Application Note

Pharma & Biopharma

Analysis of Artificial Tear Eye Drops For Elemental Impurities

Using an ICP-MS and USP <232>/<233> and ICH Q3D(R2)/Q2(R1) protocols.

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Introduction

As pharmaceutical products are released to the market, worldwide regulatory agencies have the responsibility to ensure their safety and effectiveness. To meet this obligation, all potential toxic and harmful contaminants, including elemental impurities, must be monitored to ensure drug products comply with the maximum allowable concentrations. This is addressed by agencies such as the United States Pharmacopeia (USP), the International Council for Harmonization of Technical Requirements (ICH), and the European, Chinese, and Japanese Pharmacopoeias (Ph. Eur., CHP, and JP).These various bodies have come together to create comprehensive elemental impurity standards, which are defined in ICH guideline Q3D(R2) (*1*) and USP National Formulary (NF) chapter <232> (*2*).

The latest ICH and USP methods specify 24 elements to be monitored that have permitted daily exposure (PDE) in µg/day assigned based on the methods provided by USP and ICH. Table 1 shows the regulated elements and PDEs for the ICH and USP methods.

Table 1. ICH Q3D(R2) and USP <232> PDE limits for 24 monitored 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

Depending on which pharmaceutical product is used and how it is administered, the elements included in the product risk assessment and the PDEs relating to each element can vary. While all products must be assessed for Class 1 and Class 2A elements, parenteral and inhalational drugs are assessed for Class 3 elements where considered necessary. Risk assessments should consider elements that are added deliberately or unintentionally. Compared with orally or cutaneously administered drugs, products for parenteral or inhalational administration tend to have much lower PDEs. Because elemental impurities are minimally absorbed from topically or mucosally applied drugs, these are not mentioned specifically in the new chapters. The oral PDE limits could be used for topical and mucosal medicines.

To assess the suitability of an analytical method for the ICH/USP general chapters, performance testing is required to demonstrate accuracy, specificity, sensitivity, and reproducibility. In ICH Q2(R1) (*3*) and USP <233> (*4*), specificity must be demonstrated. Specificity provides a measure of the procedure's capacity to definitively assess analytes in the presence of other elements and sample matrix interferences. This application note presents data to illustrate the validation of a procedure for the measurement of elemental impurities in artificial eye drops.

The growing need for elemental analysis and low levels of quantification lends itself to the comprehensive Agilent workflow, with our family of inductively coupled plasma (ICP), atomic absorption (AA), and microwave plasma (MP) instruments, as well as our large catalog of inorganic standards and user-friendly software with customized reports. This portfolio allows Agilent to deliver a single-sourced total workflow solution from sample introduction to reporting.

Experimental

Sample preparation and method validation procedures for system suitability testing on any instrumentation used for the analysis of elemental impurities in pharmaceutical materials are defined by ICH and USP (*4*).

Twenty-four elements were added to a 5% acid matrix (9:1 HNO_3:HCl) at the appropriate concentration for the parenteral limits of 0.5, 0.8, 1.0, and 1.5 J for calibration using the Agilent USP 232 parenteral kit (part number 5191-4536). The J value is the concentration in solution for each analyte PDE, and is described in a previous publication (*5*).The standard kit consists of three bottles with different elements combined based on matrix compatibility for maximum stability. Another feature for ease of sample preparation is that each element is present at the appropriate relative concentration so that when the calculated J value is obtained based on dosage and weight, the same volume from each bottle of standard is needed to make the spiked sample and calibration. For example, for a parenteral drug product with a maximum daily dose of 5 g, diluted 1 g to a final volume of 50 mL, a 1 J concentration can be calculated for all of the elements to give the spike volume to be aliquoted from each standard bottle. Table 2 lists a breakdown of these standards.

Table 2. The Agilent USP 232 chemical standards kit contains one internal standard mix and three calibration standard mixes. The elements and corresponding concentration are listed for each mix.

ICH/USP 232 Parenteral Combined-1 (µg/mL)	
Ag	10.0
Ba	700
Cr	1,100
Cu	300
Li	250
Mo	1,500
Sb	90.0
Se	80.0
Sn	600
Tl	8.00
ICH/USP 232 Parenteral Combined-2 (µg/mL)	
Au	100
Ir	10.00
Os	10.00
Pd	10.00
Pt	10.00
Rh	10.00
Ru	10.00

ICH/USP 232 Parenteral Class 1 and 2 Parenteral Elements (µg/mL)	
As	15.00
Cd	2.00
Co	5.00
Hg	3.00
Ni	20.00
Pb	5.00
V	10.00
Pharma Internal Standard 1 (µg/mL)	
Bi	5.00
Ge	5.00
In	5.00
Lu	5.00
Sc	5.00
Te	5.00

Sample preparation

In this study, system suitability tests were run using generic sterile artificial tear eye drops (SATED) spiked at the parenteral PDE limits. Ophthalmic solutions do not have designated PDEs set by USP and ICH. However, based on the route of administration, the guidelines allowed the application of parenteral PDEs without modification.[1] Using a daily dose of 5 g/day, the J values for the 24 elements were calculated, and are shown in Table 3.

Table 3. Parenteral daily dose for SATED and J values based on 5 g/day at a dilution of 50X.

Element	PDE (µg/day)	J Value (µg/L)
Cd	2	8
Pb	5	20
As	15	60
Hg	3	12
Co	5	20
V	10	40
Ni	20	80
Tl	8	32
Ag	10	40
Se	80	320
Au	100	400
Pd	10	40
Ir	10	40
Os	10	40
Rh	10	40
Ru	10	40
Pt	10	40
Li	250	1,000
Sb	90	360
Ba	700	2,800
Mo	1,500	6,000
Cu	300	1,200
Sn	600	2,400
Cr	1,100	4,400

The active ingredients in this isotonic solution are polyvinyl alcohol (0.5%) and povidone (0.6). Three 1 mL aliquots were prepared for analysis by placing 20 drops in a 50 mL centrifuge tube then diluting to a final volume of 50 mL with 5% 9:1 HNO_3:HCl acid matrix.

To further assess the elemental impurity content, three 4 mL aliquots were prepared through microwave digestion performed by the Mars6 Microwave Digestion System (CEM, North Carolina, USA). The samples were prepared using the parameters listed in Table 4. The digested sample, which contained 20% acid in a 9:1 HNO_3:HCl ratio, was diluted four-fold to bring the acid concentration to 5% and to dilute the sample in a final volume of 50 mL of MilliQ H_2O to the level equivalent to a diluted (not digested) sample.

Table 4. Microwave acid digestion method used for the preparation of SATED.

Sterile Artificial Tear Eye Drops	
Sample/Acid	
Sample Volume	4 mL
Add HNO_3	9 mL
Add HCl	1 mL
Microwave Digestion	
Temperature	210 °C
Ramp	20 minutes
Hold	15 minutes
Pressure	800 psi
Power	900 to 1,050 W
Dilution	
Milli-Q H_2O	40 mL
Dilution	50 mL
Final Dilution	
Sample Aliquot	12.5 mL
Milli-Q H_2O	37.5 mL
Final Dilution	200X dilution

For the digested and nondigested SATED samples, standards containing all 24 elements were spiked at 0.5 and 1.0 J to evaluate recovery in the matrix samples and other system suitability metrics. Further quantitation validation, such as ruggedness, included a fresh set of six 1.0 J fortified by all 24 elements to be prepared on a separate day and analyzed.

Instrumentation

The Agilent 7900 ICP-MS, which includes an ORS[4] octopole reaction cell optimized for He collision gas, is well suited for pharmaceutical analysis. The Agilent 7850 model gives comparable data and is also well suited to routine pharmaceutical QA/QC analysis. The system was optimized using autotuning functions for the ion lens, detector, and sample introduction system. To optimize the signal while reducing the polyatomic interferences from the matrix, the collision gas flow was adjusted manually. Table 5 shows the optimized conditions.

Table 5. Agilent 7900 operating conditions for ICH Q3D(R2) and USP 232 parenteral analysis.

Parameter	Value
Instrument	Agilent 7900 ICP-MS
Plasma Mode	General purpose
RF Matching	1,550 W
Sampling Depth	8 mm
Nebulizer Gas Flow	1.05 L/min
Spray Chamber Temperature	2 °C
Extraction Lens 1	0 V
Kinetic Energy Discrimination	5 V
He Cell Gas Flow	4.4 mL/min

The Agilent SPS 4 autosampler was used for sample introduction to the ICP-MS. The 7900 ICP-MS was equipped with a standard glass concentric nebulizer (part number G3266-80004), quartz spray chamber, 2.5 mm id quartz torch, and nickel interface cones. Samples were introduced using a peristaltic pump using 1.02 mm id tubing (white/white, part number G1833-65569).Internal standard was introduced with orange/blue 0.25 mm tubing (part number G3280-67047). Samples were mixed online with the internal standard (pharmaceutical internal standard I diluted tenfold in dilute nitric acid) using the standard online internal standard addition kit (part number G3280-60590).

ICP-MS MassHunter software

Intuitive, simple, yet powerful, Agilent MassHunter software permits easy data analysis and custom reporting (Figure 1). Preset methods for USP <232>/ICH Q3D are included to save time, and allow a batch to be set up and running with just a few clicks. Predefined sample types simplify QC checks on PDE limits. Built-in reports allow users to easily view and print recovery and repeatability/ruggedness results.

Results and discussion

Validation and system suitability

Validation of analytical instruments is driven by performance-based metrics. ICH Q2(R1) and USP <233> define the criteria for performance evaluation. System suitability includes demonstrating stability of the system throughout an analytical run. USP <233> specifically calls out limit procedures and quantitative procedures to demonstrate system suitability. Limit procedures must demonstrate acceptable performance for detectability, precision, and specificity. Quantitation procedures look for accuracy, precision through repeatability and ruggedness, specificity, limit of quantitation (LOQ), range, and linearity. For this analysis, we followed the quantitative procedures.

Precision (repeatability)

To fulfill the acceptance criteria for the instrumental limit procedures, a relative standard deviation (RSD) of six independent samples spiked at 1.0 J must be less than 20%. The 7900 results show that all elements have RSDs that are well below the threshold shown in Table 6. The RSDs are less than 3% for the primary isotopes, demonstrating excellent reproducibility.

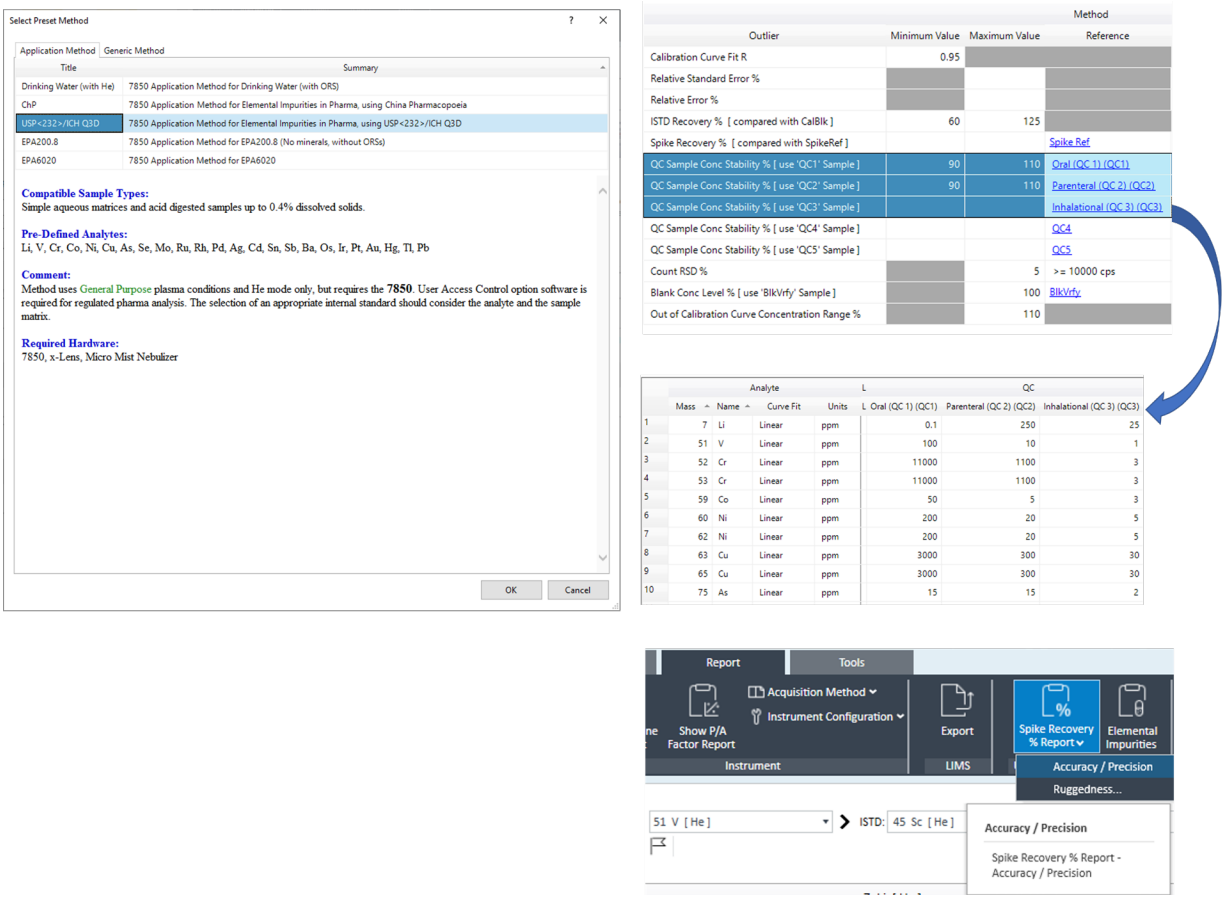

Figure 1. Preset Method setup and predefined QC checks and reports in Agilent ICP-MS MassHunter software.

Intermediate precision (ruggedness)

Ruggedness is determined by analyzing a replicate repeatability test with a new set of six fortified samples analyzed at the 1.0 J level for a total of n = 12 1 J spiked samples. The repeat analysis must be performed on a different day if the same instrument is being used, which was the case for this study. To meet validation criteria, the 12 replicates must have an %RSD of not more than 25%. The 7900 ICP-MS exhibited excellent stability, as shown in Table 6, with the %RSDs for all elements except silver being below 2%. Silver stability is notoriously affected by chloride levels in the samples, but even this element gave intermediate precision (n=12) of less than 3%.

Specificity

Detection by ICP-MS lends itself to specificity due to the nature of mass selective detection. Each of the 24 elements monitored in this study has at least one unique mass that is free of isobaric interference. Common polyatomic spectral interferences can be addressed on the 7900 ICP-MS by use of the ORS collision cell with He gas. Helium mode effectively attenuates polyatomic ions by kinetic energy discrimination, removing their contribution at the target analyte mass.

Additional confirmation of the quantitative results can be achieved by measurement of additional isotopes for many of the target elements, with the secondary isotopes used as qualifiers (*6*).

Table 6. Repeatability and ruggedness data for SATED samples fortified at 1.0 J for 24 elements. Some elements have secondary isotopes that were also analyzed.

m/z	Element	True 1 J (µg/L)	1 J Mean (Measured)	%RSD (n = 6)	%RSD (n = 12)
7	Li	1,000	966	0.7	0.8
51	V	40	40	1.1	1.2
52	Cr	4,400	4,361	1.5	1.5
53	Cr	4,400	4,367	0.8	1.1
59	Co	20	20	1.0	1.1
60	Ni	80	78	1.1	1.1
62	Ni	80	77	0.7	1.0
63	Cu	1,200	1,174	1.1	1.2
65	Cu	1,200	1,169	1.6	1.6
75	As	60	60	0.9	1.1
77	Se	40	41	1.3	1.9
78	Se	40	41	1.0	1.2
82	Se	40	41	1.0	1.1
95	Mo	6,000	5,945	1.0	1.2
97	Mo	6,000	5,924	1.3	1.5
101	Ru	40	39	1.9	1.6
103	Rh	40	39	1.5	1.4
105	Pd	320	309	1.5	1.3
107	Ag	40	39	2.7	2.0
109	Ag	40	39	3.8	2.7
111	Cd	8	8	1.2	1.4
114	Cd	8	8	1.5	1.5
118	Sn	2,400	2,394	1.4	1.4
121	Sb	360	363	1.2	1.6
135	Ba	2,800	2,781	1.5	1.7
137	Ba	2,800	2,775	1.2	1.6
138	Ba	2,800	2,789	1.8	1.7
188	Os	40	39	0.9	1.1
189	Os	40	40	0.8	0.9
191	Ir	400	392	1.0	1.1
193	Ir	400	393	1.3	1.5
194	Pt	40	39	1.3	1.2
195	Pt	40	39	1.2	1.3
197	Au	40	37	1.5	1.9
200	Hg	12	12	0.6	1.1
201	Hg	12	12	0.6	1.1
202	Hg	12	12	0.6	1.1
205	Tl	32	32	0.5	0.9
206	Pb	20	20	0.9	1.3
207	Pb	20	20	0.9	1.2
208	Pb	20	20	0.9	1.2

Quantitative procedures

Accuracy

The SATED samples were spiked at levels of 0.5, 1.0, and 1.5 J. The acceptance criteria for each spike level is for recoveries to be between 70 to 150% after subtraction of the amount in the unspiked sample. As shown in Figure 2, the recoveries easily meet this criterion, with spike recoveries within 10% at each of the levels for all 24 elements.

Additionally, the same concentration levels were used to create a calibration curve and determine the LOQ for the method. Excellent linearity was obtained for all elements, with linear regression values better than 0.999. Figure 3 presents calibration curves from the different classes of elements. Background equivalent concentrations (BECs) were all in the low ng/L (ppt) range. This is especially noteworthy for elements such as vanadium and arsenic, as there are chlorine-based polyatomic interferences that can contribute to the signal for these elements. Using He KED mode effectively removes these polyatomic ions, ensuring accurate and consistent results in varied chloride matrices.

Sample analysis: digested versus nondigested sample

All 24 elements were undetectable (less than 0.5 J) in the SATED sample. While the digested samples did show elevated concentrations when compared to the undigested samples, the calculated concentrations for all 24 elements were at least two orders of magnitude below the 0.5 J standard. Based on the maximum daily dose and the permitted daily exposure for the elements, digestion is an unnecessary step for this analysis and simple dilution is sufficient for this matrix.

Detectability

SATED samples spiked at 0.5 and 1.0 J (50 and 100% of target value) were used to demonstrate detectability. The criteria of spike recovery within 15% was applied to the mean of three replicates at 1.0 J when compared to the 1.0 J calibration standard. In addition, samples spiked at 0.5 J should be half of the calculated concentration of the samples spiked at 1.0 J. Table 7 shows that there is excellent agreement between recoveries for 0.5 and 1.0 J spiked samples compared to the calibration standards.

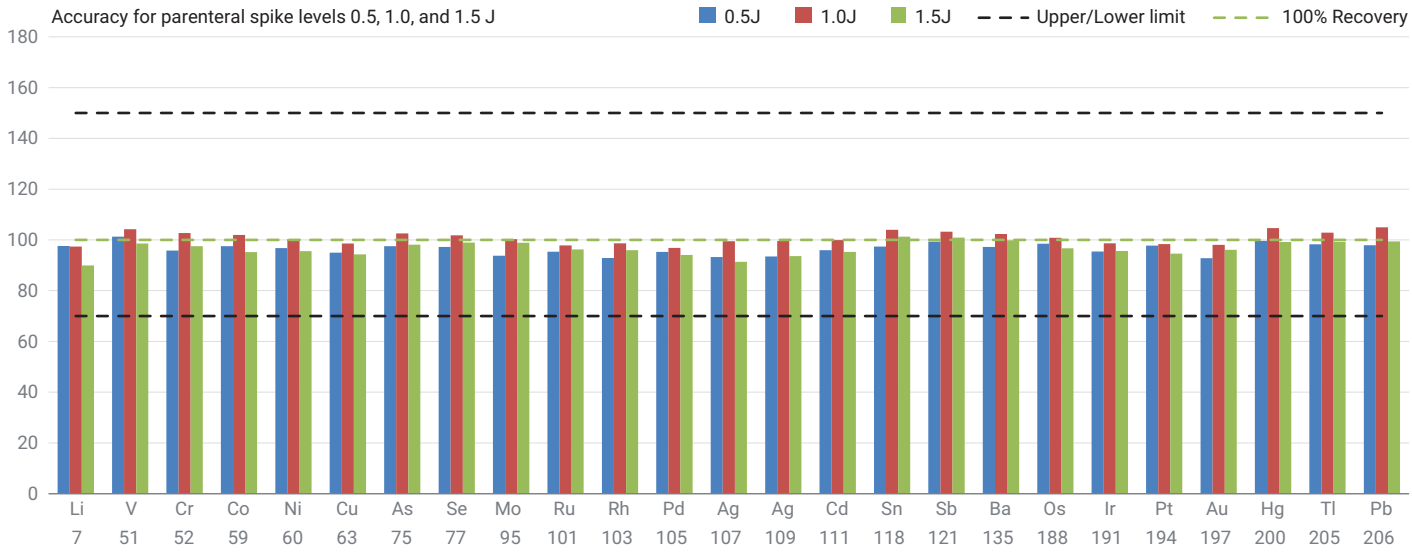

Figure 2. Accuracy results for SATED samples spiked at 0.5, 1.0, and 1.5 J obtained with the Agilent 7900 ICP-MS.

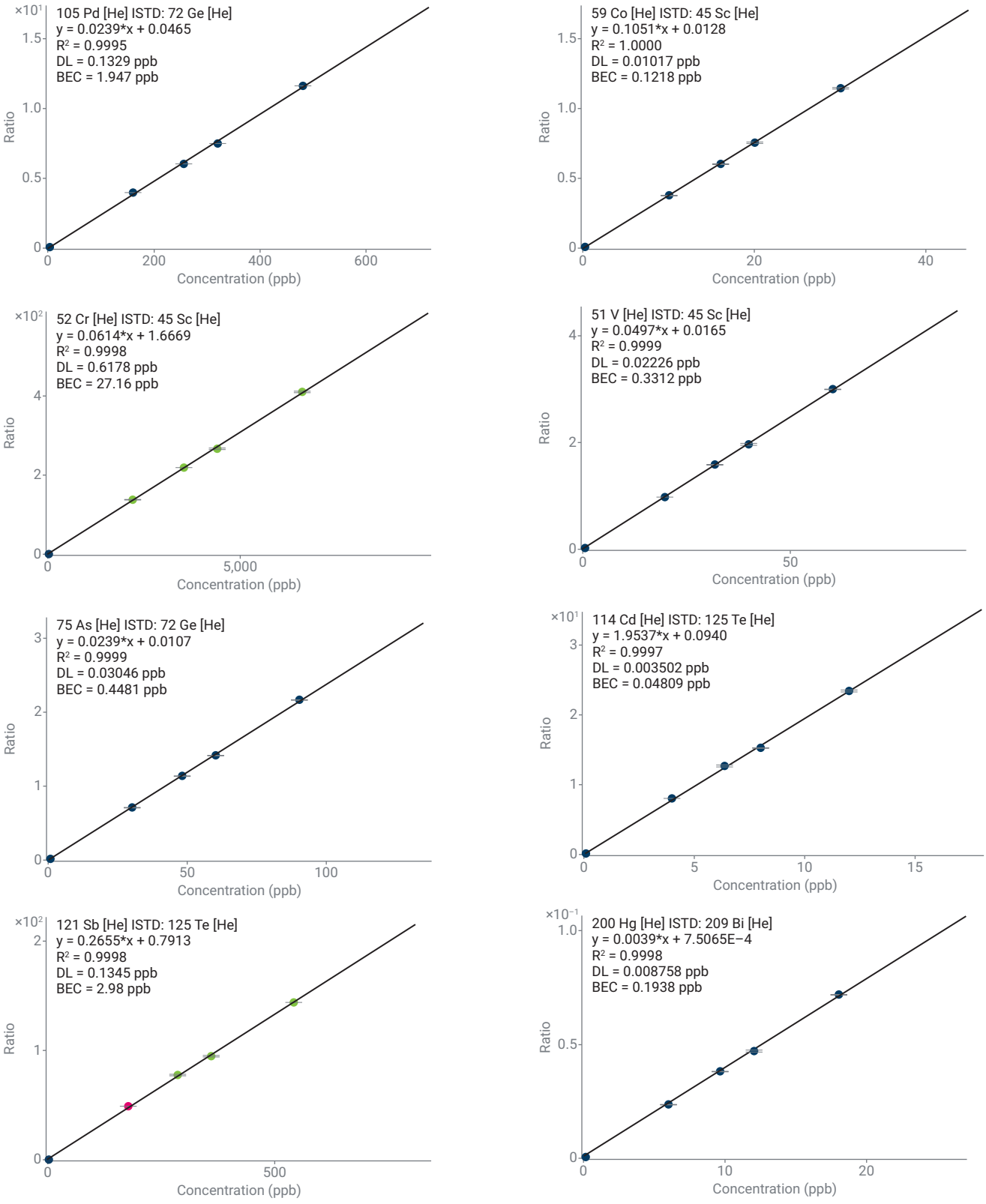

Figure 3. Calibration curves from Pd, Co, Cr, V, As, Cd, Sb, and Hg obtained on the Agilent 7900 ICP-MS.

Table 7. Detectability demonstrated at the 0.5 and 1.0 J levels.

m/z	Element	Cal Std 0.5J	Calc. 0.5J	%Recovery	Cal Std 1.0J	Calc. 1.0J	%Recovery
7	Li	557	542	97	1031	964	93
51	V	21	21	99	40	41	101
52	Cr	2,326	2,251	97	4,453	4,361	98
53	Cr	2,293	2,234	97	4,445	4,366	98
59	Co	11	10	97	20	20	98
60	Ni	43	42	97	80	78	98
62	Ni	43	41	95	80	78	97
63	Cu	641	616	96	1,216	1,173	96
65	Cu	631	608	96	1,197	1,166	97
75	As	32	31	99	60	61	102
77	Se	21	21	100	40	42	104
78	Se	21	21	99	40	41	103
82	Se	21	21	99	40	42	103
95	Mo	3,122	3,010	96	5,977	5,954	100
97	Mo	3,119	3,017	97	6,001	5,919	99
101	Ru	21	21	97	40	39	99
103	Rh	21	20	95	40	39	98
105	Pd	170	162	95	317	310	98
107	Ag	22	20	94	40	39	97
109	Ag	21	20	93	40	41	102
111	Cd	4	4	96	8	8	96
114	Cd	4	4	98	8	8	97
118	Sn	1,243	1,229	99	2,432	2,376	98
121	Sb	186	186	100	362	362	100
135	Ba	1,459	1,427	98	2,826	2,774	98
137	Ba	1,449	1,424	98	2,842	2,775	98
138	Ba	1,460	1,433	98	2,832	2,801	99
188	Os	21	20	98	40	39	97
189	Os	21	21	99	40	40	98
191	Ir	208	204	98	402	390	97
193	Ir	207	202	98	404	391	97
194	Pt	21	20	97	40	39	97
195	Pt	21	20	97	40	39	96
197	Au	20	17	87	40	37	92
200	Hg	6	6	98	12	12	100
201	Hg	6	6	98	12	12	100
202	Hg	6	6	98	12	12	100
205	Tl	17	17	97	32	32	100
206	Pb	11	10	98	20	20	101
207	Pb	10	10	98	20	20	100
208	Pb	11	10	99	20	20	101

Reporting in ICP-MS MassHunter software

Creating reports for accuracy and spike recoveries was simplified using the predefined method template for USP <232>. Using the unspiked sample as a reference, recoveries and accuracies for spiked samples were calculated with the sample background subtracted automatically. The easy-to-read table reports recoveries for each level of spikes. Figure 4 shows an excerpt of the software-generated report of the level 2 spike, which was the six replicates of 1.0 J fortified samples. For each element, the concentrations are reported along with the mean and %RSD for the measurements.

Generating a report for ruggedness is as simple as adding and deleting the appropriate files for batch analysis. A pop-up window allows easy removal and addition of samples from any batch. The resultant report shows the samples, separated by batch origin, with the concentration, % recovery, and %RSD of the concentration. Figure 5 shows an excerpt of a report.

		111 Cd [He]		114 Cd [He]		118 Sn [He]		121 Sb [He]	
	Sample Name	Conc. [ppb]	Recovery [%]	Conc. [ppb]	Recovery [%]	Conc. [ppb]	Recovery [%]	Conc. [ppb]	Recovery [%]
1	SATED NOSPK	0.011		0.003		0.265		0.038	
	Mean	0.011		0.003		0.265		0.038	
3	SATED 1.0J	7.749	96.7	7.922	99.0	2376.230	99.0	362.459	100.7
4	SATED 1.0J	7.548	94.2	7.827	97.8	2352.859	98.0	357.301	99.2
5	SATED 1.0J	7.580	94.6	7.900	98.7	2394.578	99.8	363.020	100.8
6	SATED 1.0J	7.791	97.2	8.054	100.6	2420.406	100.8	368.985	102.5
7	SATED 1.0J	7.770	97.0	8.021	100.2	2420.879	100.9	366.857	101.9
8	SATED 1.0J	7.638	95.3	7.892	98.6	2398.333	99.9	361.043	100.3
	Mean	7.679	95.8	7.936	99.2	2393.881	99.7	363.278	100.9
	RSD of Conc. [%]	1.4		1.1		1.1		1.1	

Figure 4. Excerpt from the Agilent ICP-MS MassHunter-generated report for repeatability for samples spiked at 1.0 J.

		200 Hg [He]		201 Hg [He]		205 Tl [He]		208 Pb [He]	
	Sample Name	Conc. [ppb]	Recovery [%]	Conc. [ppb]	Recovery [%]	Conc. [ppb]	Recovery [%]	Conc. [ppb]	Recovery [%]
1	SATED 1.0J	12.038	100.3	12.062	100.5	32.350	101.1	20.390	101.9
2	SATED 1.0J	11.648	97.1	11.733	97.8	31.952	99.9	19.814	99.1
3	SATED 1.0J	11.643	97.0	11.727	97.7	32.342	101.1	19.777	98.9
4	SATED 1.0J	12.071	100.6	12.110	100.9	32.726	102.3	20.461	102.3
5	SATED 1.0J	12.069	100.6	12.133	101.1	32.701	102.2	20.571	102.9
6	SATED 1.0J	11.942	99.5	11.971	99.8	32.328	101.0	20.311	101.6
1	SATED 1.0J	12.002	100.0	11.977	99.8	31.303	97.8	19.613	98.1
2	SATED 1.0J	12.312	102.6	12.211	101.8	31.431	98.2	20.110	100.6
3	SATED 1.0J	12.577	104.8	12.523	104.4	32.249	100.8	20.546	102.7
4	SATED 1.0J	12.327	102.7	12.337	102.8	32.112	100.4	20.131	100.7
5	SATED 1.0J	12.691	105.8	12.610	105.1	32.337	101.1	20.732	103.7
6	SATED 1.0J	12.413	103.4	12.366	103.1	32.060	100.2	20.309	101.5
	Mean	12.144	101.2	12.147	101.2	32.158	100.5	20.230	101.2
	RSD of Conc [%]	2.721		2.302		1.349		1.727	

Figure 5. Excerpt of a report showing ruggedness for samples spiked at 1.0 J.

Conclusion

The Agilent 7900 ICP-MS successfully completed the suitability tests for USP <232>/<233> and ICH Q3D(R2)/Q2(R1) quantitative tests as laid out by USP and ICH guidelines. Comparable results could also be achieved on the Agilent 7850 model. All tests and QC for the SATED matrix passed for accuracy, precision, ruggedness, and specificity. The total analytical workflow from chemical standards, calibration, and matrix spiking, to automatically generating USP and ICH QC reports, was achieved by Agilent instrumentation, chemical standards, and consumables. This complete solution is readily available for pharmaceutical laboratories to seamlessly incorporate into their workflows. The USP <232> parenteral standard kit makes for fast, easy calibration and matrix spiking. The 7900 ICP-MS delivers on performance, exhibiting excellent stability, as shown in the ruggedness study, where freshly prepared spike samples were analyzed over multiple days with tight precision and accuracy. The linear dynamic range of all 24 elements of interest is also outstanding, with regression values close to 1. Robustness is shown by the recoveries of matrix spikes at multiple concentrations for each element.

References

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