Application Note
Pharmaceuticals

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Validating performance of an Agilent ICP-MS for USP <232>/<233> & ICH Q3D(R2)/Q2(R1)

Reducing the time and expense of ICP-MS method development and system validation for measuring elemental impurities in pharmaceuticals

Authors

Lindsey Whitecotton, Ed McCurdy, Craig Jones and Amir Liba
Agilent Technologies Inc. USA

Samina Hussain, Exova USA

Introduction

Worldwide, regulatory authorities are responsible for ensuring that pharmaceutical products are both effective and safe. To achieve this, potentially toxic and harmful contaminants – including elemental impurities – must be identified, and limits defined for their maximum allowable intake. Limits for impurities are defined by national and regional bodies such as the United States Pharmacopeial Convention (USP), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and the European, Chinese and Japanese Pharmacopoeias (Ph. Eur. ChP and JP). With increasing awareness of the potential harmful effects of inorganic contaminants, many of these organizations have reviewed and updated their approach to monitoring elemental impurities in drug products. The most recent standards are defined in ICH guideline Q3D(R2) (*1*) and USP National Formulary (NF) chapter <232> (*2*). These chapters include an extensive list of elemental impurities that must be monitored and controlled, with lower limits for the most toxic elements. A related USP chapter, USP<2232>, covers the determination of inorganic arsenic, cadmium, lead, total mercury and methylmercury in dietary supplements (*3*).

Validation of procedures for drug product analysis is described in ICH guideline Q2(R1) "Validation of Analytical Procedures: Text and Methodology" (*4*). USP<233> (*5*) references the equivalent USP guideline, Chapter <1225> Validation of Compendial Procedures (*6*), which is harmonized with the ICH document. These chapters recommend the use of modern ICP instruments in place of the subjective and unreliable wet chemical and colorimetric tests defined in the previous Heavy Metals chapters, European Pharmacopeial Convention (Ph. Eur.) chapter 2.4.8 and USP <231>.

Many labs that perform pharmaceutical analyses may be unfamiliar with ICP techniques. Agilent provides a comprehensive workflow solution that focuses on ease of use, from sample preparation to method setup, analysis, and reporting. Since revised methods for elemental impurity testing were first proposed more than 10 years ago, Agilent has been a leading provider of instrumentation, guidance and technical support for companies setting up to perform elemental impurity analysis. Agilent ICP-MS systems are widely used and trusted in the pharmaceutical industry, delivering reliable and high-quality data, backed up by market-leading support, qualification services, and compliance solutions.

The regulated elements and permitted daily exposure (PDE) limits for the ICH and USP methods are shown in Table 1. The elements that should be included in the product risk assessment and the PDEs that apply for each element depend on the type of pharmaceutical product and the route of administration. For example, the Class 1 and Class 2A elements must be assessed in all products, while the Class 3 elements should be assessed as appropriate for parenteral and inhalational drugs. Any element that has been added intentionally or may have been introduced inadvertently should be included in the risk assessment. Drug products intended for parenteral or inhalational administration have PDEs that are mostly much lower than the limits for drugs intended for oral or cutaneous administration. Medicines intended for application via other routes, such as topical or mucosal, are not specifically mentioned in the new chapters, based on the assumption that elemental impurities are only absorbed to a limited degree (<5%) through such routes of application (*7*). However, earlier revisions of USP<232> suggested the oral PDE limits could be used for topical and mucosal medicines.

Table 1. USP <232> and ICH Q3D(R2) PDE limits for elemental impurities in drug products.

Element	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalational PDE (µg/day)	Cutaneous PDE (µg/day)
ICH/USP Class 1				
Cd – Cadmium	5	2	3 (2)[1]	20
Pb – Lead	5	5	5	50
As – Arsenic (inorganic)	15	15	2	30
Hg – Mercury (inorganic)	30	3	1	30
ICH/USP Class 2A				
Co – Cobalt	50	5	3	50(35)[3]
V – Vanadium	100	10	1	100
Ni – Nickel	200	20	6(5)[2]	200(35)[3]
ICH/USP Class 2B				
Tl – Thallium	8	8	8	8
Au – Gold	300 (100)[2]	300(100)[2]	3(1)[2]	3000
Pd – Palladium	100	10	1	100
Ir – Iridium	100	10	1	100
Os – Osmium	100	10	1	100
Rh – Rhodium	100	10	1	100
Ru – Ruthenium	100	10	1	100
Se – Selenium	150	80	130	800
Ag – Silver	150	15 (10)[2]	7	150
Pt – Platinum	100	10	1	100
ICH/USP Class 3				
Li – Lithium	550	250	25	2500
Sb – Antimony	1200	90	20	900
Ba – Barium	1400	700	300	7000
Mo – Molybdenum	3000	1500	10	15000
Cu – Copper	3000	300	30	3000
Sn – Tin	6000	600	60	6000
Cr – Chromium	11000	1100	3	11000

Permitted daily exposure (PDE) limits for elemental impurities according to each route of exposure. Shaded cells indicate where an elemental impurity should be included in the risk assessment if not intentionally added.

1. ICH Q3D (R1, 2019) PDE for Cd. USP <232>/<233>value (in parentheses)
2. ICH Q3D (R2, 2022) PDEs for Ag, Au, and Ni. USP <232>/<233>values (in parentheses)
3. Cutaneous and transcutaneous concentration limit, µg/g, (in parentheses) for sensitizers

Validating the suitability of an analytical procedure for the ICH/USP general chapters is based on performance testing, and includes requirements to demonstrate accuracy, sensitivity, specificity and reproducibility. Specificity is a requirement of method validation in ICH Q2(R1) and USP<1225> and relates to the ability of the procedure to provide unequivocal assessment of analytes in the presence of other elements and interferences that may arise from the sample matrix. In this paper, we present data to illustrate the validation of a procedure for the measurement of elemental impurities in several pharmaceutical ingredients, following the criteria defined in ICH Q3D/Q2(R1) and USP<232>/<233>.

Experimental

USP<233> defines the sample preparation and method validation procedures that should be used for system suitability testing of any instrumentation used for the analysis of elemental impurities in pharmaceutical materials (*5*).

In this study, system suitability tests were run using samples of hypromellose (a semisynthetic polymer used in eye drops and as a component of many other medicines), and sodium carbonate (Na_2CO_3), an alkalinizing agent used in products such as antacid formulations. For materials like these, which have multiple uses and are found in several different drug products, pharmaceutical laboratories may choose to perform the product risk assessment using the lower PDE limits that apply to parenteral medicines.

For each sample, spikes containing all the regulated elements were added at the appropriate concentrations for the parenteral limits (0.5 J, 0.8 J, 1.0 J, and 1.5 J), to allow all system suitability tests to be performed. A 1.5 J drift check QC standard was prepared using the oral PDE limits; this standard was used to demonstrate that the ICP-MS instrument used can accurately determine higher concentration analytes as well as trace level elements.

Sample Preparation

Some pharmaceutical products and raw materials may be analyzed neat (as is); however, many will require solubilization in aqueous solution (i.e. water, typically with the addition of acids to stabilize the elements in solution) or organic solvents. Other sample types are insoluble and will require acid digestion; USP<233> specifies the use of "concentrated acids" for digestion. Closed vessel microwave digestion is the recommended procedure to ensure that volatile elements are retained when high temperature and pressure are required to fully solubilize the sample material.

The hypromellose and Na_2CO_3 samples measured in this study were found to yield clear solutions with relatively low temperature acid digestion or room temperature solubilization. The procedures used are shown in Table 2.

The development of the Agilent ICP-MS ORS collision/reaction cell with helium collision mode means that chloride-based polyatomic interferences can be removed effectively and reliably. As a result, HCl is now commonly used for ICP-MS sample stabilization, especially when the analyte list includes elements such as Hg and the platinum group elements (PGEs), which are more chemically stable in the presence of chloride ions. Some analytes, such as Os, can benefit from a higher concentration of HCl (3%, as used in this work, or more) to ensure long-term solution stability.

The ICH/USP chapters do not specifically require that post-digestion sample stability is determined, but sample stability over several days is a common requirement in the pharmaceutical industry and has been discussed by the FDA and ICH.

Table 2. Acid digestion method used for preparation of hypromellose and Na_2CO_3 samples.

Hypromellose	
Sample/acid	
Sample weight	0.5 g
Add HNO_3	1.0 mL
Add HCl	3.0 mL
Hot block Digestion	
Digest (110 °C)	30 minutes
Cool	
Add H_2O_2	0.5 mL
Digest (110 °C)	15 minutes
Cool	
Add internal standards	Sc, Y, In, Tb
Final Dilution	
De-Ionized Water	To 100 g
Total dilution factor	200x
Na_2CO_3	
Sample/acid	
Sample weight	0.5 g
Add H_2O	30 mL
Add HNO_3	1.0 mL
Add HCl	3.0 mL
Room Temp. Digestion	
Add internal standards	Sc, Y, In, Tb
Final Dilution	
De-Ionized Water	To 100 g
Total dilution factor	200x

Instrumentation

Measuring elemental impurities in pharmaceutical materials is a well-established application for Agilent ICP-MS systems. Previous work (*8*) was performed using an earlier model of ICP-MS and the elemental impurity limits published in the May 2011 draft of USP<232>/<233>, before the limits were harmonized with those published in ICH Q3D. Subsequent revisions (R1) and (R2) to ICH Q3D have raised the limits for certain impurities.

In this study, data was collected using an Agilent 7800 ICP-MS system and the method is also applicable to the Agilent 7850, which is the successor to the 7800. Additional data was also collected using an Agilent 7900 ICP-MS to provide the second batch for evaluation of the Intermediate Precision test requirement. The Agilent 7800 instrument was equipped with the standard glass concentric nebulizer, quartz spray chamber and torch, and nickel interface cones. The system was optimized using the autotuning functions, and major instrument settings were predefined in the preset method for ICH/USP, which is provided in the ICP-MS MassHunter software. The 7800 operating conditions are shown in Table 3.

Table 3. Agilent 7800 operating conditions for the analysis of pharmaceutical samples. Most settings are predefined in the preset method.

Parameter	Value
Plasma mode	General Purpose, robust
RF forward power (W)	1550
Sampling depth (mm)	10
Carrier gas flow (L/min)	1.05
Spray chamber temperature (°C)	2
Extraction lens 1 (V)	0
Kinetic energy discrimination (V)	5
He cell gas flow (mL/min)	5

The Agilent 7800 or 7850 system is particularly well-suited for the analysis of elemental impurities in pharmaceutical samples. The system embodies the concept of easy-to-use, workflow-based operation, with most method parameters and instrumental settings being auto-optimized or predefined in the USP/ICH preset method template. This simplifies method setup and routine operation, while also ensuring consistent high performance regardless of operator expertise. Key features that support pharmaceutical analytical requirements include:

- A very high temperature, robust plasma 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 poorly-ionized PGEs: Os, Ir, and Pt.
- For very high matrix samples, the proprietary ultra high matrix introduction (UHMI) technology provides automated, calibrated and consistent aerosol dilution. UHMI allows the Agilent ICP-MS to routinely analyze samples that contain percent levels of total dissolved solids – many times higher than the typical limit for ICP-MS systems without UHMI.
- A fourth generation octopole-based collision/reaction cell (ORS^4), optimized for helium (He) collision mode, which is acknowledged as the most reliable and effective way to remove multiple polyatomic interferences from multiple analytes. He mode provides lower detection limits and more accurate results in complex and variable sample matrices (*9*). He mode also allows access to secondary or qualifier isotopes (*10*), which can be used to unequivocally identify and confirm the accuracy of results for many analytes, as required in ICH Q2(R1), USP<233> and USP<1225> (validation of compendial procedures).
- The 7800 or 7850 can also analyze all the solvents commonly used for preparation of pharmaceutical samples (*11*), and can easily be linked to an HPLC for speciation of As and Hg, if required for confirmation of the concentration of the "inorganic" forms of these elements.
- A rapid IntelliQuant semi-quantitative screening acquisition can also be performed in He mode on the 7800 or 7850, allowing unknown samples to be quickly characterized. Semi-quantitative screening is also extremely useful for the determination of any process contaminants, production failure analysis, and for extractable and leachable (E&L) studies.

The masses (isotopes) used for quantification of each regulated element are shown in Table 4, together with the collision/reaction cell gas mode used. The 7800 was operated in He mode for all analytes and all samples, illustrating the simple method setup and consistent routine operation that are characteristic of Agilent ICP-MS systems running Agilent ICP-MS MassHunter software.

Table 4 also shows the oral dose "J" values, based on a 10 g/day maximum dose and a sample preparation dilution factor of 200 (e.g. 0.5 g in 100 mL). The J values are the PDEs after correction for sample preparation dilution – i.e. the PDE limits (in µg/day) converted to concentrations in the sample solution as analyzed (in µg/mL, ppm). For ease of comparison with ICP-MS figures of merit, the J values in Table 4 have been converted to µg/L (ppb).

The method detection limits (MDLs) of the Agilent 7800 ICP-MS (in µg/L, ppb), calculated from seven separate measurements of the method blank run in the middle of the sample sequence, are shown for comparison. All the MDLs were in the low ng/L (ppt) level in solution except for certain elements (e.g. Cr, Cu, Mo, Sn, and Ba) where a high concentration in the preceding spiked samples may have contributed to a slightly increased blank level. Even these elements gave MDLs in the sub-µg/L (ppb) range.

The MDLs are several orders of magnitude lower than the J values for oral dosage drugs, confirming that the Agilent ICP-MS is suitable for all types of drug products, including parenteral and inhalational medicines, where the PDEs are much lower. MDLs are also easily low enough to satisfy the analytical requirements when large dilutions are required because of low sample mass or sample preparation requirements.

Table 4. Analytes, primary isotopes and cell mode used in this work, together with oral dose PDE limits, J values for a drug product with maximum dose of 10 g/day, prepared at 200 x dilution, and 7800 ICP-MS method detection limits. Note: J values and 7800 MDLs are stated in µg/L (ppb in solution).

Mass	Element	Cell Mode	Oral dosage PDEs (µg/day)	J values (µg/L, ppb) at 200 x dilution; 10 g/day max. dose	7800 MDLs (µg/L, n=7)
7	Li	He	550	275	0.128
51	V	He	100	50	0.063
52	Cr	He	11000	5500	0.396
59	Co	He	50	25	0.003
60	Ni	He	200	100	0.007
63	Cu	He	3000	1500	0.122
75	As	He	15	7.5	0.006
78	Se	He	150	75	0.179
95	Mo	He	3000	1500	0.223
101	Ru	He	100	50	0.004
103	Rh	He	100	50	0.004
105	Pd	He	100	50	0.038
107	Ag	He	150	75	0.005
111	Cd	He	5	2.5	0.001
118	Sn	He	6000	3000	0.298
121	Sb	He	1200	600	0.048
137	Ba	He	1400	700	0.729
189	Os	He	100	50	0.004
193	Ir	He	100	50	0.004
195	Pt	He	100	50	0.004
197	Au	He	100	50	0.207
201	Hg	He	30	15	0.030
205	Tl	He	8	4	0.019
208	Pb	He	5	2.5	0.004

Results

Validation of analytical instruments used for the latest ICH and USP general chapters is performance based, and the criteria for evaluating performance are defined in ICH Q2(R1) and USP<233>. System suitability must be demonstrated by confirming that results remain stable throughout the analytical run. Further system suitability tests are defined in USP<233> for "Limit Procedures" and "Quantitative Procedures". Limit procedures must demonstrate acceptable performance for detectability, precision, specificity; Quantitative procedures must demonstrate acceptable performance for accuracy, precision (repeatability and ruggedness), specificity, limit of quantitation, range, and linearity. These tests are broadly comparable to the tests defined in the ICH guideline for Validation of Analytical Procedures, Q2(R1). The system suitability test results reported in this work followed the tests described in USP<233>, using the analyte list and PDEs defined for oral drug products in the final version of USP<232>.

The extended batch of samples, which ran for more than nine hours, included various sample types and excipients that are used in several different drug products. The long-term stability (drift) QC check was based on the oral PDE limits. Since the samples analyzed can be used in medications intended for other routes of administration, the lower parenteral PDE limits and J values from USP<232> were used for the calibration standards and spike levels added to the samples.

Drift check

Signal drift is assessed by comparing the results obtained for a standard at 1.5 J run before and after the sample analysis. System suitability is demonstrated by drift that does not exceed 20% for each target element. The results for the 1.5 J standards run before and after the samples are shown in Table 5; all drift results were well within the 20% limit, with most elements showing signal drift of less than 3%.

The sequence represents the mixed sample types that a typical production laboratory might expect to analyze on a routine basis, The 1.5 J standard was repeated periodically throughout the run, allowing the precision of the QC check to be established. While not a required performance check, this figure is included for information in Table 5. RSDs were mostly in the range of 2 or 3% over the course of the sequence. This confirms that the initial calibration remained valid throughout the analysis batch, despite the varied sample matrices run. The excellent stability of the 1.5 J QC standard demonstrates the robustness and ease of operation of the 7800 for routine analysis of pharmaceutical samples following acid digestion.

Table 5. Drift check for 1.5 J standards (oral PDEs) run before and after sample batch. All results were within the required limit of not more than 20% drift.

					1.5 J Measured Result (µg/L)			
Mass	Element	Cell Mode	Oral dosage PDEs (µg/day)	1.5 J actual values* (µg/L)	Before samples	After samples	Drift (%)	%RSD (n=12)
7	Li	He	550	412.5	399.4	412.5	3.3	5.1
51	V	He	100	75	74.4	73.6	-1.1	1.8
52	Cr	He	11000	8250	8135.9	8155.0	0.2	2.0
59	Co	He	50	37.5	36.6	37.2	1.6	2.3
60	Ni	He	200	150	146.2	148.3	1.5	2.5
63	Cu	He	3000	2250	2227.7	2221.2	-0.3	2.8
75	As	He	15	11.25	10.9	10.7	-2.0	1.6
78	Se	He	150	112.5	113.6	107.5	-5.4	3.3
95	Mo	He	3000	2250	2133.6	2244.7	5.2	3.8
101	Ru	He	100	75	76.6	72.1	-5.9	3.1
103	Rh	He	100	75	73.2	75.4	3.0	3.8
105	Pd	He	100	75	72.3	74.7	3.3	3.7
107	Ag	He	150	112.5	114.0	108.7	-4.7	2.6
111	Cd	He	5	3.75	3.7	3.7	-1.4	2.4
118	Sn	He	6000	4500	4326.7	4513.2	4.3	2.9
121	Sb	He	1200	750	724.9	751.3	3.6	2.6
137	Ba	He	1400	1050	1055.3	1014.2	-3.9	2.9
189	Os	He	100	75	73.5	73.6	0.1	1.3
193	Ir	He	100	75	73.2	74.8	2.2	3.7
195	Pt	He	100	75	72.6	73.6	1.5	2.0
197	Au	He	100**	75	70.5	70.6	0.1	1.6
201	Hg	He	30	22.5	21.7	22.1	1.9	2.2
205	Tl	He	8	6	5.7	5.8	1.3	1.5
208	Pb	He	5	3.75	3.6	3.7	1.7	1.7

**J values for oral dosage medicine with maximum daily dose of 10 g, prepared at 200x dilution.*
***Oral dosage PDE for gold has been revised to 300 µg/day in ICH Q3D(R2). The lower USP<232> limit was used in this work.*
n=3 for all samples except %RSD (n=12)

Limit procedures

Detectability for limit procedures is demonstrated through comparison of the results for a sample spiked with the target elements at concentrations of 1 J and 0.8 J (100% and 80% of the target values). For instrumental procedures, the mean concentration (n=3) of the samples spiked at 1 J must be within ±15% of the concentration measured in the 1 J standard. Also, the samples spiked at 0.8 J must give a mean value that is lower than the concentration measured in the 1 J standard. The 7800 results are shown in Table 6, demonstrating that all results passed the acceptance criteria for detectability.

Precision (repeatability). Instrumental limit procedures must also meet acceptance criteria for precision (repeatability) by achieving a relative standard deviation of not more than 20% for six independent samples spiked at 1 J. The 7800 results for this test are also shown in Table 6; most RSDs were less than 2%, confirming that the precision criteria were easily met.

Table 6. Agilent 7800 results for accuracy and detectability at parenteral spike levels of 0.8 J and 1 J in hypromellose, demonstrating system suitability for limit procedures: Accuracy (limit of ±15%) for 1 J spike, and detectability (0.8 J spike must be less than 1 J standard). Precision for limit tests is also shown (RSD must not be more than 20%). The shaded cells indicate the secondary or 'qualifer' isotopes.

Mass	Element	True 1J (µg/L)	1J Standard	1J Spike (µg/L)*	% Recovery	0.8J Spike (µg/L)*	0.8J Spike/1J Standard	1J Spike %RSD (n=6)
7	Li	25	25.34	21.73	85.8	17.23	68.0	1.51
51	V	1	1.00	0.96	96.9	0.76	76.2	0.79
52	Cr	110	109.72	99.48	90.7	79.63	72.6	0.85
53	Cr	110	110.36	99.75	90.4	79.35	71.9	0.94
59	Co	0.5	0.50	0.44	88.9	0.35	70.8	1.21
60	Ni	2	2.01	1.82	90.5	1.44	71.7	0.82
62	Ni	2	2.02	1.80	89.1	1.43	70.8	2.21
63	Cu	30	30.09	26.40	87.7	20.75	69.0	1.10
65	Cu	30	30.38	26.64	87.7	21.05	69.3	1.07
75	As	1.5	1.47	1.54	104.6	1.23	83.3	0.87
78	Se	8	8.33	8.95	107.5	7.31	87.8	1.75
82	Se	8	8.29	8.85	106.7	7.47	90.1	2.12
95	Mo	150	153.83	147.67	96.0	117.37	76.3	1.52
97	Mo	150	153.76	146.55	95.3	116.83	76.0	1.58
101	Ru	1	1.01	0.90	89.6	0.73	72.2	1.03
103	Rh	1	1.00	0.99	98.7	0.81	80.6	0.82
105	Pd	1	0.99	0.94	94.8	0.75	76.3	1.00
107	Ag	1	1.05	0.96	91.4	0.77	73.3	1.51
109	Ag	1	1.03	0.95	92.0	0.76	74.1	1.92
111	Cd	0.2	0.20	0.20	99.4	0.16	80.5	1.86
114	Cd	0.2	0.21	0.19	93.2	0.16	76.1	0.73
118	Sn	60	61.59	57.50	93.4	45.96	74.6	0.87
121	Sb	9	9.22	9.00	97.6	7.29	79.1	0.98
137	Ba	70	71.74	66.49	92.7	53.32	74.3	1.01
188	Os	1	1.00	1.04	103.5	0.83	83.0	2.70
189	Os	1	1.00	1.03	102.8	0.82	82.2	2.40
191	Ir	1	1.00	1.03	103.0	0.82	82.4	1.89
193	Ir	1	0.99	1.03	104.0	0.83	84.0	1.78
194	Pt	1	1.00	0.92	92.4	0.73	72.9	2.20
195	Pt	1	1.00	0.92	92.0	0.74	74.1	1.45
197	Au	10	9.74	10.06	103.2	7.93	81.5	1.73
200	Hg	0.3	0.31	0.26	86.4	0.19	62.4	1.77
201	Hg	0.3	0.30	0.26	85.9	0.19	61.8	1.56
202	Hg	0.3	0.30	0.26	87.1	0.19	63.1	1.77
205	Tl	0.8	0.78	0.78	99.4	0.61	78.5	2.23
206	Pb	0.5	0.49	0.47	96.3	0.37	75.7	1.36
207	Pb	0.5	0.49	0.46	94.8	0.37	74.9	0.83
208	Pb	0.5	0.49	0.46	94.7	0.37	75.0	1.13

n=3 for all samples except 1J spike stability (n=6)
**Measured spike concentrations are reported after subtraction of the mean result for the unspiked sample*

Specificity, as defined in USP<1225> and ICH Q2(R1), is a test to determine whether the analytical procedure can unequivocally assess the target element in the presence of the sample matrix and other analytes. ICP-MS is an inorganic mass spectrometric technique and is therefore inherently specific; each analyte (element) has at least one isotope which is free from direct overlap by any other element. Other spectral overlaps (primarily molecular or polyatomic ions) are addressed by the Agilent 7800 or 7850 using the ORS[4] collision/reaction cell with helium (He) cell gas. He mode effectively attenuates polyatomic ions by kinetic energy discrimination, removing their contribution at the target analyte mass.

Further confirmation of analyte identity and concentration can be obtained by measuring multiple independent isotopes of the target elements, using the secondary isotope as a qualifier or confirmatory measurement. Table 6 includes 7800 data for these secondary isotopes (shaded in gray) for several elements, confirming good agreement with the results reported from the primary isotopes.

Quantitative procedures

Accuracy for quantitative procedures is demonstrated through measurement of spiked samples at concentrations ranging from 0.5 J to 1.5 J. The acceptance criteria are that the spike recoveries (mean of the concentration measured in three independent samples, corrected for the amount present in the unspiked sample) must be within the range of 70% to 150% of the true spike value at all spike levels. In this work, digested hypromellose samples were spiked at levels of 0.5 J, 1.0 J, and 1.5 J.

The accuracy test is also used to confirm that the procedure meets the method requirements for limits of quantification (LoQ), measurement range, and linearity. Figure 1 displays representative examples of the 7800 ICP-MS calibrations used for the accuracy test. The Class 1 elements (As, Cd, Hg, and Pb) are presented, along with two low-level Class 2A elements (V and Co) and Pd and Pt, which are examples of the PGEs that should be monitored if they may have been added as process catalysts during production.

In all cases, linear calibrations were obtained, with low background equivalent concentrations (BECs) and LoQs in the ng/L (ppt) range. All method requirements for LoQ, range, and linearity were easily met.

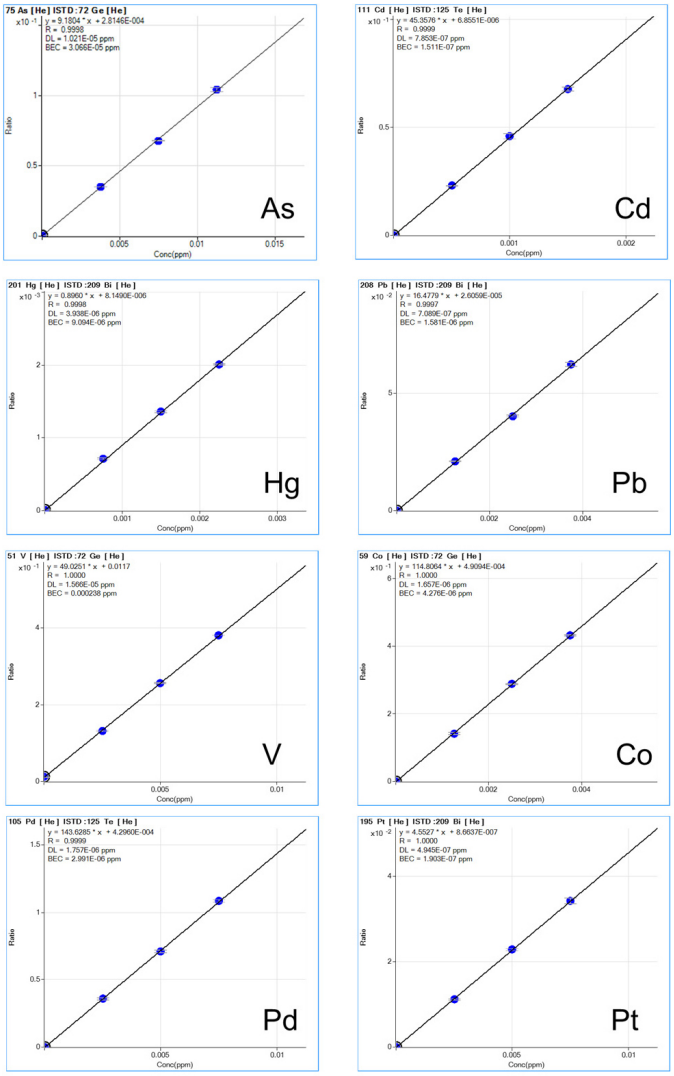
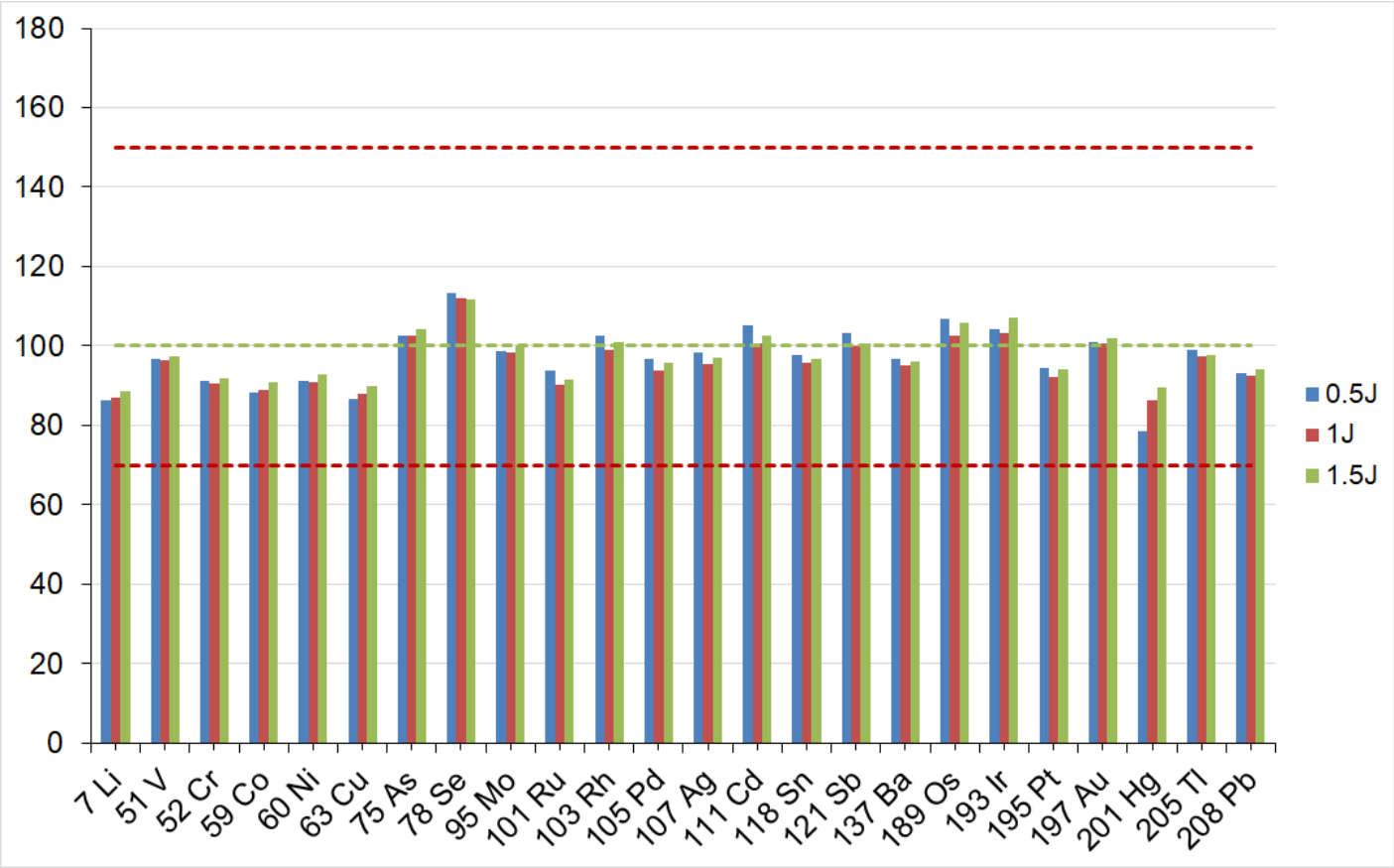


Figure 1. Agilent 7800 calibrations for As, Cd, Hg, Pb, V, Co, Pd, and Pt in He mode, demonstrating limits of quantification in the ng/L range or below, and good sensitivity and linearity for all elements.

Of the calibrations shown in Figure 1, it should be noted that Hg, Pd, and Pt are only stable for extended periods when the sample matrix contains a complexing acid, such as the HCl added to the solutions measured in this work. In the absence of HCl, these elements often exhibit raised backgrounds, non-linear calibrations, and poor recoveries. The low DLs and BECs for V and As also illustrate the effective removal of the chloride-based polyatomic ions (ClO on V at mass 51, and ArCl on As at mass 75) in He mode on the Agilent 7800.

The spike recovery results used to assess accuracy are presented in Figure 2, for spikes at 0.5 J, 1 J, and 1.5 J in the hypromellose samples, based on the parenteral limits and a sample dilution factor of 200. Accurate recoveries, well within the required range of 70% to 150%, were obtained for all target elements at all three spike levels.

Figure 2. Agilent 7800 ICP-MS results for accuracy at parenteral spike levels of 0.5 J, 1 J, and 1.5 J in hypromellose at 200x dilution; n=3. All 7800 results were within the acceptance criteria of 70%-150% recovery, as indicated by the high and low limit lines.



n=3 for all samples except 1 J spike stability (n=6)
**Measured spike concentrations are reported after subtraction of the mean result for the unspiked sample*

Precision (repeatability) is assessed by measuring six independent samples spiked with the target analytes at the target concentration (1 J). The acceptance criteria are for the RSD to be not more than (NMT) 20%. The 7800 results for precision are shown in Table 7, confirming that the six independent results for the 1 J spike had a precision far below the required limit of 20%; most elements had %RSDs around 2% or below.

Intermediate precision (also known as "ruggedness") requires that the repeatability test is run again, either on a different day, with a different instrument, or by a different analyst, with the requirement for the overall precision (n=12) to be not more than 25% RSD. The results for ruggedness are also included in Table 7, where the second set of 6 independent samples was run by a different operator, on a different day, and on a different instrument, an Agilent 7900 ICP-MS. The overall precision of the 12 independent measurements across the two batches was well within the acceptance criteria of not more than 25% RSD,

Spike recoveries and precision (repeatability) at a spike level of 1 J for the Na_2CO_3 samples also measured in the batch are presented in Table 8. This material is used in a variety of drug products, and was also assessed against the PDE limits for parenteral products.

Table 7. Agilent 7800* ICP-MS results for precision at 1 J parenteral spike level in hypromellose at 200x dilution. All results met the acceptance criteria of ≤ 20% RSD for repeatability and ≤ 25% RSD for intermediate precision. The shaded cells indicate the secondary or 'qualifer' isotopes.

			Repeatability (n=6)		Ruggedness (n=12)*	
Mass	Element	True 1J (µg/L)	1J Mean+	%RSD	1J Mean+	%RSD
7	Li	25.0	21.7	1.5	23.5	8.1
51	V	1.0	1.0	0.8	1.0	3.0
52	Cr	110.0	99.5	0.9	107.6	7.9
53	Cr	110.0	99.7	0.9	107.9	7.9
59	Co	0.5	0.4	1.2	0.5	4.5
60	Ni	2.0	1.8	1.2	1.9	4.7
62	Ni	2.0	1.8	3.3	1.9	5.1
63	Cu	30.0	26.4	1.1	28.2	6.7
65	Cu	30.0	26.6	1.1	28.1	5.2
75	As	1.5	1.5	0.9	1.6	1.7
78	Se	8.0	9.0	1.7	9.2	2.2
82	Se	8.0	8.8	2.1	9.4	5.5
95	Mo	150.0	147.7	1.5	146.3	1.9
97	Mo	150.0	146.6	1.6	146.6	1.3
101	Ru	1.0	0.9	1.0	0.9	3.1
103	Rh	1.0	1.0	0.8	1.0	1.0
105	Pd	1.0	0.9	1.2	0.9	1.1
107	Ag	1.0	1.0	1.5	1.0	3.0
109	Ag	1.0	0.9	1.9	1.0	2.9
111	Cd	0.2	0.2	1.9	0.2	5.3
114	Cd	0.2	0.2	0.7	0.2	11.6
118	Sn	60.0	57.5	0.9	59.0	2.9
121	Sb	9.0	9.0	1.0	9.0	1.3
137	Ba	70.0	66.5	1.0	68.5	3.4
188	Os	1.0	1.0	2.7	0.9	10.3
189	Os	1.0	1.0	2.4	0.9	9.4
191	Ir	1.0	1.0	1.9	1.0	2.5
193	Ir	1.0	1.0	1.8	1.0	2.3
194	Pt	1.0	0.9	2.2	1.0	4.2
195	Pt	1.0	0.9	1.5	1.0	4.3
197	Au	10.0	10.1	1.7	10.3	2.8
200	Hg	0.3	0.3	1.8	0.3	2.9
201	Hg	0.3	0.3	1.6	0.3	3.9
202	Hg	0.3	0.3	1.8	0.3	2.8
205	Tl	0.8	0.8	2.2	0.8	2.8
206	Pb	0.5	0.5	1.4	0.5	7.1
207	Pb	0.5	0.5	0.8	0.5	7.6
208	Pb	0.5	0.5	1.1	0.5	2.6

** The second batch included in the ruggedness check was run on an Agilent 7900 ICP-MS, by a different operator, on a different day*
+ Measured spike concentrations are reported after subtraction of the mean result for the unspiked sample

Table 8. Agilent 7800 ICP-MS results for spike recovery and precision at 1 J parenteral spike level in Na_2CO_3 at 200x dilution. All results met the acceptance criteria of recovery within 70% to 150% and RSD (n=6) ≤ 20%. The shaded cells indicate the secondary or 'qualifer' isotopes.

			Na_2CO_3		
Mass	Element	True 1J (µg/L)	1J mean (n=6)+	%RSD	% Recovery
7	Li	25.0	21.0	1.3	83.8
51	V	1.0	1.0	1.3	99.4
52	Cr	110.0	100.9	2.3	91.7
53	Cr	110.0	100.5	1.9	91.4
59	Co	0.5	0.4	2.0	86.9
60	Ni	2.0	1.7	0.8	83.5
62	Ni	2.0	1.7	1.7	84.3
63	Cu	30.0	23.7	2.2	79.1
65	Cu	30.0	24.0	1.9	79.9
75	As	1.5	1.4	1.5	94.6
78	Se	8.0	9.2	2.1	114.6
82	Se	8.0	9.0	2.6	112.3
95	Mo	150.0	146.7	1.3	97.8
97	Mo	150.0	144.6	1.1	96.4
101	Ru	1.0	0.9	1.3	92.0
103	Rh	1.0	1.0	0.9	98.7
105	Pd	1.0	0.9	1.2	92.8
107	Ag	1.0	0.9	1.3	90.4
109	Ag	1.0	0.9	1.4	89.8
111	Cd	0.2	0.2	1.1	98.6
114	Cd	0.2	0.2	2.1	100.5
118	Sn	60.0	59.9	2.0	99.8
121	Sb	9.0	9.4	1.7	104.1
137	Ba	70.0	68.8	1.9	98.2
188	Os	1.0	0.9	8.4	89.7
189	Os	1.0	0.9	7.4	89.1
191	Ir	1.0	1.0	1.2	97.8
193	Ir	1.0	1.0	1.3	98.1
194	Pt	1.0	1.0	1.2	97.8
195	Pt	1.0	1.0	1.3	97.3
197	Au	10.0	9.6	0.7	96.0
200	Hg	0.3	0.3	8.2	87.0
201	Hg	0.3	0.3	9.1	86.2
202	Hg	0.3	0.3	8.9	86.7
205	Tl	0.8	0.8	0.8	97.0
206	Pb	0.5	0.5	1.7	97.1
207	Pb	0.5	0.5	1.9	97.0
208	Pb	0.5	0.5	1.8	96.4

+ Measured spike concentrations are reported after subtraction of the mean result for the unspiked sample

Conclusions

The methodology described in the latest General Chapters USP<232>/<233> and ICH Q3D(R2) provides an opportunity for pharmaceutical laboratories to update their methods and instrumentation to provide more reliable and useful data on elemental impurities in pharmaceutical products. In combination with sample preparation using aqueous solubilization, organic solubilization, or acid digestion an Agilent 7800 or 7850 ICP-MS can determine all regulated elements at the required levels in a range of pharmaceutical samples. Simple method development and routine operation are provided by the robust plasma with UHMI, the ORS^4 collision/reaction cell with standard He mode, and the very wide dynamic range detector (10 orders linear range). These capabilities mean that a variety of acid digested sample types can be analyzed using simple, predefined methods, with the standard instrument configuration, and requiring only a single set of conditions for all analytes. The workflow-based operation of the Agilent ICP-MS vastly reduces the time and expense associated with traditional method development and system validation.

Validation of system suitability delivered data for both limit and quantitative procedures that was easily within the method requirements for accuracy, stability, and spike recovery. Detection limits were all several orders of magnitude lower than the target levels at which the elemental impurities are controlled. This provides the reassurance that the 7800 or 7850 meets the analytical requirements for all types of pharmaceutical materials regulated under the ICH and USP chapters, including drug products and components intended for parenteral or inhalational administration.

Identification and quantification of all 24 target analytes in ICH Q3D(R2) and USP<232> was achieved using a single He cell gas mode on the Agilent 7800. He mode removes potential polyatomic interferences from all isotopes of the analytes, thereby making secondary or qualifier isotopes available for confirmation of the result from the primary isotope; this supports the requirement for the method to be able to "unequivocally assess" each target element.

The Agilent 7800 or 7850 also provides a full mass spectrum screening capability, is tolerant of all commonly-used organic solvents, and can be easily integrated with an HPLC system to provide separation and analysis of the different forms or species of As and Hg. This approach may be required to confirm the levels of the "inorganic" forms of these elements, as specified in ICH Q3D(R2) and USP<232>.

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