Proposed new ICH and USP methods for elemental impurities: The application of ICP-MS and ICP-OES for pharmaceutical analysis

White paper

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Abstract

The United States Pharmacopeial Convention (USP), in parallel with the International Conference on Harmonisation (ICH), is developing new methods for inorganic impurities in pharmaceuticals and their ingredients. The current USP method, <231> "heavy metals limit test", is acknowledged to be inadequate and is due to be replaced with new General Chapters USP<232> (Limits) and <233> (Procedures) in December 2015. The new methods will address the limitations of the current method, extending the list of analytes, reducing maximum permitted exposure limits and taking account of the route of exposure. The new methods will also introduce the use of closed vessel sample digestion and modern instrumental techniques to ensure the accurate recovery and determination of individual analyte concentrations. This White Paper discusses the development of the new USP General Chapters and the ICH Guideline for Elemental Impurities (Q3D) and how Agilent's 7900 ICP-MS and 5100 ICP-OES address the requirements of the proposed new methods.

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Introduction

The presence of impurities in pharmaceutical samples is a concern, not only because some contaminants are inherently toxic, but also because they may adversely affect drug stability and shelf-life, or may cause unwanted side-effects. As a result, both organic and inorganic (elemental) impurities must be monitored and controlled in raw materials, including: water, used for drug manufacturing; intermediates; active pharmaceutical ingredients (APIs); excipients (stabilizers, fillers, binders, colors, flavors, coatings, and so forth), and in the final dosage form. Impurities resulting from the production process, such as catalyst residues and contaminants from production process equipment, must also be monitored.

Regulations relating to the safety and effectiveness of medicines are developed and enforced separately in many countries and regions, but many pharmaceutical companies market their products globally. Consequently, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was formed in 1990 to work towards coordinating the maximum permitted exposure limits and analytical methods on a worldwide basis. ICH, which includes the regulatory bodies from the US, Europe and Japan, as well as representatives from other countries and the pharmaceutical industry, has defined a Guideline for Elemental Impurities (Q3D). ICH Q3D is currently at the Step 2b stage (draft Guideline released for consultation) and is awaiting approval from all participating regulatory bodies.

Pharmaceutical products manufactured for use in the USA must comply with the limits and procedures for measuring contaminants (including elemental impurities) defined by the United States Pharmacopeial Convention (USP), while the regulatory body responsible for enforcement is the Food and Drug Administration (FDA). USP is developing new methodology for monitoring inorganic (elemental) impurities in pharmaceutical materials in parallel with ICH Q3D. The proposed new General Chapters USP<232> (Limits) and <233> (Procedures) will become official on 1 August 2015 and are due to be implemented in December 2015.

In Europe, the Committee for Medicinal Products for Human Use (CHMP), of the European Medicines Agency (EMA) published guidelines in 2000 for controlling 14 elements in drug products (CHMP/SWP/4446/2000). However these guidelines focus on the residues of catalysts or reagents added during the manufacturing process, whereas the new ICH and USP methods will include several toxic elements that may be present as contaminants.

The current USP method used for monitoring inorganic contaminants in pharmaceutical samples is a 100 year-old colorimetric test, defined in General Chapter <231>. This method, known as the "heavy metals limit test", is based on precipitation of 10 sulfide-forming elements (Ag, As, Bi, Cd, Cu, Hg, Mo, Pb, Sb and Sn), in a reaction with a reagent such as thioacetamide. The resulting colored precipitate is compared visually to a 10 ppm Pb standard to determine compliance with the heavy metal limit. Besides the obvious potential variability associated with a subjective visual comparison, USP<231> is a limit test based on the sum of the 10 elements, and so does not give individual concentrations for each element. Also, it cannot be used for the determination of many elements of interest such as Cr, and the platinum group elements (PGEs) that are commonly used as production catalysts. Moreover, the use of thioacetamide and H_2S is not allowed in many parts of the world.

ICH Q3D and USP<232> include a wider range of analytes including catalysts and elemental contaminants from raw materials, the manufacturing process, the environment and container closure systems (CCS). Also the maximum permitted levels in the new methods are defined according to toxicity, rather than method capability. In USP<233>, the use of modern instrumentation such as multi-element ICP-MS and ICP-OES techniques is recommended, instead of the colorimetric test used in USP<231>.

USP<233> also defines the suggested sample preparation options that should be used, including closed vessel microwave digestion to ensure complete digestion and retention of volatile elements. By contrast, the sample preparation method defined in USP<231> requires ignition of the sample in a furnace at up to 600 °C. Such a high temperature inevitably leads to loss

of volatile analytes, including the critical toxic element Hg [1, 2, 3].

In an article published under the "Stimuli to the Revision Process" of the 1st Pharmacopeial Forum (PF) in 1995, Blake noted that "because of the loss of metals during ignition, the validity of test results obtained with the current USP [<231>], JP (Japanese Pharmacopoeia) and EP (European Pharmacopoeia) general test procedures is questionable" [1]. In a subsequent article in 2000, Wang proposed the use of a modern instrumental method (ICP-MS) in place of the colorimetric test defined in USP<231>. Wang's article identified some of the limitations of USP<231>, noting that "methods based on the intensity of the color of sulfide precipitation are non-specific, insensitive, time-consuming, labor intensive, and more often than hoped, yield low recoveries or no recoveries at all." [4].

Recognition of these issues led to a program to replace USP<231> with a new instrumental method that is more reliable, accurate, sensitive, specific, and robust. Three proposed new USP General Chapters relating to elemental impurities are being developed in parallel: USP <232>, <233> and <2232>. USP <2232> is limited to dietary supplements, while USP <232> and <233> deal with pharmaceutical ingredients and products.

Table 1 shows the Permitted Daily Exposure (PDE) limits for the new list of 15 analytes (As, Cd, Hg, Pb, V, Cr, Ni, Mo, Cu, Pt, Pd, Ru, Rh, Os and Ir) defined in USP<232> [5]. The most recent (December 2013) revision of USP<232> was published for public comment on 1 March 2014 in Pharmacopeial Forum (PF) 40(2). This draft has been updated to include revisions recommended by the Elemental Impurities Expert Panel, to partially align USP<232> with the limits published in ICH Q3D Step 2 [6]. Some differences between the two sets of limits remain; ICH Q3D defines limits for 24 elements in total, including Li, Co, Se, Sn, Sb, Ba, Au, Ag and Tl, which are not listed in USP<232>. Both methods include the more toxic elements (As, Cd, Hg and Pb, sometimes referred to as the "Big Four") which are controlled at much lower levels than the other analytes, and must be measured in all samples.

The analyte list and limits in ICH Q3D [6] and USP<232> [5] have been developed based on toxicological data, rather than method capability (as was the case for USP<231>), and for the first time the list includes inorganic catalysts (the PGEs Pt, Pd, Ru, Rh, Os and Ir). Catalytic metals must be measured if they may have been added during synthesis or sample processing, in common with the existing EMA guidelines.

Table 1. ICH Q3D, USP<232> and EMA analytes and Permitted Daily Exposure (PDE) limits (µg/day) for elemental impurities in drug products. Limits shown are for drugs intended for oral administration; different limits apply for parenteral and inhalational routes of administration [5]

ICH class	Element	ICH (µg/day)	USP (µg/day)	EMA (µg/day)
Class 1	As - Arsenic (inorganic)	15	15	na
	Cd - Cadmium	5	5	na
	Hg - Mercury (inorganic)	40	15	na
	Pb - Lead	5	5	na
Class 2A	Co - Cobalt	50		
	Mo - Molybdenum	180	180	250
	Se - Selenium	170		
	V - Vanadium	120	120	250
Class 2B	Ag - Silver	170		
	Au - Gold	130		
	Ir - Iridium	1000*	100	100**
	Os - Osmium	1000*	100	100**
	Pd - Palladium	100	100	100
	Pt - Platinum	1000	100	100
	Rh - Rhodium	1000*	100	100**
	Ru - Ruthenium	1000*	100	100**
	Tl - Thallium	8		
Class 3	Ba - Barium	13000		
	Cr - Chromium	11000	nc	250
	Cu - Copper	1300	1300	2500
	Li - Lithium	780		
	Ni - Nickel	600	600	250
	Sb - Antimony	1200		
	Sn - Tin	6400		
Class 4	Mn - Manganese			2500
	Zn - Zinc			13000
	Fe - Iron			13000

* PDE is based on Pt, due to insufficient data
** Subclass limit - PDE is based on the sum of these elements
na Not included in EMA guidance
nc Not considered a safety concern except for drugs administered by inhalation

The daily exposure limits in Table 1 must be scaled for the recommended maximum daily dose, so for a drug product with a daily dose of 10 g, the elemental impurity level in the dosage form (measured in µg/g) must be 10x lower than the limits shown. Even so, the required PDE limits shown in Table 1 can easily be measured directly with modern instrumental techniques such as ICP-OES or ICP-MS referenced in USP<233> [7]. However, many drug products will require acid digestion, with its associated dilution of the original sample, which means that the concentrations measured in the sample solution presented to the instrument will be significantly lower than the PDE limits in the drug product. Furthermore, many novel drugs are based on increasingly sophisticated and costly active pharmaceutical ingredients (APIs), which may only be available in very small amounts. The dilution associated with the preparation of these milligram-scale sample weights means that careful consideration needs to be given to the instrumentation selected for the analysis. The Agilent 5100 ICP-OES has the sensitivity and linear dynamic range to readily handle oral drug products and excipients where the maximum dosage is ≤10 g/day. However, for the lowest limits of detection and widest linear calibrations (up to 11 orders in the case of the Agilent 7900 ICP-MS) ICP-MS is the ideal technique, especially for parenteral and inhalation drug products, where the limits are much lower than for oral medicines. Low limits of detection are particularly important for some of the potentially toxic trace elements that must be controlled at the lowest levels in drug products, notably As, Cd, Hg and Pb.

USP<232> includes a section relating to the elemental form (species) of elements, and notes that As and Hg are of particular concern as some forms are much more toxic than others. The PDE for As is based on the inorganic forms and, if the measured (total) As concentration exceeds the PDE limit, the sample must be re-analyzed using a procedure that allows the different As species to be separated and quantified. This is required because inorganic As—arsenite (As (III)) and arsenate (As(V))—is much more toxic than the common organic forms, such as arsenobetaine. Speciation analysis is necessary to separate the different chemical forms and confirm that the level of inorganic As (the sum of arsenite and arsenate) is below the PDE. Similarly, the Hg limit is based on inorganic Hg (Hg^{2+}), which is the form most likely to be found in drug products; methyl mercury (MeHg) is the more toxic form, but its presence in pharmaceuticals is considered unlikely. However MeHg should be separated and measured specifically if samples are derived from material (for example, fish tissue) that may contain the compound in significant amounts. The chromatographic separation of the different forms of these elements leads to lower signal intensities than for the combined "total" elemental concentration, which necessitates lower detection limits from the instrumentation used.

The ICH, USP<232> and EMA daily dose PDE limits defined in Table 1 are for drugs intended for oral administration; different limits apply for drugs intended for administration by other routes. For example, drug products delivered by parenteral administration must meet a modified PDE that is typically much lower than the limit for oral administration. Large volume parenteral (LVP) medicines (daily dose greater than 100 mL) may be controlled by measurement of the elemental impurities in each component of the LVP, in which case they must meet a limit that is as much as 100 times lower than the oral limit. For example, each individual component of an LVP must contain less than 0.15 µg/g of inorganic Hg, and less than 1 µg/g of each of the catalyst elements (Ir, Os, Pd, Pt, Rh and Ru).

To convert the exposure limits (PDEs) to the concentrations in the drug product or its components (API, excipients, etc), USP<232> and ICH Q3D suggest several approaches. For example, USP<232> provides individual component limits for drug substances and excipients, assuming a maximum daily dose of less than or equal to 10 g/day, shown in Table 2. These component limits are intended to be used for manufacturing quality control rather than final product certification, as they allow drug manufacturers to control the concentration of impurities in the raw materials and intermediates used in the final drug product. In ensuring product quality by controlling manufacturing processes and raw material composition, ICH Q3D and USP<232> align with the goals of Quality by Design (QbD), which is increasingly used in pharmaceutical manufacturing to understand and control the sources of variability in products and processes. As with the PDE limits, the concentration limits shown in Table 2 are also based on drugs

intended for oral administration, with different limits applying to drugs intended for inhalation or parenteral administration.

Table 2. Component limits for elemental impurities in drug substances and excipients for drug products with a maximum oral daily dose ≤ 10 g/day [5,6]. Component limits for drugs intended for parenteral or inhalational administration are significantly lower for most elements.

ICH Class	Element	ICH Q3D** (µg/g)	USP<232>** (µg/g)	EMA CHMP/ SWP/ 4446/ 2000 (current) (µg/g)
Class 1	As - Arsenic (inorganic)	1.5	1.5	na
	Cd - Cadmium	0.5	0.5	na
	Hg - Mercury (inorganic)	4	1.5	na
	Pb - Lead	0.5	0.5	na
Class 2A	Co - Cobalt	5		
	Mo - Molybdenum	18	18	25
	Se - Selenium	17		
	V - Vanadium	12	12	25
Class 2B	Ag - Silver	17		
	Au - Gold	13		
	Ir - Iridium	100*	10	10***
	Os - Osmium	100*	10	10***
	Pd - Palladium	10	10	10
	Pt - Platinum	100	10	10
	Rh - Rhodium	100*	10	10***
	Ru - Ruthenium	100*	10	10***
	Tl - Thallium	0.8		
Class 3	Ba - Barium	1300		
	Cr - Chromium	1100	nc	25
	Cu - Copper	130	130	250
	Li - Lithium	78		
	Ni - Nickel	60	60	25
	Sb - Antimony	120		
	Sn - Tin	640		
Class 4	Mn - Manganese			250
	Zn - Zinc			1300
	Fe - Iron			1300

* PDE is based on Pt, due to insufficient data
** Proposed
*** Subclass limit - PDE is based on the sum of these elements
na Not included in EMA guidance
nc Not considered a safety concern except for drugs administered by inhalation

For any sample requiring digestion or dilution, the PDE and concentration limits must be corrected for the dilution factor applied during sample preparation. For example the PDE limit for Cd in oral drug products is 5 µg/day, or 0.5 µg/g in the dosage form for a drug with a maximum daily dose of 10 g/day. A dilution factor of 250 times during sample digestion (for example, 0.2 g sample digested and diluted to a final volume of 50 mL) would give a concentration limit in the sample digest (the "J" value) of 2 µg/L (ppb) for Cd. Accurate recovery must be demonstrated at 0.5 J (1 µg/L), requiring a detection limit below this level, refer to Table 2. Table 3 shows how the J value varies, depending on the digestion/dilution level.

Table 3. Calculation of actual J values (µg/L, ppb) with different digestion levels for products with an oral daily dose ≤10 g. For more J values at 250 x dilution, see Table 4.

Element	"J" at 250 x dilution	"J" at 50 x dilution
As-Arsenic (inorganic)	6	30
Cd-Cadmium	2	10
Hg-Mercury (inorganic)	6	30
Pb - Lead	2	10

Table 4 shows the ICH Q3D proposed oral drug product component limits in a typical digested sample solution (at 250x dilution). The proposed limits in USP<232> are also shown and are mostly the same except that the PGEs (catalyst residues) all have limits 10x lower than ICH Q3D except in the case of Pd. The instrumental detection limits of the 7900 ICP-MS are also included in Table 4, confirming that the 7900 ICP-MS is easily able to meet the detection limit requirements for pharmaceutical analysis, even for small sample sizes and when large dilution factors are applied. Component limits for drug products and excipients that would be delivered by parenteral or inhalational administration are significantly (up to 100x) lower than the oral limits for many elements. For example the component limit for Pd in USP<232> is 10 µg/g for drugs intended for oral administration, 1.0 µg/g for parenteral administration, and 0.1 µg/g for inhalational administration. Even when the dilution factor is taken into account, these levels in the digested sample are still easily within the range of the 7900 ICP-MS.

Sample preparation

Table 4. Component Limits (J values) for elemental impurities in 250 x (0.2 g digested to final volume of 50 mL) diluted samples as analyzed, together with 7900 ICP-MS Instrumental Detection Limits (IDLs) (µg/L, ppb) Maximum Impurity Level applies to products with an oral daily dose ≤10 g*

ICH class	Element	ICH Q3D** µg/L, ppb	USP<232> ** µg/L, ppb	Agilent 7900 ICP-MS IDLs*** µg/L, ppb
Class 1	As - Arsenic (inorganic)	6	6	0.005
	Cd - Cadmium	2	2	0.0001
	Hg - Mercury (inorganic)	16	6	0.001
	Pb - Lead	2	2	0.0002
Class 2A	Co - Cobalt	20		0.0002
	Mo - Molybdenum	72	72	0.0002
	Se - Selenium	68		0.02
	V - Vanadium	48	48	0.005
Class 2B	Ag - Silver	68		0.0005
	Au - Gold	52		0.0002
	Ir - Iridium	400	40	0.0002
	Os - Osmium	400	40	0.0005
	Pd - Palladium	40	40	0.0001
	Pt - Platinum	400	40	0.0002
	Rh - Rhodium	400	40	0.0001
	Ru - Ruthenium	400	40	0.0002
	Tl - Thallium	3.2		0.0001
Class 3	Ba - Barium	5200		0.0005
	Cr - Chromium	4400		0.002
	Cu - Copper	520	520	0.002
	Li - Lithium	312		0.01
	Ni - Nickel	240	240	0.002
	Sb - Antimony	480		0.0002
	Sn - Tin	2560		0.001
Class 4	Mn - Manganese			0.001
	Zn - Zinc			0.002
	Fe - Iron			0.01

* Component limits for drugs intended for parenteral or inhalational administration are significantly lower for most elements
** Proposed
*** IDLs measured at preferred isotope in a matrix of 1% HNO_3/0.5% HCl

A wide range of pharmaceutical sample types may require analysis using ICH Q3D and USP<232>/<233>, so it is not practical for the methods to provide a detailed sample preparation approach that would be suitable for all sample types. Some pharmaceutical samples can be analyzed undiluted, while others can be prepared using simple dilution or solubilization in an aqueous solvent (such as water or dilute acid) or a suitable organic solvent (such as 2-butoxyethanol:water (25:75) [3], DMSO or DGME). Methods that utilize a simple dilution or solubilization in an aqueous or organic solvent must take account of chemical stability and, in the case of organic solvents, variable volatility of the compounds present in the sample. For many APIs, dilution in an organic solvent is the preferred approach, in which case it may be necessary to include some means of stabilizing the analytes to avoid variable recovery due to the presence of more or less volatile species compared to the calibration standard [8].

Many excipients, intermediates, APIs and final products will be insoluble in any of the commonly-used aqueous or organic solvents, and so will require acid digestion. USP<233> specifies the use of "strong acids" for digestion of such insoluble samples, although it is left to the individual laboratory to develop and validate the acid composition and digestion method that gives acceptable recovery and sample stability for their samples. Nevertheless, there are some general points that will apply to most sample types that require digestion:

- The elements in ICH Q3D and USP<232> include Hg and the PGEs. These elements are chemically unstable at low concentrations in an oxidizing matrix such as nitric acid (HNO_3) or nitric/peroxide (HNO_3/H_2O_2) [9, 10]. USP<233> specifies that samples for analysis by ICP-MS must include an appropriate stabilizer when Hg is to be measured (Hg is a required analyte in all samples measured under the revised General Chapters). To ensure the stability of Hg and the PGEs in pharmaceutical sample digests, it is recommended that HCl is added to all solutions at a concentration of around 1%, to act as a complexing agent. Au (III) chloride is sometimes recommended for stabilizing Hg in solution, but is not suitable for pharmaceutical sample preparation since Au is a required (Class 2B) analyte in ICH Q3D.
- Pharmaceutical products may be a complex combination of the API, plus fillers, binders, colorings and coating agents. These coatings may be organic polymers that are formulated to resist

acid attack in the stomach and thereby control the point at which the drug substance is released in the small intestine. Given the range of sample types and their variable and complex matrices, it is likely that microwave digestion will typically be employed in order to ensure complete digestion of pharmaceutical samples, and closed vessel microwave digestion is the preferred digestion technique referred to in USP<233> for solid samples. Closed vessel digestion also eliminates any issues of loss of volatile elements such as Hg, which is a problem with USP<231>, as already discussed.

Validation

The method validation requirements of USP<233> depend on the procedure used (one of the specified ICP procedures, or an alternative procedure), and whether the procedure defined in a given monograph is a limit test or a quantitative determination. Limit tests must confirm detectability, repeatability, and specificity of the measurement, while quantitative determinations must demonstrate accuracy, precision (repeatability and ruggedness), and specificity.

The system suitability and performance testing validation of the Agilent ICP-MS for both limit and quantitative procedures as defined in USP<233> is described in a separate application note [14].

Instrumentation

One of the goals of the proposed new USP General Chapters is to replace the current subjective, colorimetric test (USP<231>) with a modern instrumental analytical method [11]. ICP-MS and ICP-OES are the instruments referred to in USP<233>.

Benefits of ICP-MS

The benefits of ICP-MS in terms of low detection limits for all of the regulated elements and speciated analysis have been discussed previously, and the Agilent 7900 ICP-MS system is particularly well-suited to the analysis of the variable, high-chloride matrices, which will be typical for digested pharmaceutical samples:

- The 7900 ICP-MS provides the highest plasma temperature of any commercial ICP-MS (indicated by the lowest CeO/Ce ratio of around 1%). This delivers improved matrix decomposition and better ionization of poorly ionized elements such as As, Cd, Hg, and the PGEs Os, Ir and Pt. A Peltier-cooled spray chamber is the preferred ICP-MS hardware configuration described in USP<233>, and is standard on the 7900 ICP-MS instrument. The 7900 ICP-MS can also be fitted with Agilent's unique Ultra High Matrix Introduction (UHMI) system, which delivers excellent matrix tolerance through precisely controlled and reproducible aerosol dilution. This technology further increases plasma robustness, giving better ionization and lower levels of interference, while also significantly reducing exposure of the interface and ion lenses to undissociated sample matrix when high dissolved solids samples (up to 25% salt matrix) are analyzed.
- The 7900 ICP-MS includes the fourth generation Octopole Reaction System (ORS^4), optimized for helium (He) collision mode with kinetic energy discrimination (KED) for interference removal. He-mode removes plasma and matrix-based polyatomic interferences regardless of sample composition and without the time-consuming sample-specific or analyte-specific optimization that is a characteristic of ICP-MS methods that utilize reactive gases [12]. He-mode on the 7900 ICP-MS allows samples that contain high and variable amounts of chloride (for example, from HCl in a typical pharmaceutical sample digest) to be run without compromising the detection of elements that can suffer from chloride-based polyatomic overlaps. These elements include ^{75}As (overlap from $^{40}Ar^{35}Cl$), ^{51}V ($^{35}Cl^{16}O$), ^{52}Cr ($^{35}Cl^{16}O^{1}H$) and ^{53}Cr ($^{37}Cl^{16}O$), all of which the 7900 ICP-MS can determine accurately in the presence of high % levels of HCl.
- He-mode on the 7900 ICP-MS also eliminates the polyatomic interferences from all isotopes of each analyte, so secondary or qualifier isotopes are available for analyte confirmation. This is especially useful for pharmaceutical analysis, as USP<233> states that the procedure must be able to "unequivocally" assess each target element

in the presence of other sample components such as other analytes and matrix components. The use of secondary isotopes as qualifier ions is a well-established and unique capability of the 7900 ICP-MS with He-mode [13].

- In cases where an API or other material can be solubilized in an organic solvent, the ICP-MS instrument must be able to tolerate the routine analysis of such solvents. Since the 7900 ICP-MS includes a Peltier-cooled spray chamber as standard, no change to the standard spray chamber is required in order to permit the aspiration of organic solvents. An optional 5th mass flow controller can be added to allow addition of oxygen to the plasma to combust the organic matrix, and the sample introduction and interface parts are easily exchanged for solvent-resistant versions. Furthermore, the advanced frequency matching RF generator and updated torch design and plasma ignition parameters of the 7900 ICP-MS ensure that the system tolerates volatile organic solvents; even non-water soluble solvents can be run directly.
- The 7900 ICP-MS is easily integrated with an Agilent or third party HPLC (liquid chromatography/ion chromatography) system, allowing separation of the different 'species' or chemical forms of an element, as required for As and Hg if the 'total' concentration of the element exceeds the PDE.
- A rapid semi-quantitative screening acquisition can also be performed in He-mode on the 7900 ICP-MS, allowing unknown samples to be quickly characterized. This mode of operation can also be applied to the determination of any process contaminants or for production failure analysis.

To confirm that He-mode on the 7900 ICP-MS was effective at removing the Cl-based interferences derived from the HCl used during digestion, the elements most affected (V and As) were measured in no gas mode as well as the standard He-mode. The calibrations in both modes are shown in Figure 1, illustrating the dramatic improvement in detection limits for these elements.

Figures 1a and 1c show the calibrations in no gas mode for V and As respectively, while Figures 1b and 1d show the He-mode calibrations for the same two elements. In no gas mode, the Cl-based interferences gave raised background equivalent concentrations (BECs) for both elements (2.49 µg/L for V and 2.55 µg/L for As). He-mode provides at least a factor of 100 lower BEC for both V and As (0.023 µg/L for V and 0.005 µg/L for As), due to the effective removal of the ClO and ArCl polyatomics with He-mode in the ORS[4] of the 7900 ICP-MS.

The effective reduction of interferences to ng/L (ppt) background levels ensures that these potentially difficult elements can be determined reliably at the regulated levels in the range of variable and complex matrices commonly analyzed in pharmaceutical laboratories.

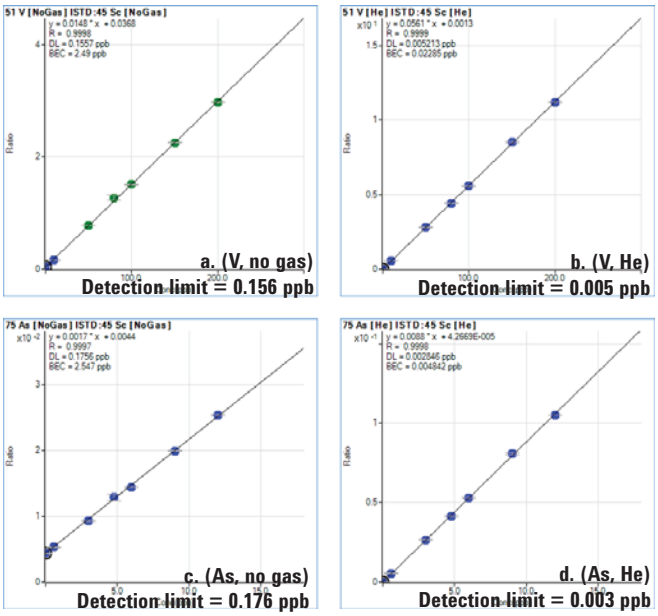

Figure 1. Calibrations for interfered elements V and As in no gas (a and c) and He-mode (b and d) showing effective removal of Cl-based interferences in He-mode (same cell conditions for all elements; acid matrix 1% HNO_3/0.5% HCl)

Benefits of ICP-OES

ICP-OES has the benefits of sensitivity in the presence of high matrix loads, simplicity of operation and high sample throughput speed.

The Agilent 5100 ICP-OES instrument is well suited to analyzing pharmaceutical samples using the USP<232> and USP<233> methodology, offering functionality and performance such as:

- Handling rapid changes in sample matrix. USP<233> will be performed on a range of complex matrices—pharmaceutical compounds dissolved in aqueous or organic solvent. The axially-viewed

vertical torch of the 5100 ICP-OES has high sensitivity and typical "radial orientation" performance to easily handle variation in sample matrix with respect to high total dissolved solids and either aqueous or organic solvents.

- The ability of the 5100 ICP-OES system to handle high matrix loads (25% TDS) ensures that higher sample masses can be digested using the recommended closed vessel microwave digestion procedure. Reduced dilution levels minimizes contamination sources and manual dilution errors which assists with detectability and accuracy as per USP <233>.
- Long term stable instrument output is essential to achieving the repeatability requirements of USP <233>. Signal stability in the 5100 ICP-OES is facilitated via mass flow gas control on all plasma gases, solid state free running RF for plasma generation and a low number of moving parts in the thermostatted optics. Figure 2 illustrates the long term stability of the 5100 ICP-OES in the presence of an extremely complex matrix.

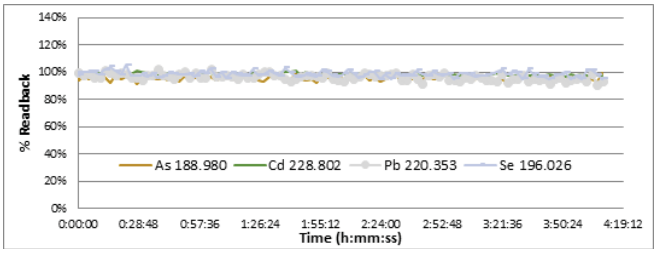

Figure 2. The long term stability of this sample, containing 250 µg/L As, Cd, Pb and Se, was < 2.4% RSD over 4 hrs. The sample matrix was 25% w/v NaCl. The measurement was performed on a 5100 ICP-OES using a Dual View torch, 2.4 mm injector and Argon Humidifier Accessory (AHA). No recalibration and no internal standard correction was used.

- The CCD detector in the 5100 ICP-OES has a wide wavelength range that enables "in method" confirmation of USP<232> target analyte concentration. This is done by verifying the calculated concentration from primary emission wavelengths with the calculated concentration at alternate emission wavelengths for the same element. This technique also illustrates USP<233> specificity and provides the analyst confidence of unbiased analysis. Table 5 illustrates an "in method" verification of Cd concentration by simultaneously measuring 2 separate Cd emission wavelengths three times.
- The broad wavelength range of the 5100 ICP-OES, coupled with the instrument's sensitivity and resolution enables USP target analytes to be clearly resolved from the 14 other target analytes that are likely to be present in the digestions or solvent mixtures. Figure 3 illustrates the resolved spectrum of Cd at 226.502 nm. The spectrum demonstrates the resolution and sensitivity capability of the 5100 ICP-OES for another common matrix for pharmaceutical analysis, an oil sample dissolved in kerosene. The Cd is at a concentration of 35 µg/L in the oil/solvent solution.

Table 5: Concentration of Cd in oil sample from 2 different emission wavelengths at approximately 35 ppb concentration.

Measurement	Measured concentration of Cd, at 214.439 nm (mg/L)	Measured concentration of Cd, at 226.502 nm (mg/L)
1	0.0374	0.0354
2	0.0393	0.0345
3	0.0361	0.0348

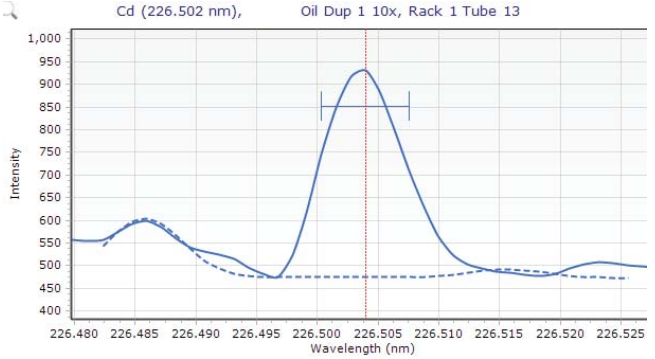

Figure 3: Cd 226 spectrum in a 21 element oil and solvent mixture.

Which instrumental technique to choose?

If your laboratory analyzes drug products or components that require digestion/dilution or solubilization in organic solvents, then the low detection limits of the 7900 ICP-MS may be essential. Similarly, if your drug products are intended for parenteral or inhalational administration (where the PDE limits are significantly lower), accurate measurement will be routinely achieved using the Agilent 7900 ICP-MS.

If your lab is:

- focused on oral dosage raw material and drug products requiring little to no sample dilution,
- requires high sample throughput, and
- cost conscious

then the Agilent 5100 ICP-OES is the perfect fit for your analysis requirements.

Table 6. Regulatory compliance requirements for sample analysis in pharmaceutical manufacturing.

Compliance requirement	Compliance solution
System validation, including design qualification (DQ), manufacturing QC, lifecycle management, installation and operational qualification (IQ/OQ), and performance verification (PV or PQ) for analytical instruments and software	Manufacturing quality records, certificates of software validation, and equipment qualification records
Control of access to the workstation for instrument control and data processing (restricted user access with password protection)	User access control (UAC) software
Electronic records control (secure storage, file versioning, audit trail, electronic signatures, and archive/retrieval)	Integrated software and computer systems that combine with UAC functions to manage the electronic records generated during the lab's activities
System operation, suitability testing, procedures, and physical access to the laboratory and records	Performance test results from system suitability tests (SST); standard operating procedure (SOP) documentation for analytical test methods; staff training records, etc Appropriate controls for physical laboratory access

Regulatory compliance for pharmaceutical manufacturing

21 CFR Part 11 and EU/PIC/S Annex 11

Regulatory compliance is a key aspect of sample analysis in pharmaceutical manufacturing. Part 11 in Title 21 of the US Code of Federal Regulations (commonly referred to as 21 CFR Part 11) governs food and drugs in the US, and includes the US Federal guidelines for storing and protecting electronic records and applying electronic signatures. The equivalent regulations in the European Union are defined in EU GMP Annex 11. These regulations also form the basis of the standards adopted by the 48 regulatory authorities (to date) that make up the Pharmaceutical Inspection Co-operation Scheme (PIC/S). US FDA 21 CFR Part 11 and EU/PIC/S Annex 11 aim to ensure the security, integrity and traceability of electronic records, including data, analytical reports and other records (such as daily performance checks) associated with the operation of an analytical instrument.

The four areas of compliance related to analytical results are shown in Table 6.

Agilent provides a range of software solutions to support laboratories in meeting regulatory compliance requirements: Agilent's OpenLAB Data Store and OpenLAB ECM (Enterprise Content Manager) provide secure, server-based storage, version control and records management functions for ICP-MS data.

Agilent SDA (Spectroscopy Database Administrator) is applicable to Agilent ICP-OES and ICP-MS instruments and works seamlessly with the ICP Expert software for ICP-OES and the ICP-MS MassHunter software to provide a simple, cost effective compliance solution for a single ICP-OES or ICP-MS installation.

For Agilent's ICP-OES instruments, Agilent SDA provides multi-level user access with functionality regulated through privilege settings for each password controlled user. Agilent SDA for ICP-OES uses a Spectroscopy Configuration Manager (SCM), which is a simple tool that creates, configures and maintains data in relation to system security, user management and data paths.

In conjunction with the ICP-MS MassHunter User Access Control software for the 7900 ICP-MS, Agilent's OpenLAB Data Store, OpenLAB ECM and SDA offer a range of solutions to satisfy the requirements of 21 CFR Part 11 and EU/PIC/S Annex 11 in laboratories ranging from those operating a single ICP-MS instrument, right through to global enterprises with many instruments installed across multiple global sites. User Access Control provides traceability, while security and integrity are ensured by the server-based file management of OpenLAB Data Store or ECM, or the PC work station-based SDA. Using a database or LCDF (location, cabinet,

drawer, folder) structure, analytical results and PDF report files are securely stored in checksum-protected files. Agilent's flexible, multi-level ICP-MS User Access Control software integrates with Agilent's compliance software to provide security, integrity and traceability for ICP-MS data, essential for full compliance with regulatory requirements. Combined with manufacturing quality certification and full installation and operational qualification services (IQ and OQ) for ICP-MS hardware and software, Agilent provides the most complete range of compliance services for regulated laboratories.

Conclusions

The development of new methodology for the preparation and analysis of pharmaceutical samples described in ICH Q3D and USP<232>/<233> provides an opportunity for pharmaceutical laboratories to update their methodology and instrumentation to address the serious limitations of the current heavy metals limit test (USP<231>) and align with the principles of Quality by Design. The new General Chapters USP<232>, <233> and <2232> recommend new sample preparation and stabilization methods, and outline new analytical methods based on modern ICP instrumentation.

Agilent Technologies manufactures ICP-OES and ICP-MS technologies that provide ideal capabilities for ICH Q3D and USP <232> across a broad range of pharmaceutical products. The Agilent 7900 ICP-MS provides an ideal analytical capability for USP<232>, with low limits of detection and wide dynamic range (up to 11 orders of magnitude) for all of the regulated elements. This is combined with excellent matrix tolerance to handle the high and variable matrices encountered in pharmaceutical laboratories, while He-mode delivers effective interference removal, and access to secondary isotopes for confirmation.

The 7900 ICP-MS has the added capability of speciation analysis to separate and quantify different species of elements where toxicity is related to elemental form. The 7900 ICP-MS also provides a rapid screening or semi-quantitative analysis capability to check for other elemental contaminants or for process control. Quality certification, full validation service and integration with Agilent's OpenLAB DataStore, ECM or SDA ensures that the 7900 ICP-MS offers the most complete compliance solution for pharmaceutical manufacturers wishing to implement ICH Q3D or USP<232>/<233>.

The Agilent 5100 ICP-OES provides a simple cost-effective solution to USP<232> analysis for raw material and finished oral drug products. The hardware and software technology provides speed, capability to handle complex matrices, stability and simplicity of operation and maintenance. These charateristics ensure rapid implementation can be achieved to ensure compliance to the relevant chapters of USP.

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