Application Note

Pharmaceuticals

Accurate and Robust Measurement of Elemental Impurities in Pharmaceuticals by ICP-MS

Implementation of Indian Pharmacopeia General Chapter 5.10 compliant workflow using the Agilent 7850 ICP-MS

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Introduction

Elemental impurity testing is a vital part of pharmaceutical quality assurance because trace metals can enter drug products at various points of the manufacturing process. Impurities may originate from raw materials and excipients, leach from processing equipment, remain as residues from catalysts, or arise through environmental or packaging related contamination.[1] Even at very low concentrations, certain metals pose toxicological risks, making their assessment and control essential for ensuring product safety.

To address these risks, global regulatory bodies—including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other members of the International Council for Harmonization (ICH)—require manufacturers to perform systematic risk assessments and ongoing monitoring of elemental impurities.[2–5] The harmonized ICH Q3D guideline provides the framework for this evaluation by defining toxicology based permitted daily exposure (PDE) limits. It also outlines

expectations for analytical testing, reporting, and control strategies across a variety of dosage forms.

To align with these international regulatory standards, the draft Indian Pharmacopeia (IP) General Chapter 5.10 has been developed to harmonize with the corresponding requirements of the European, Japanese, and U.S. Pharmacopeias.[6] Harmonization will ensure that India's regulatory framework reflects globally accepted best practices for assessing and controlling elemental impurities. It will also ensure that pharmaceutical products manufactured for the Indian and global markets meet internationally aligned safety standards. As part of these harmonized expectations, IP General Chapter 5.10 mandates the quantitative determination of specified elemental impurities using validated, high performance analytical technologies such as ICP MS or ICP OES. These techniques provide the sensitivity, selectivity, and sample throughput required to reliably measure trace-level elemental impurities and demonstrate compliance with PDE based limits.

An Agilent 7850 ICP-MS was used in this study to meet the trace level elemental impurity requirements defined in IP General Chapter 5.10. Designed to quantify elements at low concentrations, the 7850 achieves detection limits suitable for accurate, confident measurement of impurities at sub ppb levels. Its advanced ORS[4] collision cell technology uses helium (He) mode to effectively remove polyatomic interferences across multiple analytes,[7] enabling reliable measurement of secondary or qualifier isotopes. This capability supports analyte confirmation as required by regulatory guidelines, including IP 5.10, ICH Q2(R1), USP <233>, and USP <1225>. The combination of sensitivity and spectral clarity is essential when testing regulated pharmaceutical products, where accuracy, reproducibility, and compliance with pharmacopeial limits are required.

The 7850 ICP-MS delivers robust performance in real-world pharmaceutical environments, where complex matrices and routine, high throughput testing are the norm. The high-temperature plasma improves matrix tolerance, minimizes matrix-induced interferences, and enhances ionization efficiency.[8] This capability provides higher and more consistent sensitivity for poorly ionized elements such as As, Cd, and Hg, as well as platinum group elements (PGEs) including Os, Ir, and Pt.

The 7850 ICP-MS system's high matrix tolerance also enables efficient handling of diverse sample types, including active pharmaceutical ingredients (APIs), excipients, and finished dosage forms, without excessive dilution or instrument downtime. Long term signal stability ensures consistent results throughout long analytical runs, minimizing re-analysis and supporting dependable quality control (QC) testing.

The 7850 offers streamlined, workflow-based operation with intuitive software and pre-configured method templates that are aligned with pharmacopeial guidelines. Instrument parameters are automatically optimized, simplifying method development, minimizing operator intervention, and ensuring consistent analytical performance.

This application note outlines an end-to-end analytical workflow designed to help laboratories comply with the elemental impurity requirements of IP General Chapter 5.10 using ICP MS. Twenty four elements were determined in three types of oral drug products, and the method was evaluated against the performance criteria specified in IP 5.10.

Experimental

Instrumentation

An Agilent 7850 ICP-MS equipped with the ORS[4] cell and Agilent SPS 4 autosampler was used. The ICP-MS was configured with the standard glass MicroMist concentric nebulizer, Peltier-cooled quartz spray chamber, torch (2.5 mm injector), standard nickel sample and skimmer cones, and two-stop, Easy-fit white/white peristaltic pump tubing.

The instrument's sample introduction system includes a high-precision 10-roller peristaltic pump, an efficient low-flow nebulizer, and a Peltier-cooled spray chamber with a controllable temperature range of –5 to +20 °C. This Scott-type double-pass spray chamber enables the ICP-MS to analyze both aqueous and organic solvents. The spray chamber was maintained at 2 °C (default setting) to promote aerosol condensation and provide stability against laboratory temperature fluctuations, supporting consistent plasma performance, improving the signal-to-noise ratio, and enabling low limits of detection. These performance attributes are important for the quantification of trace-level impurities in complex samples.

The instrument was controlled using Agilent ICP-MS MassHunter software. Typical instrument operating parameters are listed in Table 1. The highlighted parameters were predefined by selecting the General Purpose plasma setting, while lens voltages were automatically tuned for optimal performance using the software's autotune feature. Method parameters (recommended list of elements, preferred isotopes, integration times, etc.) were loaded from the "ICH/USP" preset method, allowing the analyst to quickly create a new batch method.

Table 1. Agilent 7850 ICP-MS operating parameters.

ICP-MS Parameter	Value
Plasma Mode	General Purpose
RF Power	1550
Spray Chamber Temp (°C)	2.0
Sampling Depth (mm)	10.0
Nebulizer Gas Flow (L/min)	1.05
Lens Tune	Autotune
Helium Flow Rate (mL/min)	5.0
KED (V)	3

The shaded parameters are predefined by selecting the General Purpose plasma setting

Elemental impurity limits (J value)

The maximum allowable levels of elemental impurities in finished pharmaceutical products are defined in terms of PDE. These limits consider both the concentration of each element in the product and the drug's maximum recommended daily dose. For samples requiring digestion or dilution before analysis, the PDE values (expressed in µg/day) must be converted to solution concentration limits (µg/L) for the prepared sample. This conversion is performed by applying the appropriate sample preparation dilution factor. The dilution factor must be included during method development to ensure that analyte concentrations fall within the instrument's calibrated working range while still meeting the required sensitivity and regulatory limits. The target concentration value in the prepared sample, referred to as the "J-value", defines the maximum permitted concentration limit for the analyte in that sample (Equation 1). The J-value is also used to define the calibration levels and concentrations of QC solutions.

$$J = PDE/(Total\ dilution \times Max\ Daily\ Dose) \quad (1)$$

Three different over-the-counter (OTC) oral drug products were used as samples.

Table 2 shows the oral dose J values for the elemental impurities in the samples, based on a maximum daily dose of 10 g/day and a sample preparation dilution factor of 500 (0.1 g in 50 mL).

Table 2. Elemental impurities by class, oral PDE concentrations, and J values.

Class (and Number) of Elements	Elemental Impurities	Oral PDE, µg/day	Component Limits, µg/g	J Value, µg/L (ppb)
Class 1 (4)	Pb	5	0.5	1
	Cd	5	0.5	1
	As	15	1.5	3
	Hg	30	3	6
Class 2A (3)	Co	50	5	10
	V	100	10	20
	Ni	200	20	40
Class 2B (10)	Tl	8	0.8	1.6
	Au	300	30	60
	Pd	100	10	20
	Ir	100	10	20
	Os	100	10	20
	Rh	100	10	20
	Ru	100	10	20
	Se	150	15	30
	Ag	150	15	30
	Pt	100	10	20
Class 3 (7)	Li	550	55	110
	Sb	1200	120	240
	Ba	1400	140	280
	Mo	3000	300	600
	Cu	3000	300	600
	Sn	6000	600	1200
	Cr	11000	1100	2200

Sample preparation

Three different OTC oral drug products in tablet form were bought in a supermarket. The samples were labeled as Oral Drug Product 1, 2, and 3.

Each tablet was ground to a homogeneous powder before weighing 0.10 ± 0.0005 g into a polytetrafluoroethylene (PTFE) microwave digestion vessel. Each sample was predigested in 0.1 mL HCl and 6 mL HNO_3, followed by microwave digestion (Milestone, Italy) using the parameters shown in Table 3. Once cooled to room temperature, the digested solutions were transferred to a 50 mL Agilent autosampler tube (part number 190047900) and made up to volume using de-ionized water.

Table 3. Microwave digestion program.

Step	Time (min)		Power (W)	Temperature (°C)
	Digestion	Hold		
I	15	5	1800	110
II	5	5		150
III	5	10		180
Cooling				Room temperature

All sample types—including sample replicates, spiked samples, method blanks, and the intermediate-precision spiked samples for the three oral drug products—were prepared using the same procedure, as described in Table 3 and Figure 1.

Standard preparation

Calibration standards were prepared for each target analyte at the following levels: 0, 0.10, 0.25, 0.50, 0.75, 1.0, 1.50, and 2.25 J using NIST-certified Agilent reference materials (CRMs). The CRMs included ICH/USP target elements standard A; ICH/USP oral target elements standard D; ICH/USP oral target elements standard C_v2; and ICH/USP oral target elements standard B.

The calculated J values for each analyte (after applying the 500x dilution factor and 10 g/day as maximum daily dose) are shown in Table 4. All the calibration standards were freshly prepared in 1% HCl (v/v) and 5% HNO_3 (v/v).

An internal standard (ISTD) solution (Sc 2.0 µg/mL; In and Bi 1.0 µg/mL each) was prepared from an Agilent USP 232 pharma internal standard stock. The ISTD solution was added online through a tee connector.

Table 4. Calibration standard concentrations (ppb) prepared for all 24 elemental impurities per IP General Chapter 5.10.

Elemental Impurities	Calibration Standard Concentration (ppb) at Different J Values						
	0.10 J	0.25 J	0.50 J	1.0 J	1.5 J	2.0 J	2.25 J
Pb	0.1	0.25	0.5	1	1.5	2	2.25
Cd	0.1	0.25	0.5	1	1.5	2	2.25
As	0.3	0.75	1.5	3	4.5	6	6.75
Hg	0.6	1.5	3	6	9	12	13.5
Co	1	2.5	5	10	15	20	22.5
V	2	5	10	20	30	40	45
Ni	4	10	20	40	60	80	90
Tl	0.16	0.4	0.8	1.6	2.4	3.2	3.6
Au	6	15	30	60	90	120	135
Pd	2	5	10	20	30	40	45
Ir	2	5	10	20	30	40	45
Os	2	5	10	20	30	40	45
Rh	2	5	10	20	30	40	45
Ru	2	5	10	20	30	40	45
Se	3	7.5	15	30	45	60	67.5
Ag	3	7.5	15	30	45	60	67.5
Pt	2	5	10	20	30	40	45
Li	11	27.5	55	110	165	220	247.5
Sb	24	60	120	240	360	480	540
Ba	28	70	140	280	420	560	630
Mo	60	150	300	600	900	1200	1350
Cu	60	150	300	600	900	1200	1350
Sn	120	300	600	1200	1800	2400	2700
Cr	220	550	1100	2200	3300	4400	4950

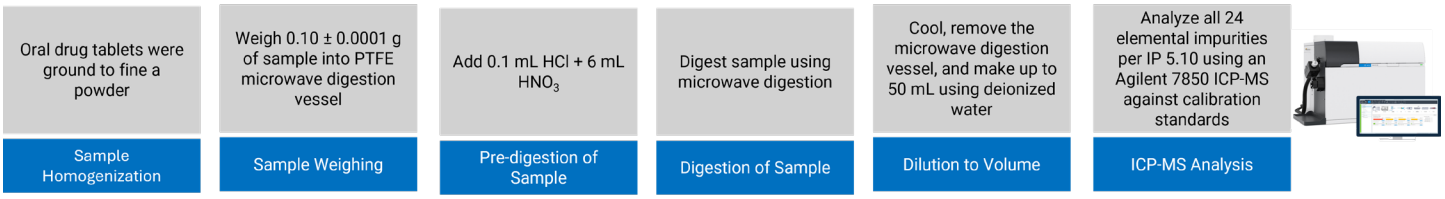


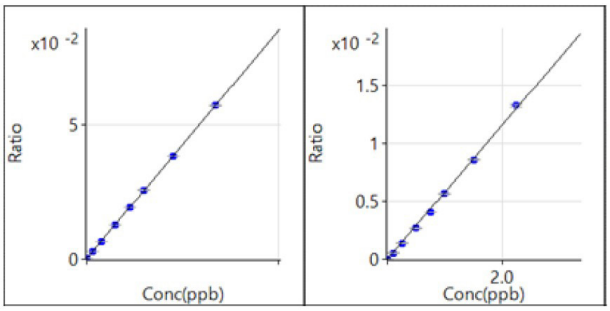
Figure 1. Analytical workflow for the analysis of elemental impurities pharmaceutical samples in accordance with draft IP General Chapter 5.10 using the Agilent 7850 ICP-MS.

Results and discussion

Linearity

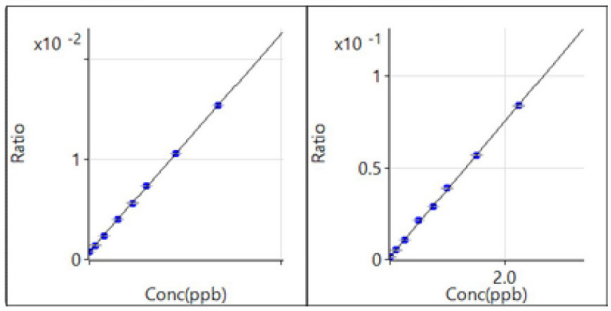
Linearity was demonstrated by plotting seven-point linearity curves for each target element from 0.10 to 2.25 J. The 7850 ICP-MS is equipped with an automated dual-mode detector offering a 10-order linear dynamic range. Low-intensity signals are measured in "pulse-counting" mode, in which each ion that strikes the detector is recorded as a count. At higher signal intensities, the pulse-count mode would be overloaded, and the response would become non-linear. So, at these high signal levels, the detector switches to a "low gain" mode, using analog signal detection.

Representative calibration curves for the class 1 elements, As, Cd, Hg, and Pb (Figure 2) and calibration data for all 24 elements (Table 5) demonstrate the wide linear dynamic range of the 7850 ICP-MS. Correlation coefficients above 0.999 confirm the linearity needed to measure trace- and major-level elements in a single run.



75 As [He]
ISTD: 45 Sc
y = 8.458E-3 x + 2.502E-4
R 1.0000
DL 0.003491
BEC 0.02958

111 Cd [He]
ISTD: 115 In
y = 5.795E-3 x + 6.066E-6
R 0.9995
DL 0.0005143
BEC 0.001047



201 Hg [He]
ISTD: 209 Bi
y = 1.087E-3 x + 7.748E-4
R 1.0000
DL 0.03151

208 Pb [He]
ISTD: 209 Bi
y = 3.695E-2 x + 1.359E-3
R 0.9998
DL 0.01866

Figure 2. Representative calibration curves of four elemental impurities (As, Cd, Hg, and Pb) required by IP General Chapter 5.10, demonstrating the high sensitivity, analytical range, and linearity of the Agilent 7850 ICP-MS.

Table 5. Gas mode, calibration coefficient (R), Instrument Detection Limits (IDLs)*, and dilution-adjusted IDLs for 24 elemental impurities using the Agilent 7850 ICP-MS.

Elemental Impurities	Gas Mode	R Value	IDL, ppb	IDL x 500, ppb
7 Li	He	1.0000	0.0492	24.59
51 V	He	1.0000	0.0026	1.29
52 Cr	He	1.0000	0.0052	2.61
59 Co	He	0.9996	0.0061	3.05
62 Ni	He	0.9997	0.0229	11.46
63 Cu	He	0.9996	0.0250	12.52
75 As	He	1.0000	0.0035	1.75
78 Se	He	0.9999	0.6459	322.95
95 Mo	He	0.9996	0.0043	2.14
101 Ru	He	0.9995	0.0013	0.66
103 Rh	He	0.9996	0.0000	0.01
105 Pd	He	0.9997	0.0011	0.53
107 Ag	He	0.9995	0.0124	6.19
111 Cd	He	0.9995	0.0005	0.26
118 Sn	He	0.9996	0.0166	8.30
121 Sb	He	0.9997	0.0021	1.03
137 Ba	He	0.9997	0.0037	1.85
189 Os	He	0.9994	0.0147	7.35
193 Ir	He	1.0000	0.0005	0.24
195 Pt	He	1.0000	0.0007	0.36
197 Au	He	1.0000	0.0036	1.80
201 Hg	He	1.0000	0.0315	15.76
205 Tl	He	1.0000	0.0002	0.11
Pb†	He	0.9998	0.0187	9.33

** IDLs were calculated from the calibration graphs (3 x standard deviation (SD) of the concentration of the calibration blank, n=10), while the dilution-adjusted DLs take account of the dilution factor of 500x.*
† Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.

Quality control drift check

Drift checks were performed using three levels of QC standards prepared at 0.5, 1.0, and 1.5 J for each target element. The QC standards were measured six times, both before and after the batch analysis. Drift (% difference) between measurements verifies the stability and reliability of the ICP MS data and supports regulatory compliance, particularly for methods aligned with IP General Chapter 5.10 and ICH Q3D.

For all elements at 0.5, 1.0, and 1.5 J (Tables 6–8), drift remained below 8%, well within the 20% acceptance limit, including for secondary isotopes (shaded rows). This excellent stability and precision, with all 12 measurements below 5%, demonstrate the robustness of the 7850 ICP-MS in He mode over 13 hours of runtime.

Table 6. Drift check of QC level 0.5 J standards run before and after sample batch, including for some secondary isotopes (shaded rows), and precision (%RSDs) of measurements over a 13 h run.

Elemental Impurities	Actual Value at 0.5 J, ppb	Before Batch Analysis			After Batch Analysis			% Drift	QC Check Throughout the Batch Analysis		
		Average (n=6), ppb	SD	%RSD	Average (n=6), ppb	SD	%RSD		Average (n=12), ppb	SD	RSD% (n=12)
7 Li	55	54.65	0.3	0.5	54.69	0.7	1.3	0.1	54.67	0.5	1.0
51 V	10	10.00	0.1	0.6	10.25	0.2	1.7	2.5	10.13	0.2	1.8
52 Cr	1100	1107.44	7.4	0.7	1138.67	19.0	1.7	2.8	1123.06	21.3	1.9
53 Cr	1100	1110.58	6.5	0.6	1138.80	18.5	1.6	2.5	1124.69	19.8	1.8
59 Co	5	4.84	0.1	2.0	5.06	0.1	1.7	4.5	4.95	0.1	2.9
60 Ni	20	19.16	0.1	0.3	19.81	0.3	1.7	3.4	19.48	0.4	2.1
62 Ni	20	19.11	0.1	0.5	20.04	0.2	1.2	4.9	19.57	0.5	2.6
63 Cu	300	288.52	1.0	0.3	302.79	4.7	1.6	4.9	295.65	8.1	2.8
65 Cu	300	288.67	1.2	0.4	301.67	4.2	1.4	4.5	295.17	7.4	2.5
75 As	1.5	1.52	0.0	1.3	1.52	0.0	1.5	0.5	1.52	0.0	1.4
78 Se	15	15.03	0.1	0.8	15.00	0.3	1.7	0.2	15.01	0.2	1.3
82 Se	15	14.45	0.3	2.2	15.08	0.2	1.5	4.4	14.76	0.4	2.9
95 Mo	300	284.96	0.8	0.3	298.03	5.0	1.7	4.6	291.50	7.6	2.6
97 Mo	300	284.31	1.1	0.4	296.38	5.0	1.7	4.2	290.35	7.2	2.5
101 Ru	10	9.37	0.1	0.6	9.68	0.2	1.7	3.3	9.52	0.2	2.1
103 Rh	10	9.51	0.0	0.4	9.84	0.2	1.6	3.5	9.67	0.2	2.1
105 Pd	10	9.48	0.1	0.5	9.72	0.1	1.4	2.5	9.60	0.2	1.7
107 Ag	15	15.20	0.1	0.6	15.35	0.3	1.9	1.0	15.28	0.2	1.4
109 Ag	15	15.26	0.0	0.2	15.39	0.3	2.0	0.8	15.33	0.2	1.4
111 Cd	0.5	0.47	0.0	0.6	0.48	0.0	1.2	1.9	0.47	0.0	1.3
114 Cd	0.5	0.47	0.0	0.3	0.48	0.0	1.7	2.4	0.48	0.0	1.7
118 Sn	600	588.99	1.7	0.3	584.36	10.5	1.8	0.8	586.67	7.6	1.3
121 Sb	120	114.80	0.2	0.2	117.34	2.0	1.7	2.2	116.07	1.9	1.6
135 Ba	140	133.24	0.5	0.3	135.20	2.3	1.7	1.5	134.22	1.9	1.4
137 Ba	140	134.44	0.4	0.3	135.89	2.5	1.9	1.1	135.17	1.9	1.4
138 Ba	140	132.61	0.4	0.3	134.81	2.2	1.7	1.7	133.71	1.9	1.4
188 Os	10	9.25	0.1	0.9	9.07	0.2	2.0	2.0	9.16	0.2	1.8
189 Os	10	9.22	0.1	0.9	9.03	0.2	2.0	2.1	9.13	0.2	1.8
191 Ir	10	9.18	0.1	0.8	8.78	0.2	1.8	4.4	8.98	0.2	2.7
193 Ir	10	10.02	0.0	0.5	10.28	0.2	2.0	2.6	10.15	0.2	1.9
194 Pt	10	9.98	0.1	0.5	10.16	0.2	1.7	1.8	10.07	0.2	1.5
195 Pt	10	9.98	0.1	0.6	10.16	0.2	1.8	1.9	10.07	0.2	1.6
197 Au	30	29.41	0.4	1.3	28.92	0.5	1.8	1.7	29.17	0.5	1.7
200 Hg	3	3.00	0.1	4.8	3.06	0.0	1.6	2.0	3.03	0.1	3.5
201 Hg	3	2.99	0.1	4.3	3.05	0.0	1.4	1.8	3.02	0.1	3.2
202 Hg	3	2.99	0.1	4.4	3.05	0.0	1.6	2.0	3.02	0.1	3.3
205 Tl	0.8	0.80	0.0	0.6	0.81	0.0	1.7	1.8	0.80	0.0	1.5
Pb[†]	0.5	0.47	0.0	0.8	0.46	0.0	2.9	3.0	0.47	0.0	2.6

[†] Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.

Table 7. Drift check of QC level 1.0 J standards run before and after sample batch, including for some secondary isotopes (shaded rows), and precision (%RSDs) of measurements over a 13 h run.

Elemental Impurities	Actual Value at 1.0 J, ppb	Before Batch Analysis			After Batch Analysis			% Drift	QC Check Throughout the Batch Analysis		
		Average (n=6), ppb	SD	%RSD	Average (n=6), ppb	SD	%RSD		Average (n=12), ppb	SD	RSD% (n=12)
7 Li	110	108.48	1.2	1.1	105.58	1.7	1.6	2.7	107.03	2.1	1.9
51 V	20	20.18	0.1	0.6	19.90	0.2	1.1	1.4	20.04	0.2	1.1
52 Cr	2200	2234.41	12.1	0.5	2207.06	27.8	1.3	1.2	2220.73	24.9	1.1
53 Cr	2200	2236.85	11.6	0.5	2206.26	28.3	1.3	1.4	2221.55	26.1	1.2
59 Co	10	9.83	0.0	0.4	10.14	0.1	1.2	–3.1	9.99	0.2	1.8
60 Ni	40	39.56	0.2	0.4	40.90	0.4	1.1	–3.4	40.23	0.8	1.9
62 Ni	40	39.51	0.2	0.5	40.70	0.5	1.2	–3.0	40.10	0.7	1.8
63 Cu	600	595.26	2.7	0.4	613.76	6.8	1.1	–3.1	604.51	10.8	1.8
65 Cu	600	593.48	2.7	0.5	611.18	6.6	1.1	–3.0	602.33	10.4	1.7
75 As	3	3.04	0.0	0.6	2.93	0.0	1.4	3.4	2.98	0.1	2.1
78 Se	30	30.22	0.3	0.9	29.25	0.3	1.1	3.2	29.73	0.6	2.0
82 Se	30	29.72	0.2	0.6	29.96	0.4	1.4	–0.8	29.84	0.3	1.1
95 Mo	600	586.70	2.5	0.4	592.31	6.7	1.1	–1.0	589.51	5.6	1.0
97 Mo	600	586.04	2.6	0.4	589.40	6.4	1.1	–0.6	587.72	5.0	0.8
101 Ru	20	19.30	0.1	0.6	19.32	0.3	1.3	–0.1	19.31	0.2	1.0
103 Rh	20	19.54	0.1	0.7	19.47	0.3	1.4	0.4	19.50	0.2	1.1
105 Pd	20	19.48	0.1	0.8	19.30	0.3	1.3	0.9	19.39	0.2	1.1
107 Ag	30	28.72	0.4	1.4	26.86	0.8	2.9	6.5	27.79	1.1	4.1
109 Ag	30	29.10	0.5	1.6	26.89	0.5	1.9	7.6	28.00	1.3	4.5
111 Cd	1	0.96	0.0	0.9	0.94	0.0	1.8	2.1	0.95	0.0	1.8
114 Cd	1	0.97	0.0	0.5	0.95	0.0	1.2	1.2	0.96	0.0	1.1
118 Sn	1200	1172.18	7.6	0.7	1179.46	13.4	1.1	–0.6	1175.82	11.1	0.9
121 Sb	240	235.25	1.4	0.6	236.12	3.0	1.3	–0.4	235.69	2.3	1.0
135 Ba	280	274.10	1.6	0.6	272.69	3.4	1.2	0.5	273.39	2.6	1.0
137 Ba	280	272.55	1.2	0.5	272.32	3.3	1.2	0.1	272.44	2.4	0.9
138 Ba	280	272.37	1.4	0.5	271.35	3.6	1.3	0.4	271.86	2.6	1.0
188 Os	20	18.62	0.2	0.9	17.80	0.3	1.5	4.4	18.21	0.5	2.6
189 Os	20	18.59	0.1	0.7	17.82	0.3	1.6	4.2	18.20	0.5	2.5
191 Ir	20	18.46	0.2	1.0	17.59	0.2	1.4	4.7	18.02	0.5	2.8
193 Ir	20	20.08	0.1	0.7	20.27	0.2	1.1	–1.0	20.17	0.2	1.0
194 Pt	20	20.05	0.2	0.8	20.14	0.3	1.4	–0.5	20.10	0.2	1.1
195 Pt	20	20.04	0.1	0.6	20.15	0.2	1.1	–0.5	20.09	0.2	0.9
197 Au	60	60.06	0.3	0.6	59.51	0.9	1.5	0.9	59.78	0.7	1.2
200 Hg	6	6.04	0.1	0.9	6.07	0.1	1.3	–0.5	6.05	0.1	1.1
201 Hg	6	6.05	0.1	0.9	6.06	0.1	1.2	–0.2	6.05	0.1	1.0
202 Hg	6	6.02	0.0	0.8	5.94	0.1	1.0	1.4	5.98	0.1	1.1
205 Tl	1.6	1.60	0.0	0.6	1.58	0.0	1.0	1.5	1.59	0.0	1.1
Pb[†]	1	0.96	0.0	2.6	0.98	0.0	3.0	–1.4	0.97	0.0	2.8

[†] Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.

Table 8. Drift check of QC level 1.5 J standards run before and after sample batch, including for some secondary isotopes (shaded rows), and precision (%RSDs) of measurements over a 13 h run.

Elemental Impurities	Actual Value at 1.5 J, ppb	Before Batch Analysis			After Batch Analysis			% Drift	QC Check Throughout the Batch Analysis		
		Average (n=6), ppb	SD	%RSD	Average (n=6), ppb	SD	%RSD		Average (n=12), ppb	SD	RSD% (n=12)
7 Li	165	162.07	3.1	1.9	161.49	2.0	1.3	0.4	161.78	2.5	1.5
51 V	30	29.98	0.5	1.7	30.54	0.4	1.4	−1.9	30.26	0.5	1.8
52 Cr	3300	3336.17	61.4	1.8	3393.11	53.1	1.6	−1.7	3364.64	62.3	1.9
53 Cr	3300	3331.54	59.5	1.8	3381.72	50.3	1.5	−1.5	3356.63	58.7	1.7
59 Co	15	14.99	0.3	2.0	16.00	0.3	2.1	−6.7	15.49	0.6	3.9
60 Ni	60	60.10	1.2	1.9	64.37	1.1	1.8	−7.1	62.24	2.5	4.0
62 Ni	60	60.04	1.1	1.9	64.09	1.2	1.8	−6.7	62.06	2.4	3.8
63 Cu	900	909.07	17.7	1.9	970.16	16.9	1.7	−6.7	939.61	35.9	3.8
65 Cu	900	908.29	18.5	2.0	966.96	18.1	1.9	−6.5	937.62	35.3	3.8
75 As	4.5	4.52	0.1	2.2	4.51	0.1	1.6	0.3	4.51	0.1	1.8
78 Se	45	44.79	0.8	1.8	44.51	0.8	1.7	0.6	44.65	0.8	1.7
82 Se	45	44.56	0.9	2.1	47.18	1.0	2.1	−5.9	45.87	1.7	3.6
95 Mo	900	893.63	17.7	2.0	933.56	18.9	2.0	−4.5	913.60	27.2	3.0
97 Mo	900	890.72	17.9	2.0	927.26	17.0	1.8	−4.1	908.99	25.3	2.8
101 Ru	30	29.33	0.6	2.0	30.27	0.5	1.8	−3.2	29.80	0.7	2.4
103 Rh	30	29.58	0.6	2.2	30.62	0.6	1.8	−3.5	30.10	0.8	2.6
105 Pd	30	29.50	0.6	2.1	30.40	0.6	2.1	−3.0	29.95	0.8	2.5
107 Ag	45	42.67	1.4	3.3	41.81	0.8	1.8	2.0	42.24	1.2	2.8
109 Ag	45	42.51	1.0	2.3	41.80	1.7	4.1	1.7	42.15	1.4	3.3
111 Cd	1.5	1.46	0.0	2.1	1.49	0.0	1.8	−1.8	1.47	0.0	2.1
114 Cd	1.5	1.46	0.0	1.9	1.50	0.0	1.9	−2.6	1.48	0.0	2.3
118 Sn	1800	1772.15	32.2	1.8	1821.52	37.6	2.1	−2.8	1796.83	42.2	2.3
121 Sb	360	355.67	6.3	1.8	365.63	6.8	1.8	−2.8	360.65	8.1	2.2
135 Ba	420	410.69	7.5	1.8	418.87	9.4	2.3	−2.0	414.78	9.2	2.2
137 Ba	420	410.81	7.8	1.9	419.04	8.6	2.1	−2.0	414.93	8.9	2.1
138 Ba	420	410.90	7.5	1.8	418.36	8.8	2.1	−1.8	414.63	8.7	2.1
188 Os	30	28.13	0.4	1.6	27.18	0.6	2.3	3.3	27.65	0.7	2.6
189 Os	30	28.11	0.5	1.6	27.11	0.6	2.0	3.6	27.61	0.7	2.6
191 Ir	30	28.00	0.5	1.8	27.04	0.6	2.0	3.4	27.52	0.7	2.6
193 Ir	30	29.86	0.6	2.1	30.60	0.4	1.4	−2.5	30.23	0.6	2.1
194 Pt	30	29.89	0.6	2.0	30.67	0.5	1.6	−2.6	30.28	0.7	2.2
195 Pt	30	29.92	0.6	1.9	30.63	0.5	1.6	−2.4	30.27	0.6	2.1
197 Au	90	89.73	2.0	2.3	90.96	1.3	1.4	−1.4	90.34	1.7	1.9
200 Hg	9	8.94	0.1	1.1	8.70	0.1	1.5	2.7	8.82	0.2	1.9
201 Hg	9	8.95	0.1	1.6	8.68	0.1	1.5	3.0	8.82	0.2	2.2
202 Hg	9	8.93	0.1	1.3	8.69	0.1	1.6	2.8	8.81	0.2	2.0
205 Tl	2.4	2.37	0.0	1.8	2.41	0.0	1.6	−1.8	2.39	0.0	1.9
Pb[†]	1.5	1.42	0.0	2.1	1.42	0.0	2.5	0.2	1.42	0.0	2.2

[†] Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.

Requirements of IP General Chapter 5.10

The method validation requirements of IP General Chapter 5.10 include limit and quantitative procedures. Limit procedures must confirm detectability (detection limit), precision (repeatability), and specificity of the measurement.

Limit procedures

Detectability of the analytical workflow is established by comparing results obtained from samples spiked with target elements at 1.0 and 0.8 J concentrations. For instrumental methods, the average value of the three replicate measurements of the 1.0 J sample spiked test solution must be within ±15% of the average value obtained for the replicate measurements of a reference (standard) solution at 1.0 J. Also, the mean concentration for samples spiked at 0.8 J must be lower than for the 1 J standard. The detectability results shown in Table 9 comply with the criteria defined in draft IP 5.10.

Precision for instrumental methods (repeatability) should meet the acceptable criteria with % RSDs not more than 20% for each of the target elements. Six independent samples of each of the three oral drug products were spiked at 1.0 J for all 24 target elements. The precision results presented in Table 11 met the criteria specified in draft IP 5.10.

Specificity, as defined in IP 5.10, evaluates whether the analytical procedure can accurately and unequivocally determine the target element in the presence of the sample matrix and other analytes. ICP-MS, being an inorganic mass spectrometric technique, is inherently specific since each element possesses at least one isotope that is free from direct overlap with other elements. Potential spectral interferences, primarily from molecular or polyatomic ions, are effectively controlled in the 7850 ICP-MS using the ORS^4 cell with He as the cell gas. In He mode, polyatomic interferences are reduced through kinetic energy discrimination (KED), which attenuates interfering ions and minimizes their contribution at the analyte mass.

Specificity is also demonstrated by monitoring secondary isotopes, where available, which serve as qualifiers or confirmatory measurements. The results obtained for the secondary isotopes (highlighted in gray) in the QC standards at 0.5, 1.0, and 1.5 J show good agreement with the values reported from the primary isotopes (Tables 6–8). This alignment provides additional evidence of method specificity as required by draft IP 5.10.

Quantitative procedures

The quantitative procedures need to demonstrate the following acceptable criteria:

- Accuracy (spike recoveries) of measurements of each target element at different levels from 0.5 to 1.5 J: three independent sample preparations spiked with the target analytes at each level. *Acceptance criteria*: spike recoveries must be between 70 and 150%.
- Precision (repeatability) of six independent sample preparations, spiked with the target elements at three different levels covering the specified range. *Acceptance criteria*: Relative standard deviation (RSD) should not be more than 20% for each target element in each sample.
- Intermediate precision (ruggedness). Perform the repeatability analysis again, either on a different day, with a different instrument, with a different analyst, or a combination thereof. Combine the results of this analysis with the repeatability analysis. *Acceptance criteria*: RSD should not be more than 25% for each target element.
- Specificity: the procedure must be able to unequivocally assess each target element in the presence of components that may be expected to be present in the sample, including other target elements, and matrix components.
- Range and Linearity: demonstrated by meeting the accuracy requirements.
- Quantitation Limit (QL): use the results from the accuracy study. The QL of 0.5 J is confirmed when the accuracy acceptance criteria for the 0.5 J spiked solution are met. *Acceptance criteria*: the QL should be less than or equal to 0.5 J for each target element.

Accuracy and precision

Tables 10 to 12 show the accuracy and precision study results at the 0.5, 1.0, and 1.5 J concentration levels, respectively, using the 7850 ICP-MS in He mode. All recoveries were within the acceptable range of 70–150%, and %RSDs values were below 5%, confirming the accuracy and precision of the method.

Table 9. Detectability study results for three different oral products spiked at 0.8 and 1.0 J. Acceptable criteria: Precision for limit tests should be less than 20%. Accuracy for 1 J spike (% RSD at n=3 must be ±15%), and detectability (0.8 J spike must be less than 1 J standard). The shaded cells indicate the secondary or 'qualifier' isotopes.

Elemental Impurities	True Value 0.8 J, ppb	Oral Drug Products Spiked at 0.8 J, ppb			% Recovery at 0.8 J from Oral Drug Products			True Value 1.0 J, ppb	Standard 1.0 J as QC Value, ppb	Oral Drug Products Spiked at 1.0 J, ppb			% Recovery at 1.0 J from Oral Drug Products			Limit Test of 0.8 J Spike/ 1 J Standard			Precision for 1.0 J Spiked Sample (n=3): must be ±15%		
		Product 1	Product 2	Product 3	Product 1	Product 2	Product 3			Product 1	Product 2	Product 3	Product 1	Product 2	Product 3	Product 1	Product 2	Product 3	Product 1	Product 2	Product 3
7 Li	88	87.75	87.12	85.83	100	99	98	110	107.03	107.56	107.47	108.42	100	100	101	0.82	0.81	0.80	0.65	0.61	0.31
51 V	16	16.01	15.93	16.00	100	100	100	20	20.04	20.26	20.27	20.35	101	101	102	0.80	0.79	0.80	1.01	0.51	0.37
52 Cr	1760	1761.24	1756.74	1762.61	100	100	100	2200	2220.73	2252.79	2248.95	2260.40	101	101	102	0.79	0.79	0.79	1.18	0.52	0.28
53 Cr	1760	1765.41	1756.91	1763.76	100	100	100	2200	2221.55	2251.28	2243.91	2260.85	101	101	102	0.79	0.79	0.79	1.06	0.28	0.24
59 Co	8	7.63	7.60	7.66	95	95	96	10	9.99	10.15	10.11	10.18	102	101	102	0.76	0.76	0.77	0.71	0.28	0.85
60 Ni	32	30.74	30.85	30.89	96	96	97	40	40.23	40.85	40.78	40.88	102	101	102	0.76	0.77	0.77	0.44	0.27	0.43
62 Ni	32	30.57	30.68	30.83	96	96	96	40	40.10	40.70	40.63	40.79	101	101	102	0.76	0.77	0.77	0.76	0.21	0.40
63 Cu	480	461.61	462.14	463.80	96	96	97	600	604.51	614.69	616.26	616.40	102	102	102	0.76	0.76	0.77	0.97	0.06	0.72
65 Cu	480	461.07	460.80	465.14	96	96	97	600	602.33	612.82	613.38	614.51	102	102	102	0.77	0.77	0.77	0.87	0.24	0.72
75 As	2.4	2.43	2.42	2.42	101	101	101	3	2.98	3.02	3.03	3.04	101	101	102	0.81	0.81	0.81	1.09	0.45	0.58
78 Se	24	24.20	24.28	23.87	101	101	100	30	29.73	30.36	30.28	30.09	102	102	101	0.81	0.82	0.80	1.07	0.37	0.92
82 Se	24	23.02	22.99	23.51	96	96	98	30	29.84	30.67	30.18	30.40	103	101	102	0.77	0.77	0.79	0.32	1.40	0.94
95 Mo	480	459.04	460.18	460.09	96	96	96	600	589.51	597.28	597.39	600.74	101	101	102	0.78	0.78	0.78	0.62	0.04	0.37
97 Mo	480	457.68	459.40	457.45	95	96	95	600	587.72	596.72	595.28	597.75	102	101	102	0.78	0.78	0.78	0.50	0.25	0.35
101 Ru	16	15.24	15.25	15.28	95	95	96	20	19.31	19.58	19.54	19.56	101	101	101	0.79	0.79	0.79	0.09	0.35	0.29
103 Rh	16	15.34	15.33	15.28	96	96	96	20	19.50	19.75	19.75	19.81	101	101	102	0.79	0.79	0.78	0.32	0.44	0.82
105 Pd	16	15.45	15.38	15.34	97	96	96	20	19.39	19.69	19.60	19.69	102	101	102	0.80	0.79	0.79	0.81	0.37	0.68
107 Ag	24	23.02	23.35	22.41	96	97	93	30	27.79	27.98	28.03	28.20	101	101	101	0.83	0.84	0.81	1.54	2.36	2.20
109 Ag	24	23.34	22.86	22.83	97	95	95	30	28.00	30.99	27.84	27.87	111	99	100	0.83	0.82	0.82	1.43	2.62	2.08
111 Cd	0.8	0.76	0.76	0.77	95	95	96	1	0.95	0.97	0.97	0.97	102	102	102	0.80	0.80	0.81	0.96	0.71	1.06
114 Cd	0.8	0.76	0.76	0.76	95	96	95	1	0.96	0.97	0.97	0.97	101	101	101	0.79	0.80	0.79	0.34	0.04	0.74
118 Sn	960	920.14	919.24	923.57	96	96	96	1200	1175.82	1179.87	1179.08	1182.73	100	100	101	0.78	0.78	0.79	0.61	0.57	0.77
121 Sb	192	185.43	184.92	185.13	97	96	96	240	235.69	235.70	235.30	236.87	100	100	101	0.79	0.78	0.79	0.61	0.61	0.85
135 Ba	224	216.45	216.79	216.74	97	97	97	280	273.39	273.93	273.36	274.13	100	100	100	0.79	0.79	0.79	0.46	0.39	0.64
137 Ba	224	214.54	215.47	215.54	96	96	96	280	272.44	273.15	272.56	273.41	100	100	100	0.79	0.79	0.79	0.13	0.19	0.41
138 Ba	224	213.88	214.77	215.32	96	96	96	280	271.86	272.07	272.22	272.87	100	100	100	0.79	0.79	0.79	0.32	0.09	0.25
188 Os	16	15.21	15.12	14.98	95	95	94	20	18.21	18.02	18.03	18.11	99	99	99	0.84	0.83	0.82	0.73	0.66	0.82
189 Os	16	15.19	15.13	14.84	95	95	93	20	18.20	18.01	18.02	18.10	99	99	99	0.83	0.83	0.82	0.84	0.48	0.51
191 Ir	16	15.18	15.20	15.03	95	95	94	20	18.02	17.90	17.85	17.91	99	99	99	0.84	0.84	0.83	0.54	0.28	0.13
193 Ir	16	15.83	15.89	16.00	99	99	100	20	20.17	20.30	20.24	20.46	101	100	101	0.78	0.79	0.79	0.33	0.18	0.47
194 Pt	16	15.90	15.95	15.92	99	100	100	20	20.10	20.18	20.04	20.23	100	100	101	0.79	0.79	0.79	0.35	0.10	0.66
195 Pt	16	15.95	16.00	15.92	100	100	100	20	20.09	20.15	20.10	20.24	100	100	101	0.79	0.80	0.79	0.25	0.17	0.59
197 Au	48	47.51	47.88	47.74	99	100	100	60	59.78	59.91	59.81	60.12	100	100	101	0.79	0.80	0.80	1.11	0.63	0.92
200 Hg	4.8	4.79	4.77	4.82	100	99	101	6	6.05	6.00	6.01	6.06	99	99	100	0.79	0.79	0.80	1.11	0.44	0.96
201 Hg	4.8	4.72	4.77	4.81	98	99	100	6	6.05	6.01	6.02	6.05	99	99	100	0.78	0.79	0.79	1.36	0.63	1.08
202 Hg	4.8	4.74	4.75	4.79	99	99	100	6	5.98	6.00	6.03	6.08	100	101	102	0.79	0.79	0.80	0.94	0.23	0.80
205 Tl	1.28	1.27	1.27	1.27	99	99	99	1.6	1.59	1.62	1.62	1.61	102	102	102	0.80	0.80	0.80	0.12	0.09	0.62
Pb†	0.8	0.72	0.72	0.72	90	90	89	1	0.97	0.97	0.96	0.97	99	99	100	0.74	0.74	0.74	2.84	2.97	3.50

† *Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.*

Table 10. Accuracy and precision results for spike recoveries at 0.5 J for each target element. The shaded cells indicate the secondary or 'qualifier' isotopes, (n=6).

Elemental Impurities	True Value at 0.5 J, ppb	Oral Product 1			Oral Product 2			Oral Product 3		
		Average Measured Spiked Value, ppb	%RSD	Recovery %	Average Measured Spiked Value, ppb	%RSD	Recovery %	Average Measured Spiked Value, ppb	%RSD	Recovery %
7 Li	55	55.05	1.01	100	54.37	0.94	99	54.53	1.22	99
51 V	10	10.11	0.49	101	10.06	0.95	101	10.09	1.25	101
52 Cr	1100	1122.38	0.72	102	1116.27	1.16	101	1120.81	1.14	102
53 Cr	1100	1122.28	0.52	102	1118.60	1.08	102	1121.35	1.22	102
59 Co	5	4.84	1.07	97	4.87	1.13	97	4.89	1.24	98
60 Ni	20	19.49	0.82	97	19.61	1.65	98	19.67	1.28	98
62 Ni	20	19.45	0.95	97	19.53	1.16	98	19.65	1.25	98
63 Cu	300	294.82	0.88	98	295.77	1.31	99	296.91	0.94	99
65 Cu	300	294.96	0.88	98	295.56	1.24	98	296.57	0.93	99
75 As	1.5	1.51	1.24	101	1.50	1.32	100	1.52	1.68	101
78 Se	15	15.17	0.88	101	14.98	1.03	100	15.01	1.47	100
82 Se	15	14.63	1.95	98	14.61	1.53	97	14.66	1.57	98
95 Mo	300	289.78	1.01	97	289.54	1.20	96	290.04	1.17	97
97 Mo	300	289.42	0.94	96	288.50	1.24	96	289.19	1.01	96
101 Ru	10	9.56	1.02	96	9.47	1.36	95	9.49	1.34	95
103 Rh	10	9.66	0.91	97	9.61	1.44	96	9.62	1.01	96
105 Pd	10	9.63	1.02	96	9.54	1.39	95	9.55	1.03	95
107 Ag	15	15.23	0.88	101	15.20	1.07	101	15.15	1.04	101
109 Ag	15	15.30	0.64	102	15.21	1.07	101	15.24	1.16	102
111 Cd	0.5	0.48	1.77	96	0.47	1.25	94	0.47	0.82	95
114 Cd	0.5	0.47	0.90	95	0.47	1.06	94	0.47	0.83	94
118 Sn	600	576.07	0.96	96	574.04	1.13	96	574.11	1.14	96
121 Sb	120	115.73	0.94	96	115.49	1.01	96	115.17	1.12	96
135 Ba	140	133.80	0.94	96	133.40	1.19	95	133.21	1.28	95
137 Ba	140	135.13	0.81	96	134.14	1.19	96	134.30	1.13	96
138 Ba	140	133.52	0.80	95	132.85	1.11	95	132.88	1.10	95
188 Os	10	9.08	1.33	91	9.50	4.45	95	9.08	3.91	91
189 Os	10	9.08	1.45	91	9.17	4.65	92	9.07	3.90	91
191 Ir	10	9.38	4.90	94	9.21	4.50	92	9.66	4.04	97
193 Ir	10	10.16	0.88	102	10.07	1.21	101	10.14	1.15	101
194 Pt	10	10.08	0.85	101	10.02	1.21	100	10.03	1.22	100
195 Pt	10	10.06	0.88	101	10.00	1.14	100	9.99	1.33	100
197 Au	30	29.42	1.80	98	29.25	1.52	97	29.38	1.03	98
200 Hg	3	3.00	0.99	100	2.98	1.66	99	3.01	1.16	100
201 Hg	3	3.00	1.01	100	2.99	1.84	99	3.00	1.35	100
202 Hg	3	3.00	0.73	100	2.99	1.61	99	3.01	1.41	100
205 Tl	0.8	0.80	1.00	100	0.80	1.35	100	0.80	1.25	100
Pb[†]	0.5	0.45	2.54	90	0.45	3.49	90	0.46	3.93	92

[†] Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.

Table 11. Accuracy and precision results for spike recoveries at 1.0 J for each target element. The shaded cells indicate the secondary or 'qualifier' isotopes, n=6.

Elemental Impurities	True Value at 1.0 J, ppb	Oral Product 1			Oral Product 2			Oral Product 3		
		Average Measured Spiked Value, ppb	%RSD	Recovery %	Average Measured Spiked Value, ppb	%RSD	Recovery %	Average Measured Spiked Value, ppb	%RSD	Recovery %
7 Li	110	106.84	1.27	97	107.29	0.80	97	108.12	0.83	98
51 V	20	20.14	1.18	101	20.21	0.76	101	20.26	0.98	101
52 Cr	2200	2239.27	1.36	102	2243.71	0.88	102	2252.61	0.74	102
53 Cr	2200	2239.34	1.30	102	2241.85	0.69	102	2251.77	0.69	102
59 Co	10	10.10	1.00	101	10.10	0.37	101	10.15	1.09	101
60 Ni	40	40.62	1.07	101	40.66	0.75	102	40.69	1.09	102
62 Ni	40	40.46	1.14	101	40.59	0.50	101	40.65	0.92	102
63 Cu	600	612.22	1.04	102	614.50	0.72	102	614.88	0.98	102
65 Cu	600	609.56	1.19	102	611.88	0.69	102	612.40	0.88	102
75 As	3	3.00	1.32	100	3.01	0.80	100	3.03	1.00	101
78 Se	30	30.13	1.46	100	30.12	0.97	100	29.96	1.18	100
82 Se	30	30.48	0.96	102	30.22	0.93	101	30.19	1.36	101
95 Mo	600	595.16	0.99	99	595.12	0.77	99	597.27	1.01	99
97 Mo	600	593.44	1.13	99	593.44	0.76	99	594.33	0.98	99
101 Ru	20	19.43	1.12	97	19.46	0.57	97	19.45	0.85	97
103 Rh	20	19.66	0.99	98	19.69	0.61	98	19.69	1.05	98
105 Pd	20	19.61	1.04	98	19.55	0.56	98	19.57	1.16	98
107 Ag	30	28.20	1.78	94	28.13	1.75	94	28.18	1.93	94
109 Ag	30	28.17	2.53	94	28.02	2.57	93	28.07	1.84	94
111 Cd	1	0.96	1.69	96	0.97	0.85	97	0.96	1.23	96
114 Cd	1	0.97	1.07	97	0.97	0.77	97	0.97	1.00	97
118 Sn	1200	1172.83	1.16	98	1173.94	0.66	98	1177.52	1.04	98
121 Sb	240	234.44	1.04	98	234.99	0.68	98	235.40	1.25	98
135 Ba	280	272.04	1.06	97	272.32	0.74	97	272.55	1.08	97
137 Ba	280	271.29	1.27	97	271.31	0.80	97	271.92	1.08	97
138 Ba	280	270.20	1.16	96	271.03	0.66	97	271.34	1.10	97
188 Os	20	18.06	1.72	90	18.12	1.96	91	18.16	1.58	91
189 Os	20	18.09	1.58	90	18.13	1.88	91	18.17	1.61	91
191 Ir	20	18.93	4.93	95	18.00	1.78	90	18.45	2.45	92
193 Ir	20	20.18	0.87	101	20.20	0.52	101	20.30	1.28	101
194 Pt	20	20.06	1.08	100	20.00	0.47	100	20.12	1.13	101
195 Pt	20	20.00	1.22	100	20.03	0.53	100	20.12	1.16	101
197 Au	60	59.82	1.00	100	59.92	0.75	100	59.95	1.22	100
200 Hg	6	6.00	0.95	100	6.02	0.59	100	6.04	1.27	101
201 Hg	6	5.99	1.12	100	6.02	0.66	100	6.04	1.35	101
202 Hg	6	5.99	1.07	100	6.03	0.34	100	6.05	1.24	101
205 Tl	1.6	1.61	1.10	100	1.61	0.75	100	1.61	1.29	100
Pb[†]	1	0.98	3.93	98	0.96	4.43	96	0.96	4.31	96

[†] Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.

Table 12. Accuracy and precision results for spike recoveries at 1.5 J for each target element. The shaded cells indicate the secondary or 'qualifier' isotopes, n=6.

Elemental Impurities	True Value at 1.5 J, ppb	Oral Product 1			Oral Product 2			Oral Product 3		
		Average Measured Spiked Value, ppb	%RSD	Recovery %	Average Measured Spiked Value, ppb	%RSD	Recovery %	Average Measured Spiked Value, ppb	%RSD	Recovery %
7 Li	165	162.77	1.23	99	162.22	1.28	98	163.71	1.70	99
51 V	30	30.42	1.11	101	30.44	1.38	101	30.50	1.76	102
52 Cr	3300	3381.27	1.35	102	3377.80	1.35	102	3394.70	1.70	103
53 Cr	3300	3375.71	1.35	102	3376.73	1.28	102	3384.85	1.70	103
59 Co	15	15.70	1.48	105	15.78	1.47	105	15.79	0.87	105
60 Ni	60	63.05	1.72	105	63.31	1.53	105	63.59	0.84	106
62 Ni	60	62.87	1.59	105	63.17	1.48	105	63.29	1.10	105
63 Cu	900	951.47	1.54	106	955.10	1.45	106	956.75	1.16	106
65 Cu	900	950.52	1.49	106	952.55	1.35	106	953.31	1.03	106
75 As	4.5	4.51	1.23	100	4.51	1.37	100	4.52	1.71	100
78 Se	45	44.75	1.45	99	44.54	1.25	99	44.74	1.40	99
82 Se	45	46.66	2.39	104	46.65	1.22	104	46.53	1.25	103
95 Mo	900	923.73	1.47	103	925.42	1.50	103	924.70	1.24	103
97 Mo	900	919.87	1.60	102	921.66	1.50	102	918.93	1.11	102
101 Ru	30	30.14	1.63	100	30.13	1.64	100	30.14	1.07	100
103 Rh	30	30.38	1.86	101	30.42	1.39	101	30.43	0.92	101
105 Pd	30	30.33	1.81	101	30.32	1.45	101	30.28	0.91	101
107 Ag	45	43.64	2.21	97	42.42	1.94	94	42.02	1.96	93
109 Ag	45	42.63	2.75	95	42.78	1.92	95	42.17	1.73	94
111 Cd	1.5	1.50	1.89	100	1.48	1.29	99	1.48	0.84	99
114 Cd	1.5	1.49	1.46	99	1.49	1.30	100	1.49	0.71	99
118 Sn	1800	1812.40	1.61	101	1816.17	1.43	101	1810.15	0.71	101
121 Sb	360	362.63	1.38	101	363.07	1.47	101	361.96	0.77	100
135 Ba	420	417.67	1.50	99	418.28	1.54	100	417.65	0.95	99
137 Ba	420	418.22	1.39	100	418.23	1.35	100	417.11	0.77	99
138 Ba	420	418.24	1.35	100	418.57	1.19	100	417.36	0.72	99
188 Os	30	27.72	1.43	92	27.63	1.29	92	27.64	0.74	92
189 Os	30	27.67	1.44	92	27.65	1.32	92	27.62	0.88	92
191 Ir	30	27.49	1.61	92	27.45	1.31	91	27.41	1.03	91
193 Ir	30	30.59	1.29	102	30.55	1.22	102	30.62	1.38	102
194 Pt	30	30.55	1.54	102	30.54	1.42	102	30.66	1.17	102
195 Pt	30	30.48	1.46	102	30.53	1.05	102	30.58	1.53	102
197 Au	90	91.00	1.59	101	91.29	1.36	101	90.98	1.60	101
200 Hg	9	9.12	1.55	101	9.14	1.34	102	9.12	1.13	101
201 Hg	9	9.11	1.47	101	9.14	1.29	101	9.14	1.21	101
202 Hg	9	9.10	1.62	101	9.11	1.51	101	9.14	1.30	101
205 Tl	2.4	2.42	1.62	101	2.42	0.99	101	2.42	1.25	101
Pb[†]	1.5	1.38	1.14	92	1.38	0.80	92	1.38	1.00	92

[†] Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.

Intermediate precision

Six replicates of each oral product spiked at 0.5, 1.0, and 1.5 J were analyzed on two separate days using the 7850 ICP-MS in He mode. The intermediate precision results (%RSDs) for each target element, shown in Table 13, were all below 7%, well within the <25% acceptance limit.

Table 13. Intermediate precision results of the target elements at 0.5, 1.0, and 1.5 J, measured on two separate days using the Agilent 7850 ICP-MS in He mode.

Elemental Impurities	Spike at 0.5 J						Spike at 1.0 J						Spike at 1.5 J					
	Oral Product 1		Oral Product 2		Oral Product 3		Oral Product 1		Oral Product 2		Oral Product 3		Oral Product 1		Oral Product 2		Oral Product 3	
	%RSD (n=12)	Recovery % (n=12)	%RSD (n=12)	Recovery % (n=12)	%RSD (n=12)	Recovery % (n=12)	%RSD (n=12)	Recovery % (n=12)	%RSD (n=12)	Recovery % (n=12)	%RSD (n=12)	Recovery % (n=12)	%RSD (n=12)	Recovery % (n=12)	%RSD (n=12)	Recovery % (n=12)	%RSD (n=12)	Recovery % (n=12)
7 Li	1.82	101	2.04	101	1.78	100	2.89	99	2.89	100	2.77	100	1.92	100	2.32	100	2.11	101
51 V	0.78	101	0.75	101	1.03	101	1.76	102	1.61	102	1.94	102	1.19	102	1.28	102	1.59	102
52 Cr	0.93	102	0.84	101	0.94	102	1.61	102	1.48	102	1.60	103	1.10	103	1.20	103	1.42	103
59 Co	1.13	96	1.32	96	1.12	97	2.01	100	1.79	100	1.73	101	1.98	103	2.14	103	1.90	104
60 Ni	1.79	96	2.10	96	1.89	97	2.50	100	2.14	100	2.26	100	2.88	103	2.97	103	2.96	103
63 Cu	1.76	97	1.79	97	1.62	98	2.10	101	1.91	101	1.94	101	2.31	104	2.47	104	2.35	104
75 As	0.97	101	1.26	100	1.47	101	1.87	101	1.47	101	1.77	102	1.32	101	1.32	101	1.46	101
78 Se	0.98	101	1.43	101	1.32	101	1.56	101	1.73	101	2.27	101	1.46	100	1.74	100	1.62	100
95 Mo	1.03	96	0.90	96	0.84	96	1.82	99	1.63	100	1.67	100	1.20	102	1.39	102	1.04	103
101 Ru	1.22	95	1.07	95	1.00	95	1.98	98	1.56	98	1.79	98	1.47	101	1.28	101	1.06	101
103 Rh	0.97	96	1.05	96	0.77	96	1.87	99	1.64	99	1.68	99	1.46	101	1.15	102	0.88	102
105 Pd	1.15	96	1.12	96	0.78	96	1.42	98	1.07	98	1.40	98	1.37	101	1.28	101	0.84	101
107 Ag	2.37	100	2.24	100	2.07	100	2.95	96	3.58	97	3.28	96	2.00	97	3.36	97	3.23	96
111 Cd	1.87	95	1.47	94	1.13	95	2.56	97	1.57	97	2.27	97	1.48	100	1.23	99	1.03	99
118 Sn	0.77	96	0.93	96	0.89	96	1.92	99	1.79	99	1.87	99	1.35	101	1.26	101	0.90	101
121 Sb	0.67	97	0.83	97	0.94	96	1.92	99	1.80	99	2.03	99	1.24	101	1.30	101	1.08	101
137 Ba	0.72	97	1.08	96	0.93	96	2.24	98	2.14	98	2.13	99	2.13	98	1.54	101	1.33	100
189 Os	3.95	94	4.91	95	4.94	94	4.46	99	4.84	95	4.78	96	3.27	93	1.71	93	3.86	97
193 Ir	1.04	101	1.00	101	0.88	101	1.77	102	1.65	102	1.85	102	1.24	102	1.01	102	1.11	102
195 Pt	1.21	100	0.81	100	0.91	100	1.68	101	1.56	101	1.59	101	1.33	102	1.17	103	1.43	103
197 Au	1.67	99	1.61	99	1.03	98	2.05	101	2.09	101	2.18	101	1.40	102	1.28	102	1.62	102
201 Hg	1.95	102	2.46	101	2.17	102	2.36	101	2.20	102	2.31	102	1.42	102	1.30	102	1.41	103
205 Tl	0.89	100	1.07	101	0.98	100	2.09	101	1.78	101	1.92	101	1.36	101	1.15	101	1.35	102
Pb†	5.91	96	6.16	95	6.01	96	4.24	101	4.21	101	3.79	99	4.73	96	4.98	97	4.45	98

† *Automatically reported by Agilent ICP-MS MassHunter software as the sum of the lead isotopes 206+207+208.*

Conclusion

The analytical approach described in draft Indian Pharmacopoeia (IP) General Chapter 5.10 for the determination of elemental impurities in pharmaceutical products was applied in this study using ICP-MS. Three over-the-counter oral tablet drugs were acid digested by microwave, spiked at various J levels, and analyzed for 24 target elements using an Agilent 7850 ICP-MS.

The 7850 ICP-MS, equipped with a robust plasma system and the ORS^4 collision/reaction cell operating in helium mode, effectively minimized polyatomic interferences and enabled accurate measurement of target isotopes and qualifier ions. Its wide dynamic range detector further supported the analysis of all three oral drug products using a single analytical method and standard operating conditions.

Instrument setup and method development were simplified by selecting General Purpose plasma conditions, applying automated lens tuning, and using the ICH/USP preset method in the Agilent ICP-MS MassHunter software.

The method met all performance criteria outlined in IP 5.10, including specificity, accuracy, spike recovery, stability, and system suitability for both limit and quantitative procedures. Instrument detection limits were significantly lower than the J values for oral drugs, ensuring reliable quantification of elemental impurities at regulatory control levels.

Overall, the results confirm that the 7850 ICP-MS provides a reliable, sensitive, and efficient platform for compliance with IP 5.10 requirements for elemental impurity testing in oral drug products. The simplified method development, robust interference removal, and workflow-based operation significantly reduce analytical complexity while supporting consistent regulatory compliance for routine pharmaceutical quality control laboratories.

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Products used in this application

Agilent products

Product Type	Description	Part Number
Sample Introduction	MicroMist glass concentric nebulizer (U-series)	G3266-80004
	Quartz torch, 2.5 mm injector	G3280-80053
Interface	Standard ICP-MS sampler cone, nickel tip with copper base	G3280-67040
	Standard nickel skimmer cone	G3280-67041
Tubing Kits	Peristaltic pump tubing (sample uptake)	5005-0020
Chemical Standards	ICH/USP target elements standard A, Hg 30 µg/mL, As 15 µg/mL, Cd and Pb 5 µg/mL in 2% HNO_3	5190-9766
	ICH/USP oral target elements standard D: Cr 11,000 µg/mL, Sn 6,000 µg/mL, Cu and Mo 3,000 µg/mL, Ba 1,400 µg/mL, Sb 1,200 µg/mL, Li 550 µg/mL in 5% HNO_3/trace HF	5190-9769
	ICH/USP oral target elements Std C_v2	5191-4555
	ICH/USP oral target elements standard B, Ni 200 µg/mL, Ag and Se 150 µg/mL, V 100 µg/mL, Tl 8 µg/mL, Co 50 µg/mL in 2% HNO_3	5190-9767
	USP 232 pharma internal standard 1	5190-9770

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