ELEMENTAL IMPURITY ANALYSIS IN PHARMACEUTICALS

ICP-MS

Addressing the new ICH and USP methods for measuring elemental impurities in pharmaceutical materials

New methods for determining elemental impurities must be implemented by the pharmaceutical industry

Control of impurities, including elemental (inorganic) contaminants, has always been a critical issue in the development and production of pharmaceutical products. However, the previous US Pharmacopeia (USP) method for trace metals, USP<231> (heavy metals limit test), though widely used, did not give adequate information regarding these potentially harmful or toxic contaminants. USP <231> was not specific or quantitative, had limited scope, and often gave poor recoveries for volatile analytes, which were lost during the high temperature ashing step.

To address these limitations, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and USP have released new, harmonized, performance-based methods: ICH Q3D, USP<232> (limits), and USP<233> (procedures) for determining elemental impurities in pharmaceutical products and raw materials. A related method, USP<2232>, applies to dietary supplements.

ICH Q3D and USP<232> define the target analytes and permitted daily exposure (PDE) limits based on toxicological data rather than method capability, and require the quantitative determination of individual metal concentrations, in place of the previous sulfide precipitate test in USP<231>.

The twenty-four target analytes in ICH Q3D and USP<232> include the "Big Four" highly toxic elements: arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb) which are controlled at the lowest levels and must be assessed in all drug products. Additional regulated elements should be limited in drug products and must be measured if they may have been introduced during the formulation process (e.g. elements naturally present in raw materials, metal catalysts, Pt, Pd, etc), or as a result of production processes.

The reference analytical techniques suggested in the new methods are ICP-MS and ICP-OES, replacing the colorimetric test used in the earlier methods.

Both ICP-OES and ICP-MS can determine all the regulated elemental impurities at the levels required for direct analysis of oral drug products. The maximum level for each analyte – known as the "J" value – is calculated from the target PDE limit in the test sample, corrected for the sample preparation dilution; i.e. "J" is the PDE equivalent concentration in the sample solution as analyzed.

ICP-MS, with its superior detection limits, can also be utilized for pharmaceutical materials that require a large dilution, either because of limited sample availability (e.g. some APIs), or due to sample preparation processes (prep dilution). ICP-MS also provides accurate analysis at the much lower J values that apply to drugs intended for parenteral and inhalational administration, where the PDE limits are significantly lower than for oral drug products.

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Figure 1 shows ICP-MS calibrations from 0.1 to 2.0 J for the "Big Four" elements, illustrating the ng/L (ppt) level detection limits that can be achieved on the Agilent 7800/7900 ICP-MS. These low detection limits are the result of the very high plasma temperature of the Agilent ICP-MS, its high ion transmission, and the effective removal of polyatomic interferences provided by the ORS[4] collision/reaction cell.

Testing pharmaceutical product quality, including the presence of inorganic contaminants, requires a risk-based assessment approach, which also supports the principles of Quality by Design (QbD). The He mode Quick Scan capability of the Agilent 7800/7900 ICP-MS provides a useful tool to identify possible additional elemental impurities (Figure 2). This capability is also valuable when testing containers and packaging used for pharmaceutical products (extractable and leachable studies).

The universal removal of polyatomic interferences in He mode also addresses the USP<233> requirement for the unequivocal identification of target analytes, which can be achieved through the use of confirmatory data from secondary or "qualifier" isotopes.

USP<232> and ICH Q3D recognize that the toxicity of an element may differ according to its chemical form or "species"—As and Hg are of particular concern. When the concentration limit of an element is exceeded, the species may be separated and individually quantified to confirm that the toxic species do not exceed the limits. This can be easily achieved using HPLC separation coupled to the 7800/7900 ICP-MS.

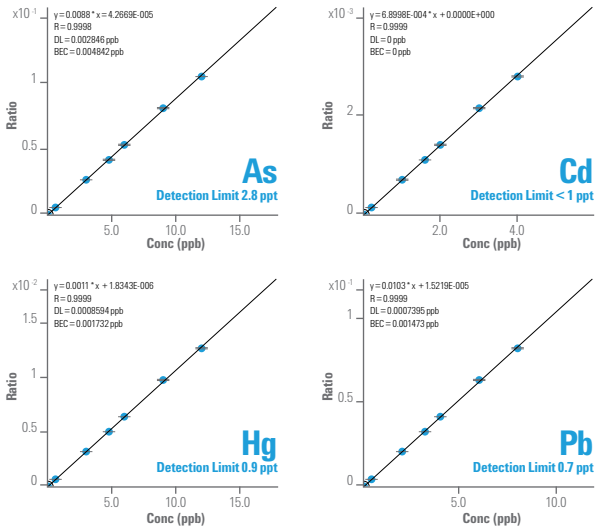

Figure 1. Agilent ICP-MS calibrations for arsenic, cadmium, mercury and lead from a single run in He mode in a matrix of 1% HNO_3:0.5% HCl, demonstrating low detection limits and effective removal of Cl-based interferences on As.

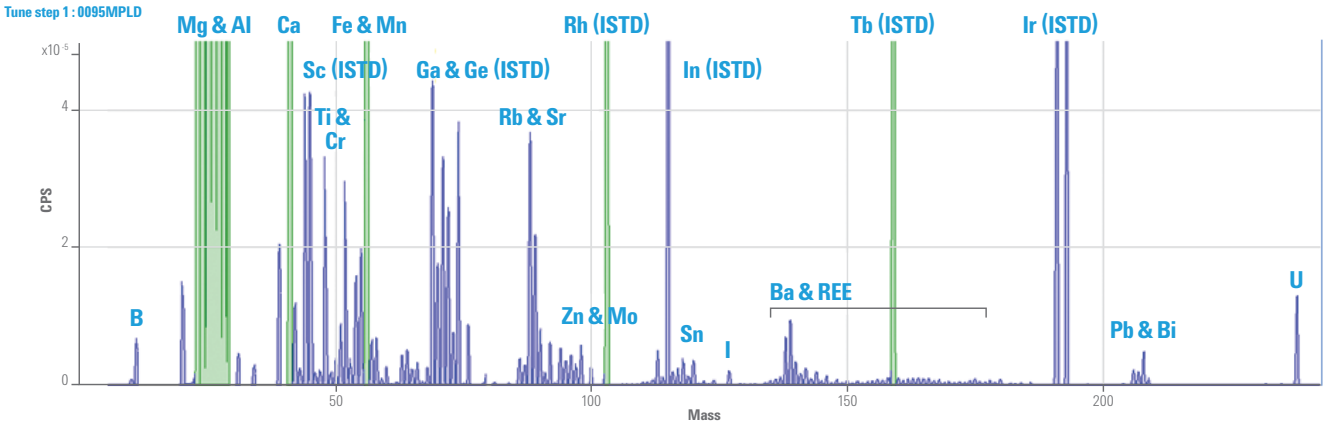

Figure 2. Agilent's 7800/7900 ICP-MS offer a powerful screening capability that utilizes helium (He) collision cell mode. He mode removes the common polyatomic interferences from all analytes, regardless of the sample matrix. It delivers a simple, easily interpreted spectrum, giving a comprehensive elemental composition from a single rapid scan. An example screening scan of a commercial antacid sample is shown above (green and purple signals are analog and pulse detector modes, respectively).

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