strategy of the drug product, without requiring any additional element-specific testing on each batch of product[11].

Other factors to consider could include:

- Security of external supply chain along with a quality history (e.g., audit history, levels of complaints, recalls, etc.) for each vendor
- Control of vendor elemental impurity specifications and elemental impurity reporting on ingredient certificates of analysis
- Security of internal supply chain.

It is anticipated that a properly executed and documented elemental impurity risk assessment for the majority of drug products may justify the use of standard cGMP as being a sufficient control strategy to ensure levels of elemental impurities meet the levels defined in ICH Q3D, without the need for additional testing.

Where the drug product elemental impurity risk assessment identifies the need for additional elemental impurity control, it is crucial to first understand the potential source of the elemental impurity(s). Once the source is known, appropriate controls, in addition to cGMP, can be applied. The flow chart in can be followed to help determine when additional controls are required and what those controls may look like.

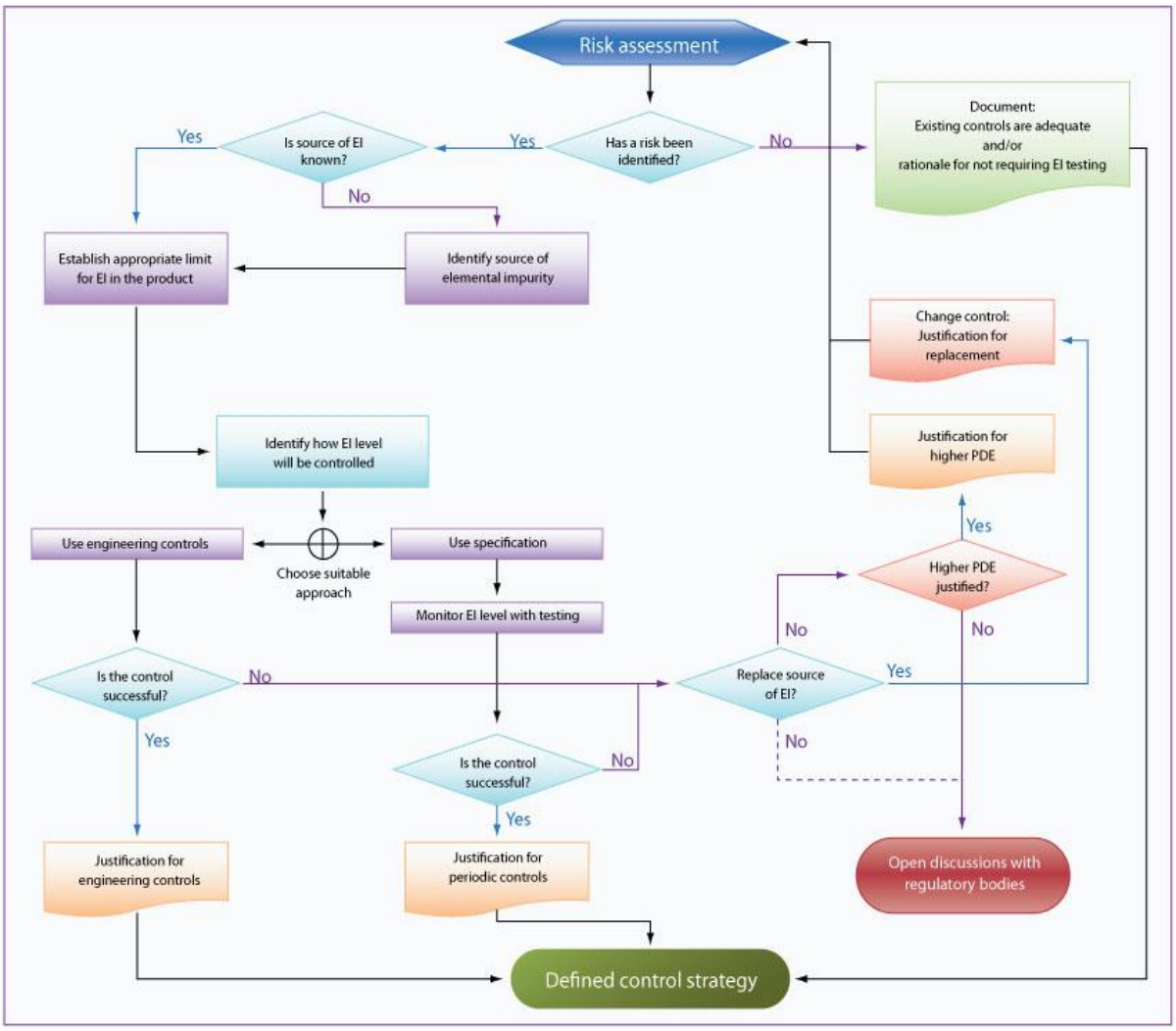

Fig: - Elemental impurity control strategy

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. 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. In many cases, this can be successfully achieved through the use of appropriate GMP controls both in terms of input materials and manufacturing processes, limiting testing to those areas clearly identified as a substantive risk.

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