Validating the Agilent 7700x/7800 ICP-MS for the determination of elemental impurities in pharmaceutical ingredients according to draft USP general chapters <232>/<233>

Application note

Pharmaceutical

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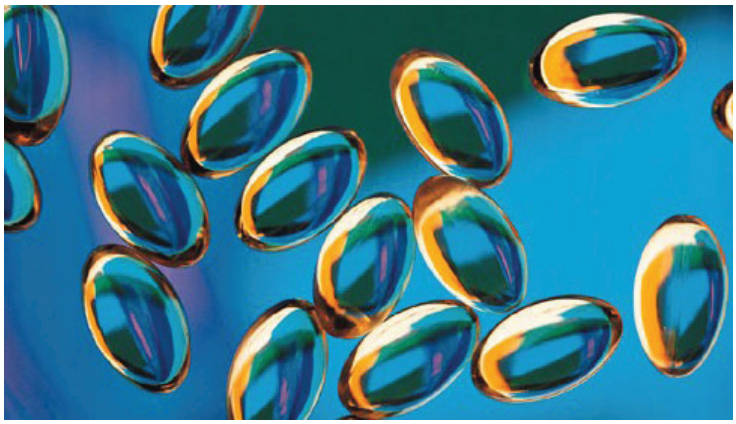

Abstract

The United States Pharmacopeia (USP) is developing new General Chapters relating to the determination of elemental impurities in pharmaceutical products and ingredients. USP<232> defines the analyte limits, while USP<233> defines sample preparation options including closed vessel microwave digestion, and recommends the use of modern instrumentation, such as multi-element ICP-MS and ICP-OES techniques. Analytical equipment qualification under USP<233> is based on performance testing, and includes requirements to demonstrate accuracy, repeatability, and the unequivocal identification of analytes. In this paper we present data to illustrate the successful validation of the Agilent 7700x ICP-MS for the measurement of elemental impurities in gelatine capsule samples, according to the May 2011 draft version of USP<232>/<233>.

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All regulated elements passed the acceptance criteria defined in USP<233>, including those elements that can suffer matrix-based interferences (such as the Cl-based overlaps on V, Cr and As). Of the elements covered by USP<232>, several are more soluble or chemically stable in a chloride matrix, particularly low concentrations of Hg and the platinum group elements (PGEs), which can be stabilized using a low % level of HCl added to all aqueous and acid digested samples. Routine addition of HCl to stabilize samples is no longer a problem for ICP-MS methods, since the resulting Cl-based polyatomic interferences are reliably removed using He cell gas, which is the standard mode of operation on the 7700x/7800.

Introduction

The United States Pharmacopeia (USP) is currently developing new methodology for monitoring inorganic (elemental) impurities in pharmaceutical materials. The proposed new General Chapters USP<232> (Limits) and <233> (Procedures) are due to be implemented in 2017. USP<232> defines new, lower Permitted Daily Exposure (PDE) limits for a wider range of inorganic (elemental) impurities: As, Cd, Hg, Pb, V, Cr, Ni, Mo, Mn, Cu, Pt, Pd, Ru, Rh, Os and Ir [1]. The list of regulated elements and PDEs is shown in Table 3.

Two instrumental techniques (ICP-OES and ICP-MS) are referenced in USP<233> [2]. However, it should be noted that the PDE limits defined in USP<232> must be adjusted depending on the type of pharmaceutical product and the route of administration. For example drug products delivered by parenteral or inhalational administration must meet a modified PDE that is 10 times lower than the limit for oral administration, while large volume parenteral (LVP) medicines (daily dose greater than 100 mL) must meet a limit 100 times lower than the base PDE. USP<232> also provides individual component limits for drug substances and excipients, assuming a maximum daily dose of less than or equal to 10 g/day. Table 3 also shows the component concentration limits in a digested solution, and the instrumental detection limits of the 7700x ICP-MS, for comparison.

USP<233> further defines the sample preparation and method validation procedures that should be used for system suitability qualification of any instrumentation used for the analysis of elemental impurities in pharmaceutical materials [2]. Validation of analytical instruments that are used for the new USP<232>/<233> method will be performance-based, and USP<233> defines the analytical and validation procedures that labs must use to ensure that the analysis is "specific, accurate, and precise".

In this study, we performed method validation and system suitability performance testing of an Agilent 7700x ICP-MS for the analysis of gelatin capsule (gelcap) samples, according to the May 2011 revision of USP <232>/<233>.

Experimental

Sample preparation

Many pharmaceutical products and raw materials will require acid digestion. USP<233> specifies the use of "strong acids" for digestion of such insoluble samples, and according to USP<233>, the preferred approach is closed vessel (high temperature and pressure) microwave digestion.

The microwave digestion method used for preparation of the gelcap samples for this study is shown in Table 1.

Agilent ICP-MS Application Specialists have established that a minimum of 0.5% HCl should be used for the stabilization of samples prepared for analysis by ICP-MS, if the analyte list includes elements such as Hg and the PGEs. In the case of some analytes, such as Os, a higher concentration of HCl (around 3%) may be required to ensure long-term solution stability. USP<232>/<233> does not specifically require that post-digestion sample stability must be determined, but sample stability over several days is a common requirement in the pharmaceutical industry and has been discussed by the FDA and the International Conference on Harmonization (ICH). Consequently, we prepared all samples in a matrix of 2% HNO_3 and 0.5% HCl to ensure stability of Hg and the PGEs.

Table 1. Microwave digestion method used for the preparation of gelcaps

Parameter	
Microwave oven	
Make and model	Milestone Ethos
Rotor type	High pressure, quartz inserts
Rotor capacity	10 vials of ~20 mL sample volume
Digestion	
Sample weight	0.2 g
HNO_3	1 mL
HCl	0.25 mL
H_2O_2	0.5 mL
De-ionized water	3.5 mL
Oven program	
Pre-digestion (room temperature)	15 min
Ramp (to 1200 W, 150 °C)	15 min
Hold (at 1200 W, 150 °C)	10 min
Cool down	30 min
Final dilution	
De-ionized water	To 50 mL
Total dilution factor	250 x

Instrumentation

An Agilent 7700x ICP-MS was used for the analysis of all 16 elements specified in the May 2011 revision of USP<232>. The full suite of analytes plus internal standards was measured in calibration standards, multiple replicates of digested samples, and samples spiked at the levels specified in USP<233>. A discussion of why the 7700x/7800 is particularly well-suited to the analysis of digested pharmaceutical samples is included in Agilent's White Paper on ICP-MS for Pharmaceutical Analysis [3], but in summary:

- The 7700x/7800 provides a very high plasma temperature, which improves matrix tolerance, reduces interferences, and provides more complete ionization (and therefore higher and more consistent sensitivity) for poorly ionized elements such as As, Cd, Hg and the PGEs Os, Ir and Pt.
- Helium (He) collision mode on the 7700x/7800 is acknowledged as the most reliable and effective way to remove multiple polyatomic interferences from multiple analytes in complex and variable sample matrices [4]. As well as providing lower detection limits and more accurate results, He mode allows access to secondary or qualifier isotopes [5], which can be used to unequivocally identify the analytes as required in USP<233>.
- The 7700x/7800 can also be configured to analyze all the solvents commonly used for preparation of pharmaceutical samples, and can easily be linked to an HPLC (and a GC) for speciation of As and Hg, if required.
- A rapid semi-quantitative screening acquisition can also be performed in He mode on the 7700x/7800, allowing unknown samples to be quickly characterized. This mode of operation is also extremely useful for the determination of any process contaminants or production failure analysis.

Analytical method

A standard Agilent 7700x ICP-MS with a Micromist nebulizer was used throughout. The operating conditions used for the analysis of gelcap samples are shown in Table 2.

Table 2. Agilent 7700x ICP-MS operating conditions for the analysis of pharmaceutical samples

Parameter	Value
Plasma mode	Normal, robust
RF forward power (W)	1550
Sampling depth (mm)	8
Carrier gas flow (L/min)	0.95
Dilution gas flow (L/min)	0.15
Spray chamber temperature (°C)	2
Extraction lens 1 (V)	0
Kinetic energy discrimination (V)	4
He cell gas flow (mL/min)	4

The Octopole Reaction System (ORS^3) of the 7700x ICP-MS was operated in helium collision mode (He mode) for all analytes and all samples, demonstrating the simple method setup and consistent routine operation that are characteristic of the 7700x. Primary and secondary (qualifier) isotopes, cell mode, internal standards, integration times and method detection limits (MDLs) compared to the PDE and Component

limits for all analytes are shown in Table 3. The MDLs were calculated from 3 times the standard deviation of 10 external measurements of unspiked gelcap samples. All of the MDLs were in the tens ng/L (ppt) level in solution, except for certain elements (for example, Mn, Cu) where the high calibration level may have contributed to a slightly increased blank level. Even these elements gave MDLs in the single ng/mL (ppb) range in solution, equivalent to sub µg/g (ppm) in the solid, still several hundred times below the required component concentration limits defined in USP<232>.

Results

System suitability check

As already discussed, the PDE levels defined in USP<232> can be measured using either ICP-OES or ICP-MS. The low limits of detection and linear calibrations over a wide dynamic range (9 orders in the case of the 7700x, 10 orders for the 7800) of ICP-MS may be necessary in cases where large dilutions are required, or where medicines intended for inhalational or parenteral administration are being measured.

Table 3. Acquisition modes, required method limits and analytical figures of merit for the Agilent 7700x.
* MDL calculated as 3σ of unspiked gelcap samples (n=10 external replicates). 1J control limits are based on a 250x dilution (e.g., 0.2 g in 50 mL). Secondary isotopes (shown in italics) were acquired where available for unequivocal confirmation of analyte results reported for the primary isotope (shown in bold)

Mass	Element	Cell Mode	Internal standard	Integration time (s)	Daily dose PDE (µg/day)	Component limits (µg/g)	1J actual values (ng/mL)	MDL* (ng/mL)
51	**V**	**He**	**Sc**	**0.5**	**250**	**25**	**100**	**0.162**
52	**Cr**	**He**	**Sc**	**0.5**	**250**	**25**	**100**	**0.176**
53	*Cr*	*He*	*Sc*	*0.1*	*250*	*25*	*100*	*0.261*
55	**Mn**	**He**	**Sc**	**0.5**	**2500**	**250**	**1000**	**1.694**
60	**Ni**	**He**	**Sc**	**0.5**	**250**	**25**	**100**	**0.359**
62	*Ni*	*He*	*Sc*	*0.5*	*250*	*25*	*100*	*0.339*
63	**Cu**	**He**	**Sc**	**0.5**	**2500**	**250**	**1000**	**1.333**
65	*Cu*	*He*	*Sc*	*0.5*	*2500*	*250*	*1000*	*1.114*
75	**As**	**He**	**Sc**	**1**	**15**	**1.5**	**6**	**0.015**
95	**Mo**	**He**	**Tb**	**0.5**	**250**	**25**	**100**	**0.180**
97	*Mo*	*He*	*Tb*	*0.5*	*250*	*25*	*100*	*0.183*
101	**Ru**	**He**	**Tb**	**0.5**	**100**	**10**	**40**	**0.063**
103	**Rh**	**He**	**Tb**	**0.5**	**100**	**10**	**40**	**0.070**
105	**Pd**	**He**	**Tb**	**0.5**	**100**	**10**	**40**	**0.063**
111	**Cd**	**He**	**Tb**	**0.75**	**5**	**0.5**	**2**	**0.005**
114	*Cd*	*He*	*Tb*	*0.75*	*5*	*0.5*	*2*	*0.004*
188	*Os*	*He*	*Bi*	*0.5*	*100*	*10*	*40*	*0.274*
189	**Os**	**He**	**Bi**	**0.5**	**100**	**10**	**40**	**0.270**
191	**Ir**	**He**	**Bi**	**0.5**	**100**	**10**	**40**	**0.065**
193	*Ir*	*He*	*Bi*	*0.5*	*100*	*10*	*40*	*0.062*
194	*Pt*	*He*	*Bi*	*0.5*	*100*	*10*	*40*	*0.064*
195	**Pt**	**He**	**Bi**	**0.5**	**100**	**10**	**40**	**0.066**
200	*Hg*	*He*	*Bi*	*2*	*15*	*1.5*	*6*	*0.059*
201	**Hg**	**He**	**Bi**	**2**	**15**	**1.5**	**6**	**0.060**
202	*Hg*	*He*	*Bi*	*2*	*15*	*1.5*	*6*	*0.061*
206	*Pb*	*He*	*Bi*	*0.5*	*10*	*1*	*4*	*0.013*
207	*Pb*	*He*	*Bi*	*0.5*	*10*	*1*	*4*	*0.014*
208	**Pb**	**He**	**Bi**	**0.5**	**10**	**1**	**4**	**0.011**

Low limits of detection are particularly important for some of the potentially toxic trace elements defined in USP<232>, notably As, Cd, Hg and Pb. Calibrations for these elements in He mode are shown in Figure 1, together with Pd and Pt, which are representative of the PGEs that USP<232> requires to be monitored if they may have been added as process catalysts during production.

Of the elements for which calibrations are shown in Figure 1, it should be noted that low concentrations of Hg, Pd and Pt are only stable for extended periods if the sample matrix contains a complexing agent, such as the 0.5% HCl added to all of the solutions measured for this validation test. In the absence of HCl, these chemically less stable elements often exhibit raised backgrounds, incomplete washout, non-linear calibrations and poor recoveries.

The system suitability check procedure described in USP<233> is essentially the same regardless of the analytical technique used for the analysis, and requires that a standardization solution at 2J (2 times the control limit corrected for sample dilution) is measured before and after the sample batch. The drift between these 2 solutions must not exceed 20%.

In order to confirm the long-term stability of the 7700x ICP-MS method, we used the 2J standard solution as a continuing calibration verification (CCV) QC check interspersed periodically between the samples during the 7 hour sequence. The results for the gelcap sample sequence are summarized in Table 4, demonstrating that the initial calibration remained valid throughout the sequence, with RSDs of 3% or less for all analytes. Overall drift was less than 7.5% for all elements and less than 2% for many. This demonstrates the robustness and ease of operation of the 7700x for the routine analysis of pharmaceutical samples following closed-vessel microwave digestion.

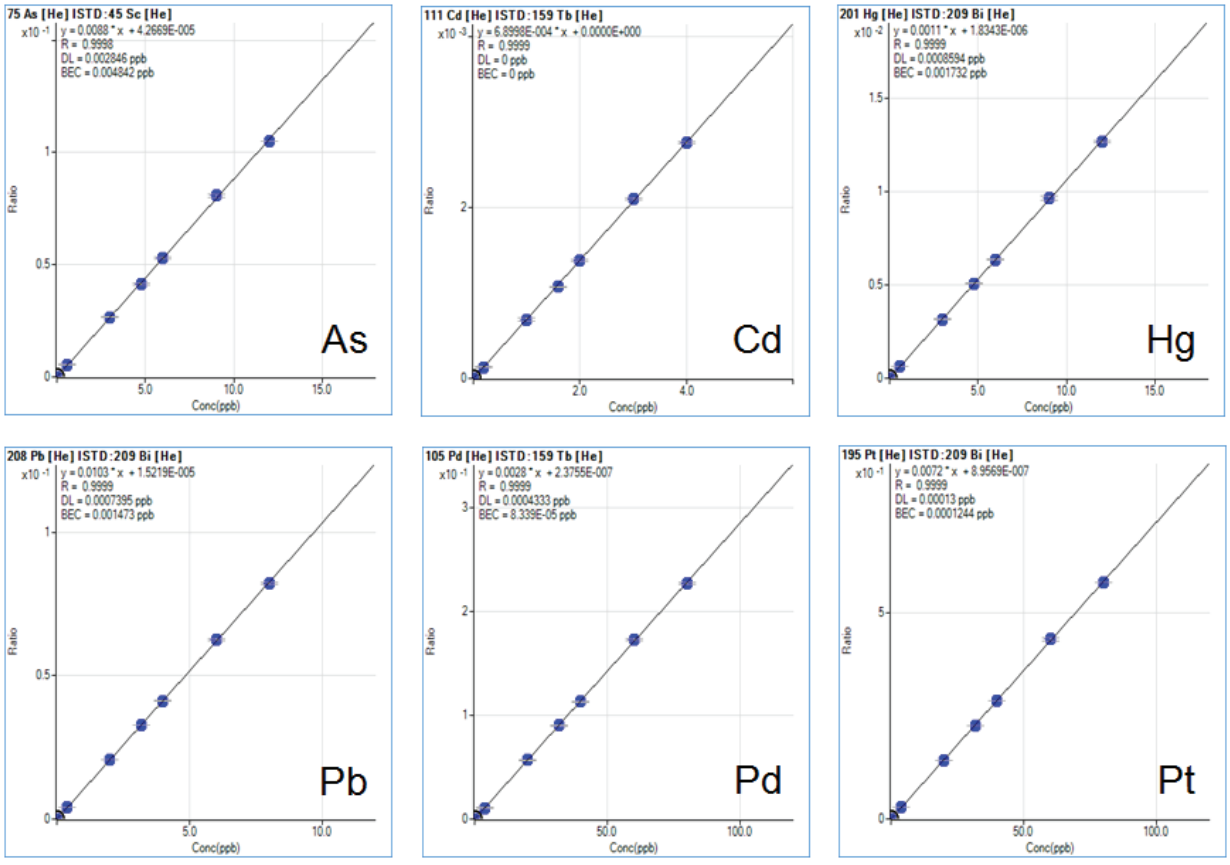

Figure 1. Calibrations for As, Cd, Hg, Pb, Pd and Pt in He mode, demonstrating limits of detection of 1 ng/L or below, and good sensitivity and linearity for all elements including Hg, Pd and Pt, which require stabilization in HCl

Table 4. Instrument validation check. Stability and drift for gelcap samples spiked at 2J.

Mass	Element	2J actual values	Measured mean (n=6)	% RSD	Drift (%)	Limit
51	V	200	202.3	0.6	-0.3	20%
52	Cr	200	202.0	0.6	-0.5	20%
53	Cr	200	202.9	0.9	-0.5	20%
55	Mn	2000	2025.8	1.2	2.6	20%
60	Ni	200	202.3	0.7	-0.9	20%
62	Ni	200	201.9	0.8	-1.5	20%
63	Cu	2000	2105.4	2.8	7.0	20%
65	Cu	2000	2112.4	3.1	7.5	20%
75	As	12	12.2	0.8	-1.7	20%
95	Mo	200	202.2	0.5	-0.5	20%
97	Mo	200	202.2	0.6	-0.5	20%
101	Ru	80	80.6	0.9	2.1	20%
103	Rh	80	80.3	0.9	2.1	20%
105	Pd	80	80.3	0.8	1.5	20%
111	Cd	4	3.9	0.8	-0.1	20%
114	Cd	4	4.0	0.6	0.0	20%
188	Os	80	78.3	1.3	-2.9	20%
189	Os	80	78.4	1.2	-2.6	20%
191	Ir	80	81.6	1.5	3.6	20%
193	Ir	80	81.7	1.4	3.2	20%
194	Pt	80	82.0	1.6	3.7	20%
195	Pt	80	82.1	1.6	4.0	20%
200	Hg	12	12.2	1.3	3.1	20%
201	Hg	12	12.2	1.6	3.6	20%
202	Hg	12	12.2	1.5	3.2	20%
206	Pb	8	8.0	0.6	0.9	20%
207	Pb	8	8.0	0.6	1.1	20%
208	Pb	8	8.0	0.6	1.2	20%

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

Method validation for limit procedures

Limit procedures require demonstration that the analytical method is capable of accurate spike recovery, and can distinguish between a test sample spiked at the Target Concentration (1J) and a sample of the same material spiked at 80% of the Target Concentration (0.8J). Spike recovery is assessed by comparing the measured result for a sample spiked at 1J, against a standard solution prepared at 1J. The spiked sample mean result must be within ±10 of the standard solution, and the result for the sample spiked at 0.8J must be less than the result for the sample spiked at 1J.

Results for the limit procedure validation of gelcaps measured using ICP-MS are shown in Table 5. The mean results for 6 external repeats of the standard at 1J, 6 gelcap samples spiked at 1J, and 6 gelcap samples spiked at 0.8J are presented. The results confirm excellent accuracy and repeatability, easily within the validation requirements for both spike recovery and discrimination between the 1J and 0.8J spike levels. Specificity is also demonstrated through the use of secondary isotopes where available, to confirm unequivocal assessment of each target element in the presence of other analytes and the matrix components.

Method validation for quantitative procedures

Quantitative procedures must demonstrate accurate spike recovery (between 70% and 150% of the spike value) for the mean of 3 samples spiked at concentrations ranging from 50% to 150% of the J value (0.5J to 1.5J) for each target element. In this validation, we used spikes at 0.5J and 1.5J, in addition to the 0.8J and 1J spikes measured for the limit procedure discussed above. 6 separate (external) samples were prepared and analyzed for each spike level.

Repeatability must be demonstrated by an external precision not more than 20% RSD for 6 separate samples spiked at the indicated levels. Ruggedness must also be assessed and must be shown to be not more than 20% RSD when the repeatability test is repeated either on different days, on different instruments, or by different analysts. As with limit procedures, specificity must be demonstrated through unequivocal assessment of each target element (that is, confirmation of the result using a secondary isotope).

Table 5. Accuracy of spike recovery at 1J in gelcaps, and discrimination between spikes at 1J and 0.8J (n=6 for each sample)

Mass	Element	Standard at 1J (n=6)		Sample at 1J (n=6)		Recovery (%)	Sample at 0.8J (n=6)		Detectability
		Mean (ppb)	%RSD	Mean (ppb)	%RSD		Mean (ppb)	%RSD	0.8J/1J (%)
51	V	103.0	1.1	104.9	1.0	102	84.05	1.7	80
52	Cr	102.5	1.0	104.1	1.0	102	83.42	1.8	80
53	Cr	102.8	1.5	104.4	1.2	102	83.71	1.5	80
55	Mn	966.4	0.9	978.3	0.8	101	804.4	1.7	82
60	Ni	103.1	1.2	105.1	1.1	102	84.39	1.9	80
62	Ni	102.3	1.0	104.8	1.1	102	83.85	1.8	80
63	Cu	1090	1.0	1106	1.3	102	868.0	1.7	79
65	Cu	1113	0.9	1127	1.2	101	909.6	1.5	81
75	As	5.93	1.6	6.18	2.4	104	4.98	3.3	81
95	Mo	102.5	1.0	105.2	1.2	103	84.23	1.8	80
97	Mo	102.6	1.1	105.3	1.3	103	84.25	1.8	80
101	Ru	40.58	3.7	40.88	3.5	101	33.02	1.9	81
103	Rh	40.65	3.6	40.97	3.5	101	33.21	2.0	81
105	Pd	40.23	3.6	40.66	3.4	101	32.93	1.8	81
111	Cd	1.98	3.6	2.00	3.8	101	1.62	2.7	81
114	Cd	2.00	3.9	2.01	3.2	100	1.63	2.2	81
188	Os	34.10	0.8	35.24	1.1	103	28.02	1.7	80
189	Os	34.16	0.8	35.26	1.0	103	28.04	1.6	80
191	Ir	41.91	0.8	41.80	1.2	100	33.15	1.8	79
193	Ir	42.02	0.6	41.92	1.3	100	33.22	1.6	79
194	Pt	42.50	0.8	42.25	1.1	99	33.35	2.0	79
195	Pt	42.51	0.6	42.23	1.1	99	33.31	1.9	79
200	Hg	6.31	0.6	6.27	0.8	99	4.99	1.5	80
201	Hg	6.29	0.8	6.27	0.9	100	4.97	1.8	79
202	Hg	6.29	0.8	6.25	0.9	99	4.97	1.7	80
206	Pb	4.09	0.8	4.11	1.0	100	3.29	1.4	80
207	Pb	4.09	0.6	4.11	1.0	100	3.30	1.9	80
208	Pb	4.09	0.9	4.12	0.8	101	3.30	1.8	80

Table 6 shows the summary results for the ICP-MS quantitative analysis of gelcaps, with 6 replicates for each spike level. All results presented were easily within the method validation requirements specified in USP<233>. Spike recoveries were all well within the required limits (70% to 150%) and repeatability was in the low % level, easily meeting the required acceptance criteria of not more than 20% RSD.

Table 7 shows the results for the repeated analysis on a different day, demonstrating the ruggedness of the method with results differing by less than 10% between the two days (less than 7.5% RSD), well within the ruggedness criteria of not more than 20% RSD. The data in Table 9 show only the ruggedness comparison for the two sets of results for the 0.5J spikes, but these are representative of the good agreement between the two sets of results at all spike levels.

Table 6. Accuracy of spike recovery and precision at 0.5J and 1.5J in gelcap samples (n=6 for each sample)

Mass	Element	Sample at 0.5J (n=6)			Recovery	Sample at 1.5J (n=6)			Recovery
		Actual (ppb)	Mean (ppb)	%RSD	(%)	Actual (ppb)	Mean (ppb)	%RSD	(%)
51	V	50	52.84	1.6	106	150	157.4	1.6	105
52	Cr	50	52.63	2.3	105	150	155.9	1.4	104
53	Cr	50	52.74	2.2	106	150	157.2	1.6	105
55	Mn	500	524.0	1.7	105	1500	1696	1.1	113
60	Ni	50	52.96	1.9	106	150	155.9	1.5	104
62	Ni	50	52.72	1.9	105	150	156.1	1.5	104
63	Cu	500	523.9	1.7	105	1500	1733	1.4	116
65	Cu	500	524.0	1.2	105	1500	1727	1.4	115
75	As	3	3.21	3.9	107	9	9.53	3.2	106
95	Mo	50	52.61	1.8	105	150	157.5	1.5	105
97	Mo	50	52.65	1.6	105	150	157.1	1.4	105
101	Ru	20	20.75	2.0	104	60	62.64	1.2	104
103	Rh	20	20.91	2.0	105	60	62.57	1.2	104
105	Pd	20	20.77	2.2	104	60	62.19	1.2	104
111	Cd	1	1.03	2.7	103	3	3.04	1.2	101
114	Cd	1	1.04	2.5	104	3	3.08	1.3	103
188	Os	20	17.15	1.8	86	60	52.51	1.3	88
189	Os	20	17.17	1.6	86	60	52.63	1.2	88
191	Ir	20	20.56	1.6	103	60	63.33	1.2	106
193	Ir	20	20.63	1.9	103	60	63.42	1.1	106
194	Pt	20	20.63	1.8	103	60	63.77	1.2	106
195	Pt	20	20.64	1.6	103	60	63.87	1.1	107
200	Hg	3	3.09	2.0	103	9	9.51	1.3	106
201	Hg	3	3.09	2.3	103	9	9.47	1.0	105
202	Hg	3	3.08	1.9	103	9	9.47	1.3	105
206	Pb	2	2.08	1.9	104	6	6.21	1.5	104
207	Pb	2	2.08	1.9	104	6	6.22	1.4	104
208	Pb	2	2.08	2.1	103	6	6.20	1.1	103

Conclusions

The new methodology for the preparation and analysis of pharmaceutical samples described in the draft General Chapters USP<232>/<233> provides an opportunity for pharmaceutical laboratories to update their methodology and instrumentation to address the limitations of the current heavy metals limit test (USP<231>). In combination with closed-vessel microwave digestion and sample stabilization using HCl, the Agilent 7700x/7800 ICP-MS is capable of determining all regulated elements at low levels in typical pharmaceutical sample digests. Simple method development and routine operation are provided by the He mode method, which uses a single set of consistent instrument operating conditions for all analytes and samples.

System performance validation delivered data that was easily within the method requirements for accuracy, stability and spike recovery, and detection limits were all several orders of magnitude lower than the levels at which the trace elements are controlled. This provides the reassurance that the 7700x/7800 will be able to meet the regulatory requirements for pharmaceutical materials regulated under USP methods, even if control limits are significantly reduced in the future.

Table 7. Ruggedness check. Comparison of 0.5J gelcap spikes run on 2 different days (n=6 for each sample).

Mass	Element	%J actual values (ppb)	Day 1 mean (ppb), n=6	Day 2 mean (ppb), n=6	% Difference (Day2/Day 1)	%RSD (of means)	%RSD (n=12)
51	V	50	52.84	50.78	-3.91	2.8	2.4
52	Cr	50	52.63	50.23	-4.56	3.3	2.9
53	Cr	50	52.74	49.60	-5.96	4.3	4.1
55	Mn	500	524.0	517.4	-1.25	0.9	1.4
60	Ni	50	52.96	50.75	-4.16	3.0	2.6
62	Ni	50	52.72	50.84	-3.56	2.6	2.8
63	Cu	500	523.9	525.1	0.22	0.2	1.3
65	Cu	500	524.0	524.1	0.02	0.0	1.0
75	As	3	3.21	3.04	-5.06	3.7	5.2
95	Mo	50	52.61	48.88	-7.09	5.2	4.3
97	Mo	50	52.65	49.54	-5.89	4.3	4.2
101	Ru	20	20.75	18.79	-9.44	7.0	5.7
103	Rh	20	20.91	18.99	-9.15	6.8	5.4
105	Pd	20	20.77	19.00	-8.51	6.3	5.1
111	Cd	1	1.03	0.98	-5.30	3.8	3.5
114	Cd	1	1.04	0.98	-5.99	4.4	3.7
188	Os	20	17.15	18.70	9.01	6.1	7.3
189	Os	20	17.17	18.71	8.95	6.1	7.1
191	Ir	20	20.56	18.86	-8.27	6.1	4.7
193	Ir	20	20.63	18.91	-8.37	6.2	4.8
194	Pt	20	20.63	18.82	-8.74	6.5	5.0
195	Pt	20	20.64	18.76	-9.10	6.7	5.2
200	Hg	3	3.09	2.90	-6.41	4.7	3.7
201	Hg	3	3.09	2.89	-6.44	4.7	3.9
202	Hg	3	3.08	2.89	-6.22	4.5	3.7
206	Pb	2	2.08	1.99	-4.55	3.3	2.8
207	Pb	2	2.08	1.99	-4.53	3.3	2.8
208	Pb	2	2.08	1.98	-4.55	3.3	2.9

Unequivocal identification and quantification of all 16 analytes regulated in USP<232> is provided using He mode on the 7700x/7800. He mode removes potential interferences from all isotopes of the analytes, thereby making secondary or qualifier isotopes available for confirmation of the result reported at the primary isotope. The 7700x/7800 also provides a full mass spectrum screening capability, is tolerant of all commonly-used organic solvents, and can be linked to a chromatography system to provide integrated separation and analysis of the different forms or species of As and Hg, as required under USP<232>.

In parallel with the development of the new General Chapters <232>/<233>, USP also created a new draft General Chapter <2232>, which deals with the regulation of Elemental Contaminants in Dietary Supplements that are labelled as conforming to USP or NF (National Formulary) standards. The July 2010 revision of USP<2232> [6] contains PDE limits only for the four most toxic elements: arsenic, cadmium, lead, and mercury. The Elemental Limits defined in USP<2232> for individual components of dietary supplements are the same as the component limits for pharmaceutical products detailed in USP<232> (shown in Table 3). USP<2232> also requires that speciation

analysis be carried out if the total concentration of either As or Hg exceeds the individual component limit.

The sample preparation and performance-based Agilent 7700x/7800 ICP-MS methodology outlined in this note can equally well be applied to regulated analysis of dietary supplements under USP<2232>, including the speciation methods for As and Hg.

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Verified for Agilent
7800 ICP-MS

Results presented in this document were obtained using the 7700x, but performance is also verified for the 7800 ICP-MS.

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