# Metal / Elemental Impurities Limits

Rev 1.5, 11/16, EF

Metal / elemental impurities are defined by USP <232> Elemental Impurities, EMA Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents, and ICH Q3D Metal Impurities guideline. These documents specify limits for the amounts of elemental impurities in drug products. 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.

It is not always possible to determine if metal catalysts or reagents are used in the manufacturing process as not all raw material producers are willing to share this information with the supply chain. Thus it is the goal for PHARMCO-AAPER to have all compendial products tested and validated as required by USP General Chapter <233> and ICH Q3D.

While USP General Chapters apply to all compendial articles, USP <232> doesn't establish limits of elemental impurities in the excipients or process solvents. Default concentrations published in ICH guideline and the USP general chapter <232> apply to a maximum daily dose in different categories of drug products. It is responsibility of the end user to evaluate suitability of any chemical for the intended use as well as to assess compound-specific limits of daily intake of metal impurities

Certain levels of metal contamination, especially ubiquitous metals, potentially may occur in any product. Metals are introduced through a number of sources, including naturally derived plant or mineral raw materials, environment, contact with manufacturing equipment, storage and transport vessels. It is not possible to answer questions about the likelihood of the metal presence in any product without quantifying limits at which presence of the metals can be disregarded.

To the best of our knowledge none of the metals listed in the abovementioned documents are present in the solvents supplied by PHARMCO-AAPER in more than part per million level concentrations.

See below for typical results for metal content in Ethyl Alcohol manufactured and supplied by PHARMCO-AAPER as listed in USP <232>, EMA Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents, and ICH Q3D Metal Impurities guideline and tested in accordance with USP General Chapter <233>:

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# ETHYL ALCOHOL

## Permitted Concentrations of Elemental Impurities Following Option 1 Guideline in drug products, drug substances and excipients[1]

Reported in µg/g (ppm)

| **Element** | **Class** | **Oral Concentration µg/g** | **Parenteral Concentration µg/g** | **Inhalation Concentration µg/g** | **TYPICAL RESULT** (in µg/g) (ppm) |
|---|---|---|---|---|---|
| Cd (Cadmium) | 1 | 0.5 | 0.2 | 0.2 | 0.00 |
| Pb (Lead) | 1 | 0.5 | 0.5 | 0.5 | 0.00 |
| As (Arsenic) | 1 | 1.5 | 1.5 | 0.2 | 0.00 |
| Hg (Mercury) | 1 | 3 | 0.3 | 0.1 | 0.00 |
| Co (Cobalt) | 2A | 5 | 0.5 | 0.3 | 0.00 |
| V (Vanadium) | 2A | 10 | 1 | 0.1 | 0.00 |
| Ni (Nickel) | 2A | 20 | 2 | 0.5 | 0.00 |
| Tl (Thallium) | 2B | 0.8 | 0.8 | 0.8 | 0.00 |
| Au (Gold) | 2B | 10 | 10 | 0.1 | 0.00 |
| Pd (Palladium) | 2B | 10 | 1 | 0.1 | 0.00 |
| Ir (Iridium) | 2B | 10 | 1 | 0.1 | 0.00 |
| Os (Osmium) | 2B | 10 | 1 | 0.1 | 0.00 |
| Rh (Rhodium) | 2B | 10 | 1 | 0.1 | 0.00 |
| Ru (Ruthenium) | 2B | 10 | 1 | 0.1 | 0.00 |
| Se (Selenium) | 2B | 15 | 8 | 13 | 0.00 |
| Ag (Silver) | 2B | 15 | 1 | 0.7 | 0.00 |
| Pt (Platinum) | 2B | 10 | 1 | 0.1 | 0.00 |
| Li (Lithium) | 3 | 55 | 25 | 2.5 | 0.00 |
| Sb (Antimony) | 3 | 120 | 9 | 2 | 0.00 |
| Ba (Barium) | 3 | 140 | 70 | 30 | 0.00 |
| Mo (Molybdenum) | 3 | 300 | 150 | 1 | 0.00 |
| Cu (Copper) | 3 | 300 | 30 | 3 | 0.00 |
| Sn (Tin) | 3 | 600 | 60 | 6 | 0.00 |
| Cr (Chromium) | 3 | 1100 | 110 | 0.3 | 0.00 |

[1]Includes all requirements for ICH Q3D-Step 4 version, EMA (EP) 5.2 and USP <232> and <233> General Chapters.

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