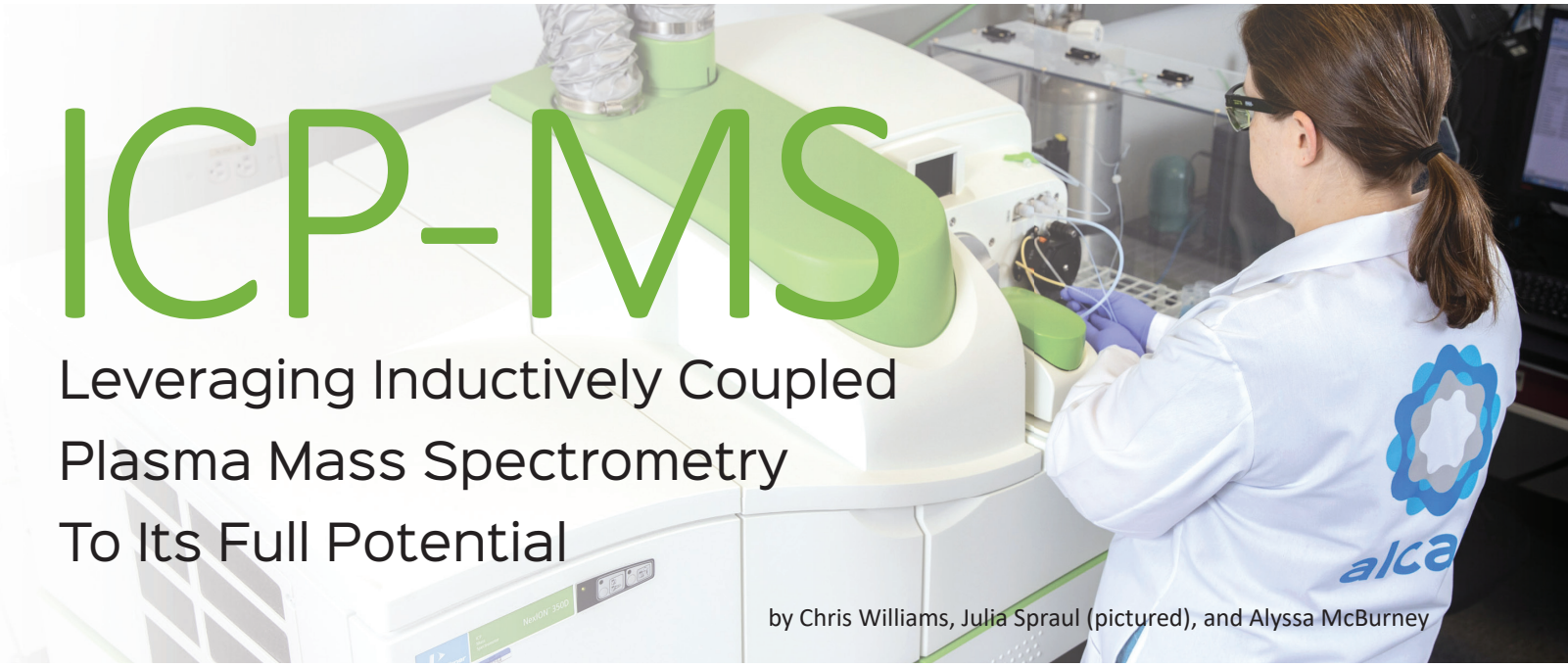
WHITE PAPER



ICP-MS

Leveraging Inductively Coupled Plasma Mass Spectrometry To Its Full Potential

by Chris Williams, Julia Spraul (pictured), and Alyssa McBurney

Today's technology has not only changed the way we receive information, but has continually adapted and progressed how we acquire information. The analysis of metals in pharmaceutical actives (API), raw material, and drug products has changed as well. ICP-MS/OES has emerged as a critical analytical platform for this analysis. Alcami offers multiple ICP-MS capabilities to support this need - including catalyst control, assay determination, organometallic compounds, and cleaning verification methods in addition to elemental impurities testing (raw material and product testing). All of these testing applications serve to maintain regulatory compliance and help deliver safe products to consumers.

Inductively Coupled Plasma Mass Spectrometry (ICP-MS) is a quickly growing technique in the pharmaceutical industry for its ability to deliver accurate and precise measurements of many metals within minutes. The general flow of analysis for ICP-MS starts with sample preparation, which can be as simple as diluting the sample material into a dilute acidic matrix or involve more complex preparation schemes that utilize extraction or digestion techniques. After the sample is in solution, it is aspirated into a fine, aerosolized mist that is introduced into the argon plasma. The argon plasma ionizes the atoms which then are streamlined towards the detector with the help of ion-focusing cones and lenses. Multiple configurations, including collision and reaction cell gases, can be interchanged to optimize the instrument's ability to detect the analyte in both simple and complex sample matrices. The versatility, short analysis time, and ability to measure many elements at once make ICP-MS a better alternative to the older stand-by methods of flame and graphite furnace atomic absorption. In this white paper, we will highlight several applications of ICP-MS in the pharmaceutical industry that capitalize on the technique's versatility outside of the scope of elemental impurities.

One of the most prominent sources for metal contamination derives from active pharmaceutical ingredients and excipients. In some cases, this is because metal catalysts like Ni, Pd, Pt, Cu, and Rh are required for the synthesis of these molecules. This necessitates a need to control the amount of the catalysts that remains in the material at the completion of the synthesis. Alcami has developed and validated methods for monitoring metal catalysts (such as Pd and Pt) in raw materials to ensure that residual amounts of catalyst are under control. The limits applied in these applications is often far below the ICH Q3D elemental impurities option 1 limit. Alcami can develop and validate ICP-MS method to analyze ppb level limits of metal catalysts.

ICP-MS is also valuable in the pharmaceutical industry for assaying metals that are intentionally added to pharmaceuticals, such as Platinum-based cancer medicines, where the metal of interest is the major component of the formulation. At Alcami, we have successfully demonstrated the ability of ICP-MS to achieve the precision and accuracy required for assay analysis by transferring, developing, and

validating methods for assay. Alcami has transferred ICP-OES assay methods to ICP-MS, for Sodium, with accuracy and precision better than 2%. We have also developed and validated for Magnesium assay in various Magnesium sulfate intravenous (IV) solutions, with similar accuracy and precision (2%). In addition to single element assays, the method development and validation of an assay for multiple metals (Cr, Mg, Zn, Se, and Cu) simultaneously in various nutritive IV formulations demonstrated the ruggedness of the ICP-MS and the ability to perform fast, accurate assay in the presence of very complex sample matrices. Interference control by the ICP-MS instrument and the use of an internal standard allowed us to perform precise and accurate determination assay on the elements of interest.

Oraganometallic compounds are also becoming more common in the pharmaceutical industry. These compounds allow enhanced and/or novel functionality of therapeutic compounds in patients. Since organometallic compounds contain bound metals in their structure the analysis presents additional challenges. Use of organometallic compounds requires the assay for intact organometallic molecule, as well as measurement of the residual unbound metal. This testing extends beyond just the API since analysis of the unbound metal is required to show the molecule maintains its structure through drug product manufacturing and shelf life. At Alcami, we have experience developing and validating ICP-MS methods that meet the needs of both of these challenges. We have validated methods for free Tin as part of Tin-containing pharmaceuticals, utilizing an extraction sample preparation scheme to separate the free Tin, with precision of ≤ 2% and accuracy of 95 - 105% for the ICP-MS analysis. We have also validated assays of Calcium and Tin in Calcium- and Tin-chelating pharmaceutical formulations.

The low detection limits and quick turnaround times that ICP-MS offers has advantages for verification of pharmaceutical manufacturing equipment cleaning processes. Several cleaning verification methods have been developed by Alcami for releasing manufacturing equipment. If the API or drug product contains a consistent and known concentration of an ICP-MS compatible Element (see included periodic table), a cleaning verification method via ICP-MS is possible and can be more sensitive than TOC and HPLC methods. Many organometallics make great case studies for this testing. By determining the maximum allowable carry-over (MAC) for the equipment and converting to the weight percent of the element of interest, the ICP-MS is sensitive enough to reach these levels. One of the methods developed by Alcami was able to determine Tin with a method quantitation limit of 30 ppb, with sample stability of four days, allowing manufacturing plenty of time to sample the equipment and send for analysis. Another cleaning method for Gallium was developed, due to the presence of Gallium in the active, with a method quantitation limit of 100 ppb. Using ICP-MS for cleaning verification methods also allows for variable sample matrices, unlike TOC. The time for analysis can be as little as a few minutes per sample, which allows manufacturing equipment to be released for use in a timely manner.

Ultimately, we all share one common goal of making sure that the pharmaceutical products available today are safe and effective for our clients and their patients. ICP-MS can be used not only for elemental impurity testing pharmaceutical applications but has the potential to meet the changing needs of our industry.