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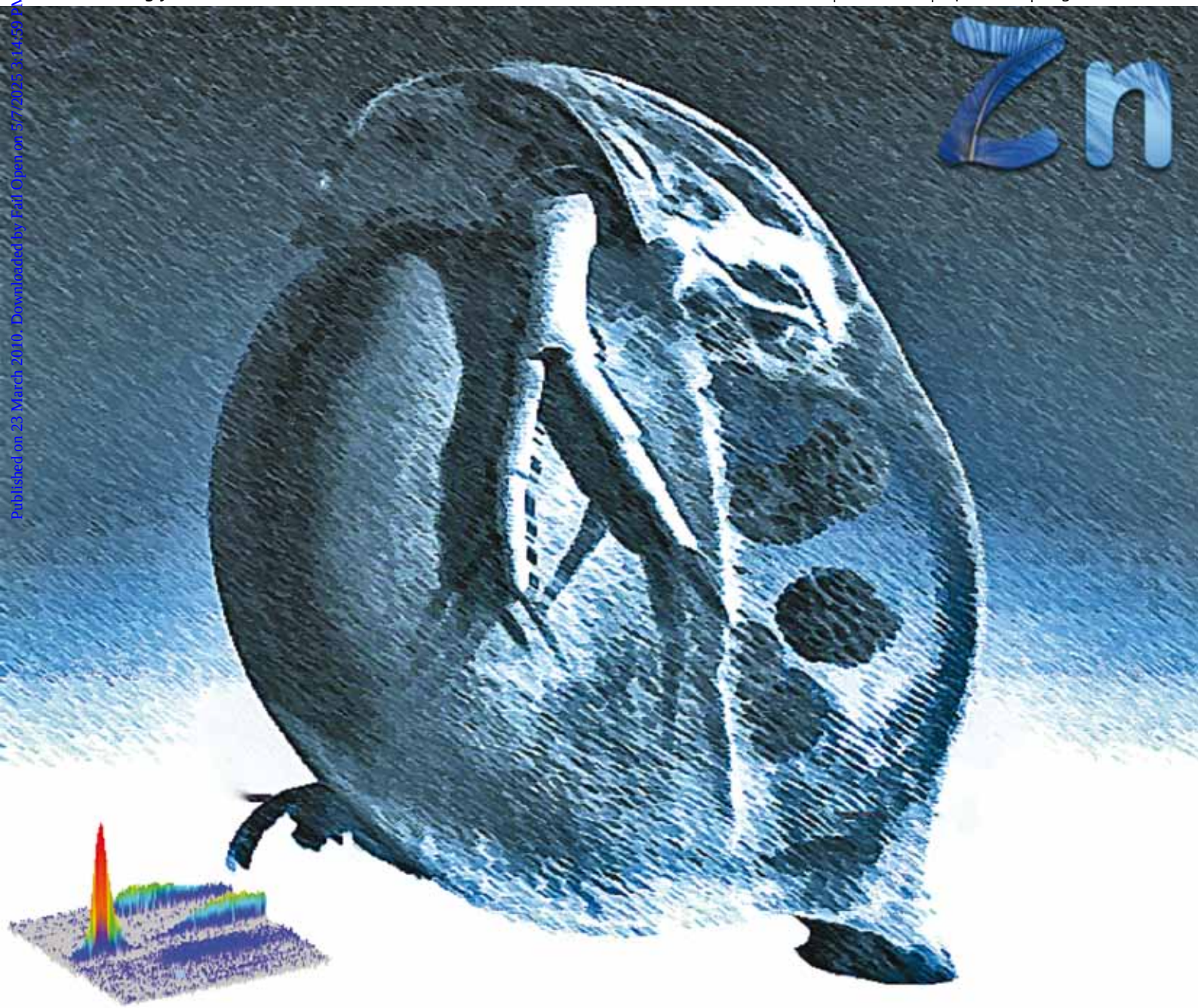

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Pharmaceutical Analysis by ICP-MS

New USP test for elemental impurities to provide better indication of potentially toxic contaminants

Heavy Metal Analysis in Pharmaceutical Materials

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

- USP <231> is a compendial (defined list) method, which only provides an indication of the sum of all the target metals
- The method uses a colorimetric test which is only applicable to sulfide-forming metals (Ag, As, Bi, Cd, Cu, Hg, Mo, Pb, Sb and Sn)
- The sample preparation typically includes a high-temperature ashing step, which can cause the loss of several target elements.

To address these limitations, USP has drafted a new performance-based method, USP <232> (limits) and USP <233> (procedures) for determining elemental impurities in pharmaceutical materials.

Proposed USP <232> Test for Elemental Impurities

USP <232> will define the target analytes and limits based on toxicological data, and will require the determination of individual metal concentrations, rather than the current group test. The reference analytical methods will be ICP-MS and ICP-OES, in place of the current colorimetric analysis. The target analytes, based on the European Medicines Agency (EMEA) list, include four highly toxic elements, arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb) which should be essentially absent. In addition, twelve "Class 2" elements should be limited in drugs and excipients and must be measured if they are added during production (e.g. catalyst residues, Pt, Pd, etc).

ICP-MS detection limits (DLs) are typically around 1000x lower than those obtainable by ICP-OES, in both aqueous and organic solvents. For the sixteen elements in USP <232>, including the critical "Class 1" contaminants, DLs on the Agilent 7700x ICP-MS are all far below the proposed regulatory levels, even allowing for the dilution or digestion that is required due to the limited sample size available for some pharmaceutical samples.

Figure 1 shows calibrations for all four of the Class 1 elements, measured in a single run, illustrating the ng/L (ppt) level DLs achieved on the 7700x. These low detection limits are the result of the very high plasma temperature, efficient ion transmission, and effective removal of polyatomic interferences provided by the 7700x. As, Cd and Hg are all difficult to ionize, As has ArCl and CaCl polyatomic overlaps and Cd can be affected by a MoO interference, so a high temperature plasma and effective interference removal are essential for this application.

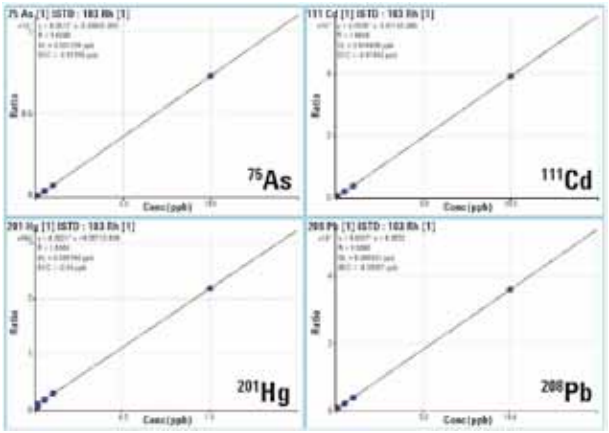

Figure 1. Calibrations for arsenic (DL 1.3 ppt), cadmium (DL 4.6 ppt), mercury (DL 9.7 ppt) and lead (DL 8.1 ppt) from a single 7700x run

7700x ICP-MS Screening for Elemental Impurities

In addition to low level and reliable (interference-free) analysis of all 16 regulated elements in the proposed new USP <232> method, the 7700x also provides a unique screening capability in combination with helium (He) cell mode. Since He mode removes the polyatomic interferences from all analytes, regardless of the sample matrix, He mode screening provides a simple, easily interpreted spectrum, giving a comprehensive elemental composition from a single rapid scan (illustrated in Figure 2).

For more information on the 7700x visit the Agilent Technologies web site at: **www.agilent.com/chem/icpms**

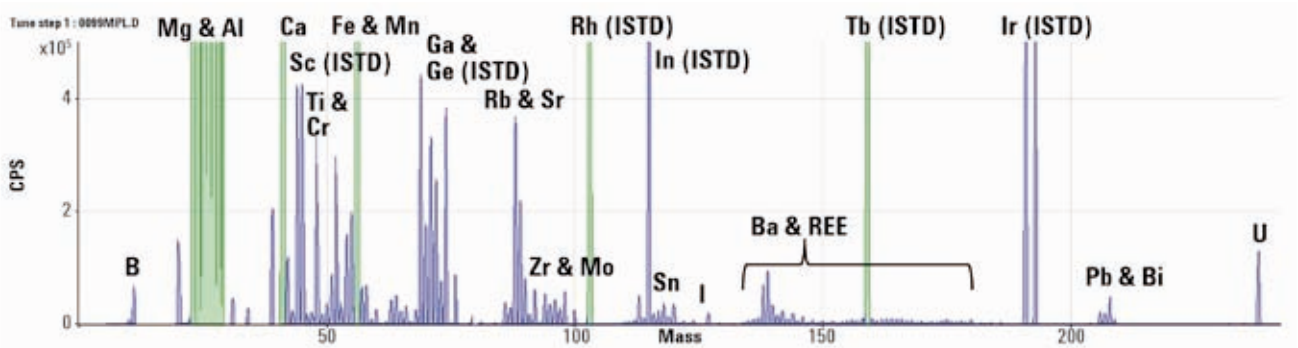

Figure 2. Full mass scan of a commercial antacid sample, illustrating the rapid screening capability of the Agilent 7700x ICP-MS in helium mode

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