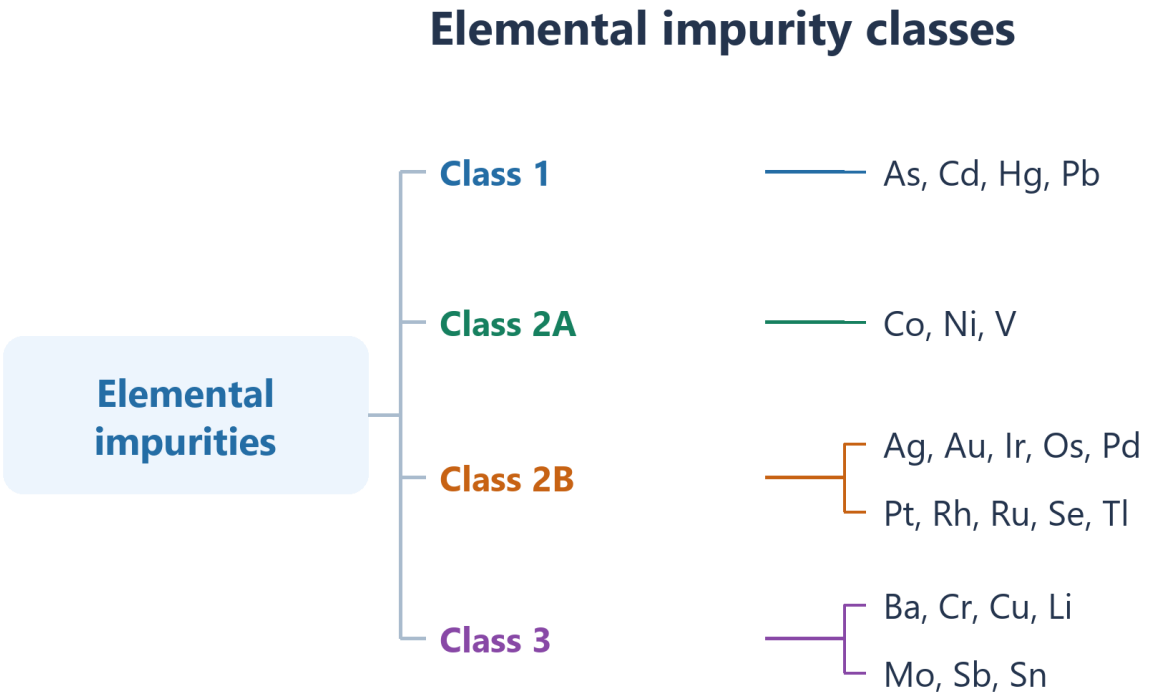
Elemental Impurities

Element Classification

Basic Idea

- Elemental impurities are classified according to their toxicity and possibility of occurrence in pharmaceutical products.
- The classification helps decide which elements need more attention during risk assessment and quality control.

Classification According to ICH Q3D



The ICH Q3D classes help organise the risk assessment for elemental impurities.

1. Class 1 Elements

- Class 1 elements are highly toxic and have limited or no therapeutic use in pharmaceutical products.
- These elements require strict control because they may be present due to environmental contamination.

Examples of Class 1 Elements

1. Arsenic (As)
2. Cadmium (Cd)
3. Mercury (Hg)
4. Lead (Pb)

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2. Class 2 Elements

- Class 2 elements have significant toxicity and are divided into two subclasses based on their probability of occurrence in pharmaceutical products.

3. Class 2A Elements

- Class 2A elements have a relatively high probability of occurrence and should be evaluated routinely.

Examples of Class 2A Elements

1. Cobalt (Co)
2. Nickel (Ni)
3. Vanadium (V)

4. Class 2B Elements

- Class 2B elements have a lower probability of occurrence but should be assessed if they are intentionally added or expected to be present.

Examples of Class 2B Elements

1. Silver (Ag)
2. Gold (Au)
3. Iridium (Ir)
4. Osmium (Os)
5. Palladium (Pd)
6. Platinum (Pt)
7. Rhodium (Rh)
8. Ruthenium (Ru)
9. Selenium (Se)
10. Thallium (Tl)

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5. Class 3 Elements

- Class 3 elements have relatively low toxicity when administered by the oral route.
- These elements are mainly considered for inhalation and parenteral products.

Examples of Class 3 Elements

1. Barium (Ba)
2. Chromium (Cr)
3. Copper (Cu)
4. Lithium (Li)
5. Molybdenum (Mo)

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6. Antimony (Sb)
7. Tin (Sn)

6. Other Elements

- Some elements are not included in the main ICH Q3D classes because they have low safety concern or are already controlled by other quality requirements.
- These elements may still be evaluated when there is a specific reason.

Control of Elemental Impurities

Basic Idea

- Control of elemental impurities involves identifying, monitoring, and reducing elemental contaminants to acceptable levels.
- The control strategy should ensure that the amount of each elemental impurity remains below the permitted daily exposure (PDE) limit.

Objectives

- To protect patients from toxic effects.
- To ensure product quality and safety.
- To comply with regulatory requirements.
- To maintain consistency in manufacturing processes.

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Permitted Daily Exposure

- Permitted Daily Exposure is the maximum amount of an elemental impurity that a patient can safely take each day.
- The limit depends on the toxicity of the element and the route of administration.
- Oral, parenteral, and inhalation routes may have different limits.

Approaches for Controlling Elemental Impurities

1. Risk Assessment

- Manufacturers should evaluate the possibility of elemental impurities entering the product.
- Risk assessment should consider raw materials, manufacturing processes, equipment, and packaging.

2. Selection of Raw Materials

- High-quality raw materials with low levels of elemental contaminants should be used.
- Supplier qualification programs should be implemented.

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3. Process Control

- Manufacturing processes should be designed to minimize contamination.
- Critical process parameters should be monitored regularly.

4. Equipment Selection and Maintenance

- Equipment should be constructed using materials that do not release harmful elements.
- Routine maintenance helps prevent contamination caused by corrosion or wear.

5. Testing and Monitoring

- Periodic testing should be performed to verify compliance with established limits.
- Validated analytical methods should be used for testing.

Control Options Recommended by ICH Q3D

- Elemental impurities may be controlled through process understanding and risk assessment.
- Supplier data may be used when appropriate.
- End-product testing may be performed when necessary.

Corrective Actions

- The manufacturer may change raw material suppliers.
- The manufacturer may improve purification steps.
- The manufacturer may replace equipment or catalysts.
- The manufacturer may improve packaging materials.
- The manufacturer may add routine testing when needed.

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Potential Sources of Elemental Impurities

Basic Idea

- Elemental impurities can originate from various sources during the manufacture, storage, and packaging of pharmaceutical products.
- Understanding the sources of contamination helps develop effective control strategies.

Common Sources of Elemental Impurities

1. Drug Substances

- Active pharmaceutical ingredients may contain elemental impurities from their manufacturing processes.
- Metal catalysts and reagents used during synthesis may remain as residues.

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2. Excipients

- Natural-source excipients may contain elemental contaminants from soil, water, or environmental exposure.
- Excipients may also acquire impurities during their manufacturing process.

3. Manufacturing Equipment

- Equipment surfaces may release metals because of corrosion, abrasion, or repeated use.
- Stainless steel equipment may contribute elements such as chromium, nickel, and iron.

4. Water Used in Manufacturing

- Water may contain trace amounts of metals if purification systems are inadequate.

5. Processing Aids and Catalysts

- Catalysts used during synthesis may remain in the final product if not removed effectively.

6. Container Closure Systems

- Packaging materials may contribute elemental impurities through leaching or interaction with the product.

7. Environmental Contamination

- Air, dust, and manufacturing environments may introduce elemental contaminants.

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Identification of Potential Elemental Impurities

- Identification of potential elemental impurities is a systematic process used to determine which elements may be present in a pharmaceutical product.
- This process is an important part of risk assessment under ICH Q3D.

Objectives

- To identify possible sources of elemental contamination.
- To determine whether testing is necessary.
- To establish appropriate control measures.

Steps in Identification

1. Review of Manufacturing Process

- Each manufacturing step should be evaluated to identify possible sources of elemental impurities.

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