ELEMENTAL IMPURITY ANALYSIS IN PHARMACEUTICALS

The Measure of Confidence

Agilent 7900 ICP-MS

ICH and USP tests for elemental impurities provide better indication of potentially toxic contaminants

Elemental Impurity Analysis in Pharmaceutical Materials

Control of impurities, including elemental (inorganic) contaminants, has always been a critical issue in the development and production of pharmaceutical products. However, the current US Pharmacopeia (USP) method for trace metals, USP<231> (heavy metals limit test), does not give adequate information regarding the potential toxicity of these contaminants for the following reasons:

- USP<231> is a subjective colorimetric test which does not provide quantitative concentration data for individual target analytes
- The method is only applicable to ten sulfide-forming metals (Ag, As, Bi, Cd, Cu, Hg, Mo, Pb, Sb and Sn) and thus excludes other important elements such as metal catalysts and environmental contaminants
- The sample preparation typically includes a high-temperature ashing step, which causes the loss of volatile element such as Hg

To address these limitations, the International Conference on Harmonisation (ICH) and USP have drafted new performance-based methods: ICH Q3D, USP<232> (limits), and USP<233> (procedures) for determining elemental impurities in pharmaceutical products.

Proposed ICH and USP Tests for Elemental Impurities

ICH Q3D and USP<232> define the target analytes and limits based on toxicological data rather than method capability, and require the quantitative determination of individual metal concentrations, in place of the current sulfide precipitate test in USP<231>. The reference analytical methods suggested in USP<233> are ICP-MS and ICP-OES, replacing USP<231>'s colorimetric analysis.

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

ICH-Q3D lists twenty four elements, including all fifteen analytes defined in USP<232>. For all of the analytes, DLs on the Agilent 7900 ICP-MS are easily low enough to allow accurate quantitation at concentrations far below the proposed regulated levels, even allowing for the large dilution that may be required due to the limited sample size available for some pharmaceutical materials e.g. APIs.

Agilent Technologies

Figure 1 shows calibrations for the "Big Four" elements measured in He mode illustrating the ng/L (ppt) level detection limits achieved on the 7900 ICP-MS. These low detection limits are the result of the very high plasma temperature, high ion transmission, and the effective removal of polyatomic interferences provided by the ORS[4] collision/ reaction cell of the 7900 ICP-MS.

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 7900 ICP-MS provides an invaluable tool to identify possible elemental impurities (Figure 2).

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 secondary or "qualifier" isotopes.

USP<232> recognizes that elemental toxicity sometimes depends on the chemical form or "species" of the element. In the case of As and Hg, where the toxicity varies greatly with the species, USP<232> requires separation and quantitation of the individual species, which can be achieved using HPLC separation coupled to the 7900 ICP-MS.

The Agilent 7900 ICP-MS offers a complete solution for elemental analysis in both aqueous and organic samples, supporting the transition to proposed new methods for elemental impurities in pharmaceutical products.

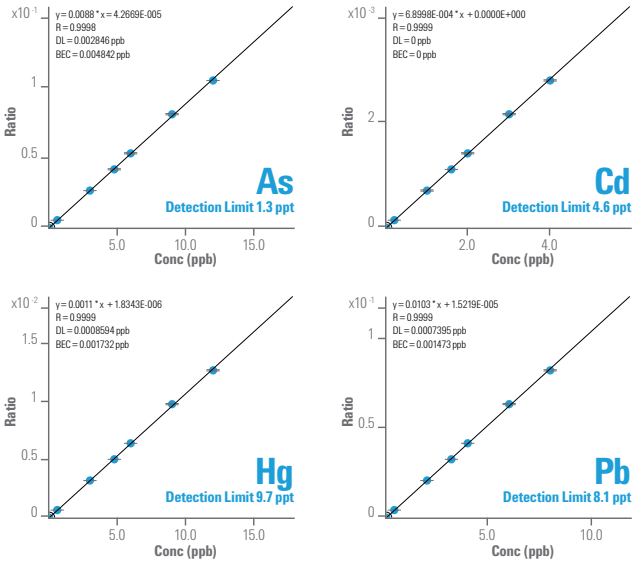

Figure 1. Agilent 7900 ICP-MS calibrations for arsenic, cadmium, mercury and lead from a single run in He mode in a matrix of 1% HNO_3:0.5% HCl, demonstrating low detection limits and effective removal of Cl-based interferences on As.

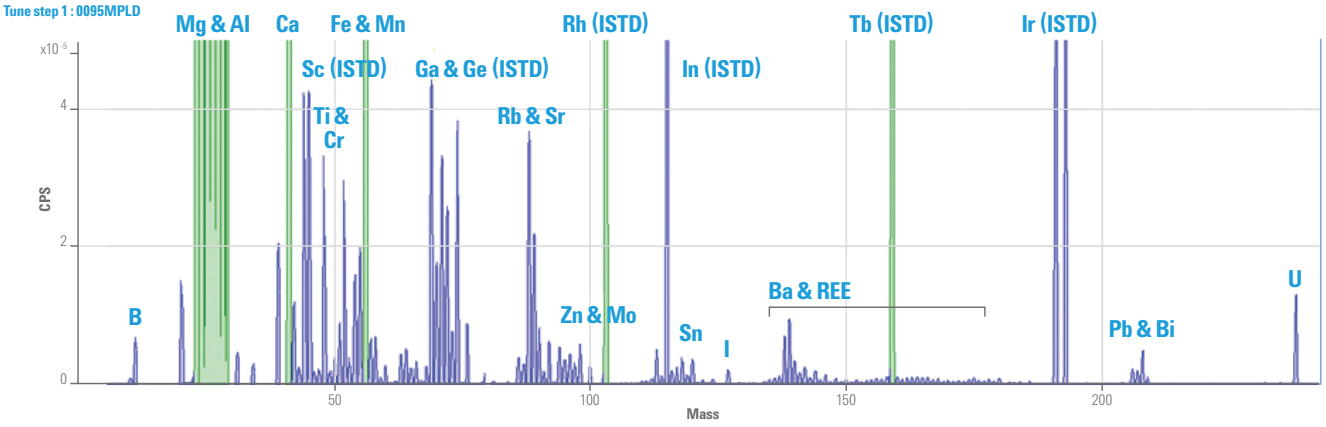

Figure 2. The Agilent 7900 ICP-MS offers a unique screening capability that utilizes helium (He) collision cell mode. He mode removes the polyatomic interferences from all analytes, regardless of the sample matrix. It delivers a simple, easily interpreted spectrum, giving a comprehensive elemental composition 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).

For more information:
Contact your local Agilent representative or visit:
www.agilent.com/chem/pharma

Published November 1, 2014
5991-5314EN

The Measure of Confidence

Agilent Technologies