Key Analytical Issues: Sample Preparation, Interferences and Variability

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Answers That Matter.

Presentation Outline

- Sample preparation objectives and challenges
- Some common interferences in ICP-MS analyses
- Small and large molecule ICP-MS case studies
- Summaries

Sample Preparation Objectives and Challenges

- Main objective: provide analytical results that correctly represent the concentration of the elemental impurity at the required level. The foundation for an appropriate analytical method.
- No single correct method or technique.
- Influences include available resources, availability of test material, dose, characteristics of specific analytes, number of analytes in a single run, attributes of test material (biological to small molecule drug product), capacity for transfer

Why ICP Mass Spectrometry?

- Ultra-trace multi-element analytical technique
  - Ultra-Trace atomic absorption techniques are single element
  - Applying Option 1 (10-g) dosing at the control threshold (30% of PDE) too low for most ICP optical emission methods for Class 1 and 2A EIs

Fundamental Instrument Configurations

- Commercial ICP-MS Instrumentation configurations
  - Quadrupole based (unit resolution)
  - Time of Flight (unit resolution)
  - Double focusing magnetic sector based (high resolution)
- The majority of pharmaceutical analyses will be conducted using quadrupole based ICP mass spectrometers …..so we will focus on that configuration
- To illustrate application of ICP mass spectrometry, experimental results generated on two test materials: parenteral sucrose and sodium chloride

Analytical Challenges

- For analysis of parenteral samples, analyte masses ranges from 7Li to 200+ (Pb and Hg). Encompasses the entire mass range of spectrometer.
- As and V included in risk assessment for oral and parenteral samples. Both suffer from chloride based interferences. Differences in interfering species can make control of backgrounds challenging with collision cell in ICP-MS
- Li response is seriously attenuated with collision cell charged, which can make analyzing all elements in a single analytical run challenging.
- High concentrations of Class 3 elements can make linearity an issue….high error near intercept.

Polyatomic interferences at unit resolution specificity…

- 51V (99% abundant)
  - Interfering species is 35Cl16O
- 75As (100% abundant)
  - Interfering species is 40Ar35Cl
- By what means is this corrected?
  - Inter-element correction
    - Monitor count-rate at 37Cl16O (53Cr)
    - Monitor count-rate at 40Ar37Cl (77Se)
  - Collision cell/reaction cell
    - Kinetic Energy Discrimination (non-reactive gases-collision cell)
    - Dynamic Reaction Cell (reactive gases *e.g.* ammonium, oxygen)

Other possible interferences at unit resolution specificity…

Isotope	Interfering Species	Comments
51V	35Cl16O	Common
52Cr	40Ar12C	Common
53Cr	37Cl16O	Common
58Ni	58Fe	Common
60Ni	59Co1H	Sourced from Co standard
63Cu	62Ni1H	ICP-MS interface, sourced from Ni standard
65Cu	49Ti16O, 64Zn1H	Ti, Zn sourced from test material, standard
75As	40Ar35Cl	Common
77Se	40Ar37Cl	Common
80Se	40Ar40Ar	Common
111Cd	95Mo16O	Sourced from test material, Mo standard
114Cd	114Sn	Sourced from test material, Sn standard
198Hg	182W16O	Sourced from test material, W standard
199Hg	183W16O	Sourced from test material, W standard
200Hg	184W16O	Sourced from test material, W standard
202Hg	186W16O	Sourced from test material, W standard

Experimental details for analysis of sucrose and NaCl…

Dose, g	10
Specimen weight, g	0.2
Final Volume, mL	100

Class	Element	Parenteral PDE, µg/Day	Permitted Conc., µg/g	Control Threshold, µg/g	Control Threshold Spike Conc., µg/L	Experimental Spike Conc., µg/L
1	**As**	15	1.5	0.45	0.9	0.12
1	**Cd**	2	0.2	0.06	0.12	0.12
2A	**Co**	5	0.5	0.15	0.3	0.12
3	**Cu**	300	30	9	18	2.4
1	**Hg**	3	0.3	0.09	0.18	0.12
3	**Li**	250	25	7.5	15	2.4
2A	**Ni**	20	2	0.6	1.2	0.6
1	**Pb**	5	0.5	0.15	0.3	0.12
3	**Sb**	90	9	2.7	5.4	2.4
2A	**V**	10	1	0.3	0.6	0.6

Standard curve specifics-used for both test materials

Final Volume, mL		0.0	0.05	0.10	0.25	0.50	1.00	0.06	
Element	Stock Standard Conc., µg/mL	Blank, µg/L	Std 1, µg/L	Std 2, µg/L	Std 3, µg/L	Std 4, µg/L	Std 5, µg/L	Spiking Conc., µg/L	Final Volume, 2% HNO_3
As	0.1	0	0.1	0.2	0.5	1	2	0.12	50
Cd	0.1	0	0.1	0.2	0.5	1	2	0.12	50
Co	0.1	0	0.1	0.2	0.5	1	2	0.12	50
Cu	2	0	2	4	10	20	40	2.4	50
Hg	0.1	0	0.1	0.2	0.5	1	2	0.12	50
Li	2	0	2	4	10	20	40	2.4	50
Ni	0.5	0	0.5	1	2.5	5	10	0.6	50
Pb	0.1	0	0.1	0.2	0.5	1	2	0.12	50
Sb	2	0	2	4	10	20	40	2.4	50
V	0.5	0	0.5	1	2.5	5	10	0.6	50

All test solutions contain 10ppb internal standard and 100ppb Au.

Spike Recovery (Accuracy) Results for Sucrose and NaCl (both prepared at 0.2g-% in 2% Nitric Acid)

Description	7Li, µg/L	45Sc IS (%)	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	89Y IS (%)	114Cd, µg/L	115In IS (%)	123Sb, µg/L	159Tb IS (%)	175Lu IS (%)	202Hg, µg/L	208Pb, µg/L	209Bi IS (%)
Sucrose Unspiked Average (n=3)	0.044	98	0.146	0.005	0.018	0.053	0.003	98	0.001	99	0.107	99	97	0.007	0.004	97
Sucrose Spiked Average (n=3)	2.381	99	0.692	0.126	0.629	2.507	0.135	97	0.124	99	2.521	98	97	0.131	0.127	98
Spiking Concentration	2.40		0.12	0.12	0.60	2.40	0.12		0.12		2.40			0.12	0.12	
Sucrose Recovery, %	97		91	101	102	102	110		103		101			103	102	

Description	7Li, µg/L	45Sc IS (%)	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	89Y IS (%)	114Cd, µg/L	115In IS (%)	123Sb, µg/L	159Tb IS (%)	175Lu IS (%)	202Hg, µg/L	208Pb, µg/L	209Bi IS (%)
NaCl Unspiked Average (n=3)	0.105	89	2.262	0.049	0.062	0.051	1.832	80	0.001	70	0.103	69	66	0.012	0.003	47
NaCl Spiked Average (n=3)	2.309	94	3.149	0.203	0.770	2.601	2.125	81	0.104	69	2.251	66	63	0.107	0.096	45
Spiking Concentration	2.40		0.12	0.12	0.60	2.40	0.12		0.12		2.40			0.120	0.120	
NaCl %Recovery	92		148	128	118	106	244		86		90			79	77	

- Only 115In used for internal standard. Note even IS response across the mass range for sucrose.
- Note attenuation of internal standards as mass increases in NaCl test solutions.
- Note concentrations of V (1.13 µg/g) and As (0.92 µg/g) in NaCl.
- Why the dramatic differences between these two materials?

Repeat analysis of sucrose and NaCl in KED mode (He)…..

- Dramatically improve specificity of isotopes with polyatomic isobaric interferences
- Attenuate count-rate for analytical isotopes as well
- For some systems (especially older collision cell equipped systems) cannot attenuate both 35ClO16 and 40ArCl35 equally well with a single set of parameters….so in some cases, they have to be analyzed separately

Slopes and background equivalent concentrations for standard curves in standard and KED modes….

Element	STD Mode Slope (CPS/µg/L)	KED Mode Slope (CPS/µg/L)	STD Mode BEC, µg/L	KED Mode BEC, µg/L
Cd	104991	45105	0.00049	0.00052
Pb	338524	290879	0.00424	0.00440
As	28870	3368	0.00970	0.00330
Hg	47252	42875	0.00143	0.00215
Co	243487	63625	0.00139	0.00028
V	233273	20815	0.01435	0.00059
Ni	52487	17862	0.00781	0.00690
Li	141966	219	0.61960	0.59361
Sb	68504	19923	0.00307	0.00335
Cu	46749	20362	0.01940	0.02276

Spike Recovery (Accuracy) Results for Sucrose and NaCl acquired in KED mode…..

Description	7Li, µg/L	45Sc IS (%)	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	89Y IS (%)	114Cd, µg/L	115In IS (%)	123SbIS (%)	159Tb IS (%)	175Lu IS (%)	202Hg, µg/L	208Pb, µg/L	209Bi IS (%)
Average Sucrose Unspiked (n=3)	0.198	101	0.011	0.003	0.015	0.113	-0.004	100	0.003	100	0.048	100	100	0.005	0.006	101
Average Sucrose Spiked (n=3)	2.409	102	0.601	0.121	0.609	2.502	0.120	100	0.122	100	2.447	99	100	0.123	0.126	101
Spike Concentration	2.40		0.60	0.12	0.60	2.40	0.12		0.12		2.40			0.12	0.12	
%Recovery	92		98	98	99	100	104		99		100			98	100	

Description	7Li, µg/L	45Sc IS (%)	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	89Y IS (%)	114Cd, µg/L	115In IS (%)	123SbIS (%)	159Tb IS (%)	175Lu IS (%)	202Hg, µg/L	208Pb, µg/L	209Bi IS (%)
Average NaCl Unspiked (n=3)	0.291	142	0.033	0.004	0.039	0.065	-0.001	111	0.002	93	0.029	88	85	0.006	0.005	59
Average NaCl Spiked (n=3)	2.906	145	0.933	0.155	0.737	2.633	0.143	111	0.104	93	2.326	87	85	0.096	0.094	58
Spike Concentration	2.40		0.60	0.12	0.60	2.40	0.12		0.12		2.40			0.12	0.12	
%Recovery	109		150	126	116	107	119		85		96			75	74	

Why does the internal standard response trend downward with increased analyte mass in NaCl?

Impact of Internal Standard Selection on Spike Recovery (Accuracy)

Only 115In IS Corrected:

Description	7Li, µg/L	45Sc IS (%)	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	89Y IS (%)	114Cd, µg/L	115In IS (%)	123SbIS (%)	159Tb IS (%)	175Lu IS (%)	202Hg, µg/L	208Pb, µg/L	209Bi IS (%)
Average NaCl Unspiked (n=3)	0.291	142	0.033	0.004	0.039	0.065	-0.001	111	0.002	93	0.029	88	85	0.006	0.005	59
Average NaCl Spiked (n=3)	2.906	145	0.933	0.155	0.737	2.633	0.143	111	0.104	93	2.326	87	85	0.096	0.094	58
Spike Concentration	2.40		0.60	0.12	0.60	2.40	0.12		0.12		2.40			0.12	0.12	
%Recovery	109		150	126	116	107	119		85		96			75	74	

Corrected by Interpolation between ISs by mass:

Description	7Li, µg/L	45Sc IS (%)	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	89Y IS (%)	114Cd, µg/L	115In IS (%)	123Sb, µg/L	159Tb IS (%)	175Lu IS (%)	202Hg, µg/L	208Pb, µg/L	209Bi IS (%)
Average NaCl Unspiked (n=3)	-0.017	142	0.017	0.002	0.023	0.034	-0.002	111	0.002	93	0.031	88	85	0.010	0.010	59
Average NaCl Spiked (n=3)	1.683	145	0.624	0.109	0.517	1.903	0.108	111	0.103	93	2.351	87	85	0.143	0.151	58
Spike Concentration	2.40		0.60	0.12	0.60	2.40	0.12		0.12		2.40			0.12	0.12	
% Recovery	70		101	89	82	79	90		84		98			111	118	

Impact of Internal Standard Selection on Spike Recovery (Accuracy), cont'd

No IS Correction:

Description	7Li, µg/L	45Sc IS (%)	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	89Y IS (%)	114Cd, µg/L	115In IS (%)	123Sb, µg/L	159Tb IS (%)	175Lu IS (%)	202Hg, µg/L	208Pb, µg/L	209Bi IS (%)
Average NaCl Unspiked (n=3)	0.108	142	-0.001	-0.002	0.005	-0.065	-0.007	111	-0.004	93	-0.098	88	85	-0.001	-0.002	59
Average NaCl Spiked (n=3)	2.585	145	0.851	0.141	0.665	2.365	0.128	111	0.092	93	2.075	87	85	0.084	0.082	58
Spike Concentration	2.4		0.6	0.12	0.6	2.4	0.12		0.12		2.4			0.12	0.12	
%Recovery	103		142	117	110	99	107		77		86			70	68	

Selected IS Correction:

Description	7Li, µg/L	45Sc IS (%)	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	89Y IS (%)	114Cd, µg/L	115In IS (%)	123Sb, µg/L	159Tb IS (%)	175Lu IS (%)	202Hg, µg/L	208Pb, µg/L	209Bi IS (%)
Average NaCl Unspiked (n=3)	0.291	142	0.015	0.004	0.033	0.065	-0.001	111	0.003	93	0.038	88	85	0.010	0.010	59
Average NaCl Spiked (n=3)	2.906	145	0.604	0.132	0.623	2.633	0.120	111	0.110	93	2.467	87	85	0.143	0.151	58
Spike Concentration	2.4		0.6	0.12	0.6	2.4	0.12		0.12		2.4			0.12	0.12	
%Recovery	109		98	107	98	107	100		90		101			111	118	

Small Molecule Drug Product ICP-MS Case Study

Representative Coated Tablet Composition

Ingredient	Approximate Quantity (mg/Tablet)
Active	15
Mannitol	200
Microcrystalline Cellulose	200
Sodium Croscarmellose	20
Magnesium Stearate	10
Color Mixture	20

Small Molecule Drug Product: Analytical Specifics

- ICH Class 1, 2A, 2B (As, Cd, Hg, Pb, V, Ni, Co, Pd, Pt, Ir, Rh, Ru)
- Sample preparation by closed vessel microwave digestion to a clear solution (silicates, titanium dioxide in solution).
- Applying Control Threshold for a 10-g dose (Option 1) as maximum LOQ (reporting limit).
- Accuracy/Repeatability experiment consists of spiked replicates at 30%, 50%, 100% and 150% of the permitted concentration levels corrected for sample dilution.

Limits and Range for Small Molecule Drug Product

Element	Permitted Concentration (10-g dose applied), (µg/g)	Reporting Limit, µg/g	Analytical Range, µg/g
As	1.5	0.45	0.45-2.2
Cd	0.5	0.15	0.15-0.75
Hg	3	0.9	0.9-4.5
Pb	0.5	0.15	0.15-0.75
Co	5	1.5	1.5-7.5
Ni	20	6	6-30
V	10	3	3-15
Pd	10	3	3-15
Ru	10	3	3-15
Pt	10	3	3-15
Ir	10	3	3-15
Rh	10	3	3-15

Sample Preparation Scheme for Small Molecule Drug Product

- 1 tablet (0.67 g) transferred to a digestion vessel.
- 2.5mL of concentrated nitric acid, 2.5mL of concentrated sulfuric acid, 1mL of hydrofluoric acid.
- Temperature monitoring only.
- Ramp to 210^{o}C, hold for 35 minutes.
- Final volume 100mL. Included 100ppb Au and 10ppb internal standard.

Small Molecule Drug Product Spiking Levels

Element	30% (Level 1) Spike (µg/L)	50% (Level 2) Spike (µg/L)	100% (Level 3) Spike (µg/L)	150% (Level 4) Spike (µg/L)
As	3	5.0	10	15
Cd	1	1.7	3.4	5
Hg	6	10.0	20.4	30
Pb	1	1.7	3.4	5
Co	10	16.7	34	50
Ni	40	66.8	136	200
V	20	33.4	66.8	100
Pd	20	33.4	66.8	100
Ru	20	33.4	66.8	100
Pt	20	33.4	66.8	100
Ir	20	33.4	66.8	100
Rh	20	33.4	66.8	100

Coated Tablet: Accuracy/Precision Raw Results

Replicate	V (µg/L)	Co (µg/L)	Ni (µg/L)	As (µg/L)	Ru (µg/L)	Rh (µg/L)	Pd (µg/L)	Cd (µg/L)	Ir (µg/L)	Pt (µg/L)	Hg (µg/L)	Pb (µg/L)
100% Spike 1/12	82.31	38.94	160.1	10.88	61.09	58.72	70.75	3.288	54.88	57.95	14.96	2.916
100% Spike 2/12	81.57	38.92	160.3	10.78	61.93	60.47	69.55	3.213	55.86	59.2	15.38	2.933
100% Spike 3/12	84.7	39.5	163.7	10.73	66.46	65.56	70.94	3.28	56.44	60.68	15.67	3.136
100% Spike 4/12	78.98	37.14	153.1	10.32	61.66	60.22	70.27	3.3	58.08	60.89	15.84	3.088
100% Spike 5/12	70.72	32.88	134.5	9.203	58.41	58.16	67.68	3.169	58.42	59.2	16.22	3.119
100% Spike 6/12	76.82	35.23	145.3	9.78	64.28	64.43	70.55	3.305	60.99	61.99	17.01	3.32
Average	79.18	37.1	152.8	10.28	62.31	61.26	69.96	3.26	57.45	59.99	15.85	3.09
s.d.	4.96	2.6	11.13	0.67	2.77	3.04	1.22	0.06	2.19	1.46	0.71	0.15
%RSD	6.27	7	7.28	6.49	4.45	4.97	1.74	1.7	3.82	2.44	4.49	4.82
%Recovery	116	111	110	99.1	90.7	90.1	104	90.8	83.1	87.7	77.3	80.8

Large Molecule Drug Product: ICP-MS Case Study

Some Analytical Specifics for Large Molecule Analyses…

- Typically the formulation is saccharide and/or salt based with a surfactant and buffering salts.
- Semi-matrix match standards to samples and use multiple internal standards. Can apply a combination approach of ICP-OES and ICP-MS if sufficient research materials available
- Some large molecule API is extremely pH sensitive and will degrade with even small volumes of acid-from commercial IS stocks for example. Care must be taken when performing spiking studies.
- Doses can be well in excess of 10-g/10-mL which can make for challenging analyses….

Large Molecule Drug Product Analysis: 140mL Dose, ICH Classes 1, 2A, 3 elements per Risk Assessment

- Samples diluted 20-fold with water. Formulation includes dilute sodium chloride. API concentration is 50mg/mL (5% w/v).
- Working standards prepared in 0.05% Triton X-100. Multiple internal standards with “interpolate” feature applied.
- As, Cd, Hg, Pb, V, Co, Ni, Li, Cu, Sb from ICH risk assessment.

Large Molecule Drug Product Spiking Levels (140mL Daily Dose)

Element	ICH Q3D PDE, µg/Day	Limit, µg/mL (140mL Daily Dose)	30% Spike Conc., µg/L (DF=20)	50% Spike Conc., µg/L (DF=20)	100% Spike Conc., µg/L (DF=20)	150% Spike Conc., µg/L (DF=20)
Cd	2	0.014	0.21	0.35	0.7	1.05
Pb	5	0.035	0.525	0.875	1.75	2.625
As	15	0.1	1.5	2.5	5	7.5
Hg	3	0.02	0.3	0.5	1	1.5
Co	5	0.035	0.525	0.875	1.75	2.625
V	10	0.07	1.05	1.75	3.5	5.25
Ni	20	0.14	2.1	3.5	7	10.5
Li	250	1.7	25.5	42.5	85	127.5
Sb	90	0.64	9.6	16	32	48
Cu	300	2.1	31.5	52.5	105	157.5

Large Molecule Drug Product Analysis: Specificity Experiment

- "N-1" specificity experiment. Spike with all elements into sample matrix with one element strategically eliminated.
- Spiking concentration at 150% of permitted concentration. Calibrate against standard curve containing all elements.
- Acceptance criteria….somewhat a subjective call. Compare to control threshold as a maxiumum.

“N-1” Specificity Experiment Results.

Description	7Li, µg/L	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	111Cd, µg/L	123Sb, µg/L	202Hg, µg/L	208Pb, µg/L
Spiked Concentration	137.5	5.5	2.75	11	165	8.25	1.1	49.5	1.65	2.75
Reporting Limit	**5**	**1**	**0.5**	**2**	**5**	**1**	**0.2**	**5**	**0.3**	**0.5**
Control Threshold	26.8	1.1	0.5	2.1	32.1	1.6	0.2	9.6	0.3	0.5
Spike: All Elements	146.81	5.56	3.01	11.93	171.00	7.80	1.01	50.67	1.58	2.68
Blank	0.42	-0.01	0.01	0.02	-1.19	0.06	0.00	-0.13	0.02	0.01
Spike: Sans Cd	150.07	5.62	3.09	12.74	175.85	8.07	0.00	51.73	1.44	2.43
Spike: Sans Pb	148.02	5.47	3.05	12.53	175.58	8.02	1.01	50.63	1.54	0.01
Spike: Sans As	150.55	5.59	3.17	12.74	177.30	0.06	1.03	51.09	1.60	2.79
Spike: Sans Hg	144.41	5.51	3.05	12.49	175.20	8.13	1.01	50.89	0.01	2.57
Spike: Sans Co	141.99	5.43	0.01	12.31	173.05	7.91	1.00	49.99	1.70	2.93
Spike: Sans V	143.55	0.00	3.05	12.60	175.10	8.14	1.03	51.11	1.51	2.60
Spike: Sans Ni	143.54	5.31	3.02	0.14	173.79	7.85	1.01	50.73	1.45	2.66
Spike: Sans Li	0.34	5.44	2.96	12.25	171.38	8.03	1.02	50.35	1.50	2.53
Spike: Sans Sb	142.64	5.45	3.06	12.52	175.17	8.04	1.03	-0.09	1.57	2.64
Spike: Sans Cu	142.13	5.42	2.98	12.42	-1.19	8.09	1.00	51.43	1.43	2.54
Spike: All Elements	141.49	5.45	3.12	12.16	173.72	8.00	1.00	51.24	1.52	2.60

Large Molecule Drug Product: ICP-MS Accuracy and Repeatability

Description	7Li, µg/L	51V, µg/L	59Co, µg/L	60Ni, µg/L	65Cu, µg/L	75As, µg/L	111Cd, µg/L	123Sb, µg/L	202Hg, µg/L	208Pb, µg/L
Unspiked Replicate 1/3	0.617	-0.021	0.009	0.219	-1.249	0.000	-0.002	-0.213	0.002	0.016
Unspiked Replicate 2/3	0.652	-0.022	0.008	0.060	-1.256	0.001	-0.002	-0.217	-0.003	0.015
Unspiked Replicate 3/3	0.644	-0.020	0.009	0.046	-1.258	0.001	-0.002	-0.217	-0.007	0.015
Average	0.638	-0.021	0.009	0.108	-1.254	0.001	-0.002	-0.216	-0.003	0.016
30% Spike Replicate 1/3	23.940	1.018	0.504	1.925	27.956	1.381	0.192	9.483	0.284	0.510
30% Spike Replicate 2/3	25.055	1.052	0.510	1.922	28.335	1.351	0.196	9.665	0.325	0.569
30% Spike Replicate 3/3	24.337	1.046	0.511	1.972	28.490	1.388	0.182	9.566	0.300	0.526
Average	24.444	1.039	0.508	1.940	28.260	1.373	0.190	9.571	0.303	0.535
s.d.	0.565	0.018	0.004	0.028	0.274	0.020	0.007	0.091	0.021	0.030
%RSD	2.311	1.742	0.711	1.462	0.971	1.450	3.909	0.950	6.920	5.623
%Recovery	**95.224**	**103.907**	**99.867**	**91.565**	**94.201**	**91.513**	**94.895**	**106.348**	**100.981**	**103.914**
50% Spike Replicate 1/3	42.536	1.811	0.868	3.374	49.786	2.361	0.326	16.571	0.509	0.889
50% Spike Replicate 2/3	41.482	1.857	0.889	3.466	50.977	2.457	0.330	17.091	0.530	0.909
50% Spike Replicate 3/3	40.991	1.812	0.880	3.419	50.055	2.394	0.319	16.552	0.494	0.859
Average	41.670	1.827	0.879	3.420	50.272	2.404	0.325	16.738	0.511	0.886
s.d.	0.789	0.026	0.011	0.046	0.625	0.049	0.006	0.306	0.018	0.025
%RSD	1.894	1.416	1.207	1.347	1.243	2.026	1.762	1.826	3.599	2.814
%Recovery	**93.787**	**104.387**	**99.455**	**94.621**	**95.757**	**91.559**	**92.787**	**106.273**	**97.307**	**99.472**
100% Spike Replicate 1/12	78.484	3.575	1.692	6.593	97.923	4.676	0.644	32.867	0.979	1.701
100% Spike Replicate 2/12	76.733	3.528	1.695	6.518	97.511	4.700	0.623	32.484	0.982	1.692
100% Spike Replicate 3/12	80.717	3.636	1.731	6.723	99.543	4.779	0.651	33.125	0.997	1.721
100% Spike Replicate 4/12	79.405	3.541	1.672	6.536	98.367	4.650	0.635	32.848	0.973	1.682
100% Spike Replicate 5/12	79.694	3.611	1.714	6.586	99.090	4.747	0.642	33.047	0.991	1.702
100% Spike Replicate 6/12	77.268	3.611	1.704	6.610	97.748	4.695	0.626	32.608	0.995	1.753
Average	78.717	3.584	1.701	6.595	98.363	4.708	0.637	32.830	0.986	1.708
s.d.	1.518	0.043	0.020	0.072	0.802	0.047	0.011	0.247	0.010	0.025
%RSD	1.928	1.202	1.180	1.094	0.816	1.002	1.697	0.751	0.967	1.484
%Recovery	**89.233**	**102.393**	**96.712**	**92.660**	**93.679**	**89.658**	**90.962**	**104.222**	**93.920**	**96.734**

Summary: ICP-MS Applications

- Unit resolution quadrupole based ICP mass spectrometers have interfering species generated within the mass spectrometer from constituent and atmospheric elements.
- Charging a collision/reaction cell with either inert (KED) or reactive (DRC) gases will attenuate the isobaric polyatomic species. It also will attenuate analyte response, severely for light elements such as lithium.
- Because the physical and chemical attributes of the interfering species for 51V and 75As are different, finding compromise analytical parameters to include both in a single analysis can be challenging using some collision cell equipped ICP mass spectrometers.

Summary: ICP-MS Applications

- The introduction of constituent ions (Na, Ca, K, Si, Ti, Mg, Zn) will cause mass biased results (attenuation as masses increase) due to changes in the electrostatic characteristics of the ion beam. Selection of multiple internal standards across the analytical mass range is highly recommended.
- Matrix matching of working standards and/or further dilution of test solution along with the use of a collision cell and multiple internal standards may be required to develop a suitable analytical method applicable to all EI's within a single analytical run.