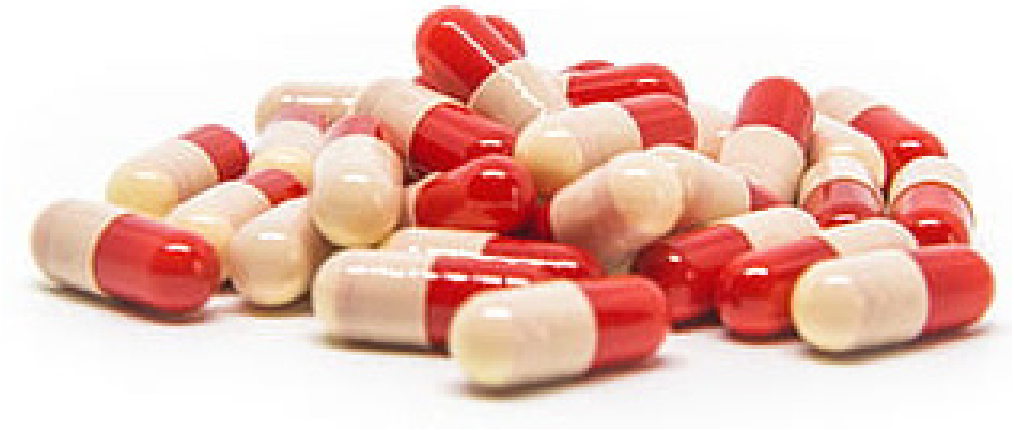
Determining Elemental Impurities in Pharmaceutical



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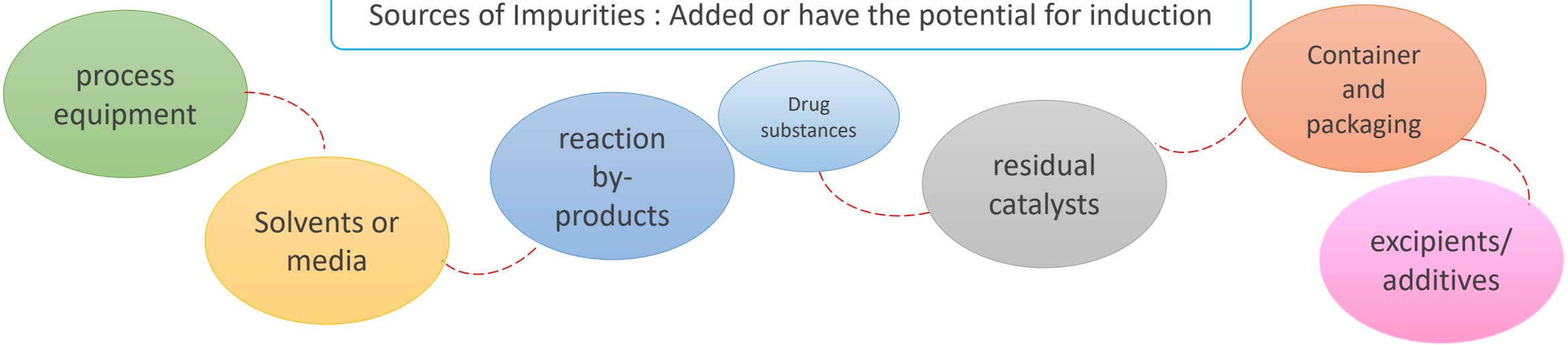
Pharmaceutical Impurities – What and Why?

Why measure impurities in pharmaceuticals

Contaminants / residues – including elemental impurities – may be toxic, or may affect the performance or shelf-life of the drug product

Sources of Impurities : Added or have the potential for induction



USP <232> <233> and <2232> Basics

USP <232> - Elemental Impurities "Limits"

Applied to drug products

- Drug substances
- Excipients
- "Big Four" – As, Cd, Hg, Pb and remaining 11 elements

USP <233> - Elemental Impurities "Procedures" are specified in

- Procedure 1 : ICP-OES
- Procedure 2 : ICP-MS

USP <2232> - Elemental Contaminants in Dietary Supplements, Information and guidance purposes

- Limits for As, Cd, Hg, Pb
- Impurity testing according to Chapter <233>

ICH-Q3D – Guideline for elemental impurities

Applicable to all drug products, does not apply to:

- Herbal products
- Allergenic extracts
- Radiopharmaceuticals
- Vaccines
- Cell metabolites
- DNA products
- Whole blood, Cellular blood components and blood derivatives; plasma/ plasma derivatives
- Dialysate solutions
- Elements deliberately included for therapeutic benefit

Elemental Impurities

USP <232> <233>
USP <2332>
ICH Q3D

- Drug Products
- Raw materials
- Dietary supplements

Pharmacopeias - Different Guidelines

Europe (Ph. Eur)	EMEA/CHMP/SWP/4446/2000
USA (USP)	USP Chapters <232> <233>
International (ICH)	ICH Q3D (adopted by FDA)

USP <232> will eventually replace other "metals" General Chapters

Lead	<251>
Arsenic	<211>
Mercury	<261>

Related method applies to dietary supplements only

<2232>

Elemental Impurities in Dietary Supplements

USP "Metals" Chapters – Current and New

Elemental Impurities

USP <232> Limit

USP <232> Procedures

Harmonised with ICH Q3D

Terminology changing: "Heavy Metals"
"Elemental Impurities"

Element classification as per ICHQ3D

Class 1 : The elements, As, Cd, Hg, Pb are human toxicant

Class 2 : Elements in this class are generally considered as human toxicants are route-depending

- Class 2A : elements have relatively high probability of occurrence in the drug product. → Co, Ni, V
- Class 2B : elements have reduced probability of occurrence in the drug product related to their low abundance, low potential and may be intentionally added during manufacture. → Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl

Class 3 : elements in this class have relatively low toxicities → Ba, Cr, Cu, Li, Mo, Sb and Sn

Assess is high PDEs, generally > 500 µg/day

Which elemental impurities should be measured?

- The elements that should be included in the product Risk Assessment are different depending on the intended route of administration
- Class 1 and Class 2A elements must be assessed In all products
- Class 3 elements should be considered for Parenteral and/or Inhalational routes of administration
- ALL listed elements should be included if they have been added intentionally

Table A.2.1: Permitted Daily Exposures for Elemental Impurities[1]

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Table A.2.1 Permitted Daily Exposures for elemental impurities ICH Q3D

Calculating the J value from the PDE

What is the J value?
J = concentration of the element of interest at the target PDE limit, appropriately diluted to the working range of the instrument.

$$J = \frac{PDE}{\text{Max. Daily dose} \times \text{dilution factor}}$$

Dilution may also be needed to bring matrix within limit of the instrument

J value and Sample Dilution

Implication for instrument selection

- Liquid samples of oral medicines (higher PDEs apply) may be able to be run directly on ICP-OES; parenteral and inhalational drugs have lower PDE limits, ICP-MS will be required

- For Solid samples, Dilution factor (prep dilution) may be reduced, allowing ICP-OES to be used. Higher dilution can be applied to bring matrix level within the range tolerated by ICP-MS

Instrument for USP<233> and ICHQ3D

Decision included :

- Sample type/dosage form; Lower limits apply to drug intended for Inhalation and Injection
- Amount of sample available and sample preparation dilution used
- Bigger dilution means lower detection limits of ICP-MS are needed

iCAP™ PRO XP ICP-OES

ICP-OES

- Mainly oral dose medicines – PDE limits are higher
- Higher matrix tolerance and large sample volume available : bulk excitants
- No dilution of sample
- Very high throughput needed

iCAP™ RQ ICP-MS

ICP-MS has much lower detection limit and provides speciation capability

- All dosage form; Oral, inhalation and Injection
- Small sample amounts available; Active pharmaceutical ingredients (**APIs)**
- Speciation for As/Hg

Analysis of elemental impurities

Sample preparation

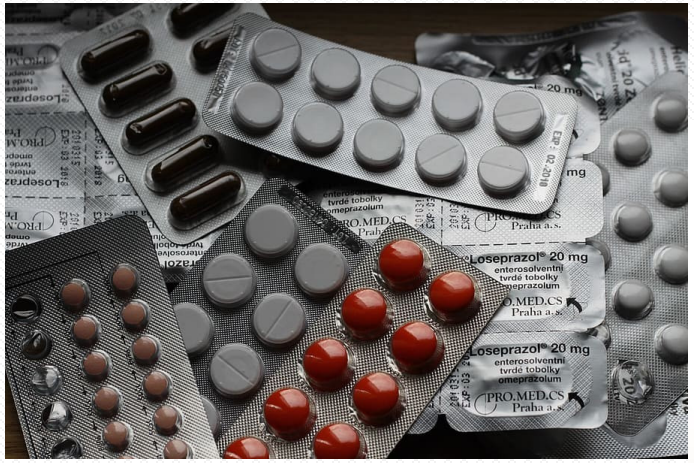
- Dilute bases
  - Aqueous of dilute acid solutions or
  - Organic solvents
- Digestions
  - Using probably concentrated acids: HNO_3, H_2O_2, HCl, H_2SO_4, $HClO_4$, HF
  - Hot plate
  - Microwave-assisted digestions

Objective

- Determination of elemental impurities in oral drugs by iCAP RQ ICP-MS
- Three pharmaceutical products were selected for analysis

Class	Element	Oral PDE (µg/day)
1A	Cd	5
	Pb	5
	As	15
	Hg	30
2A	Co	50
	V	100
	Ni	200

Antihypertensives medicine

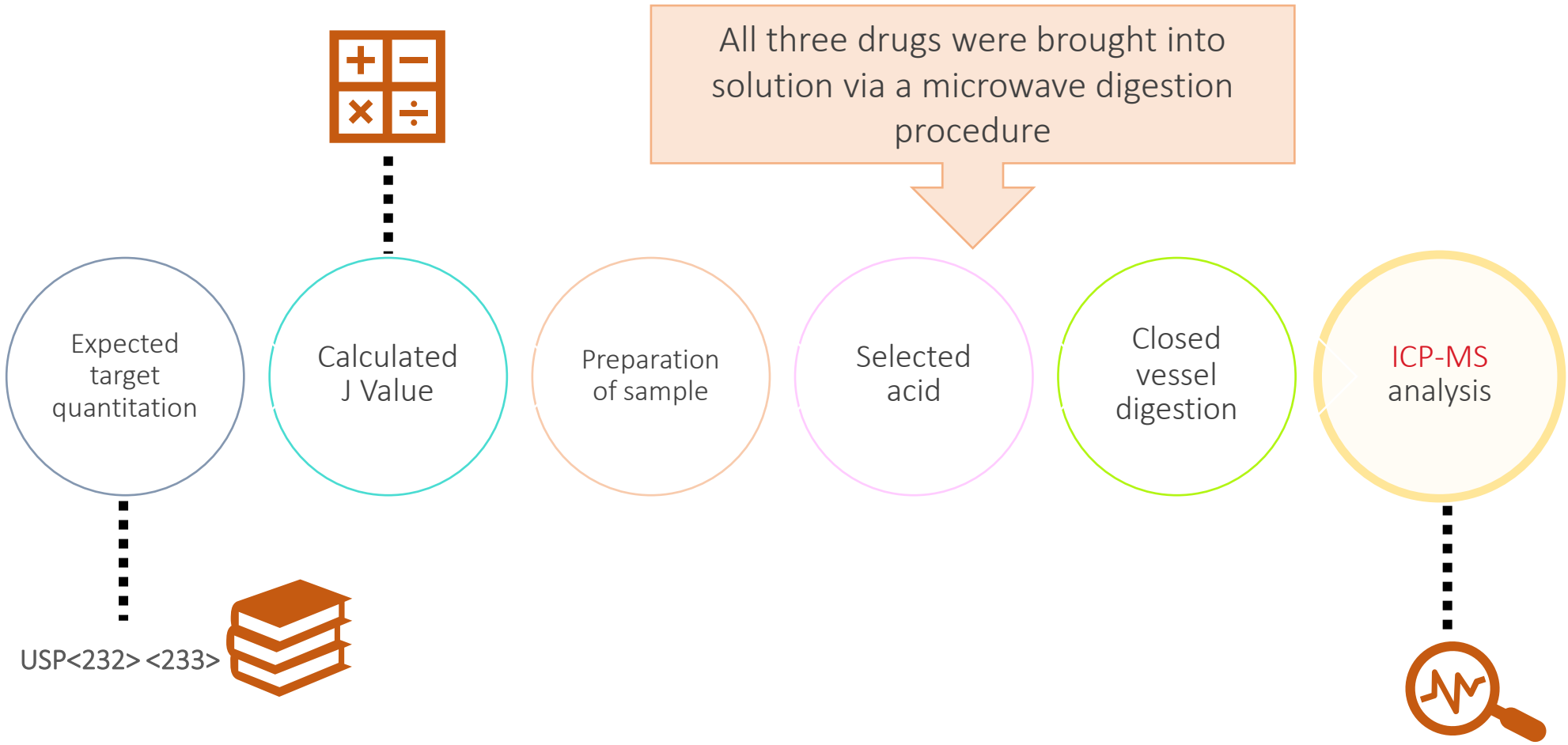


Hypolipidemic medicine

Antidiabetic medicine

A rapid, highly selective and sensitive ICP-MS method was developed for detection and quantitation of Elemental impurities in drug product

System main workflows



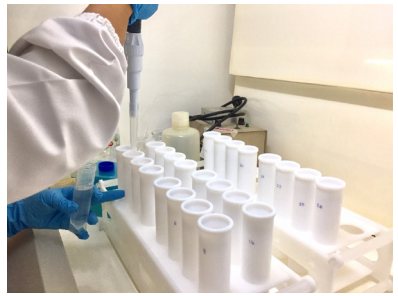
Sample Preparation Procedures for ICP

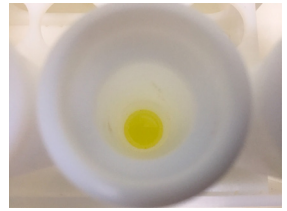
Representative sample of 3-4 tablets

Homogenization by mortar

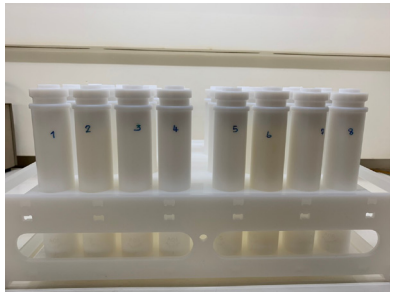
Weight the sample in vessel

Add concentred acid to the vessel in a fume hood

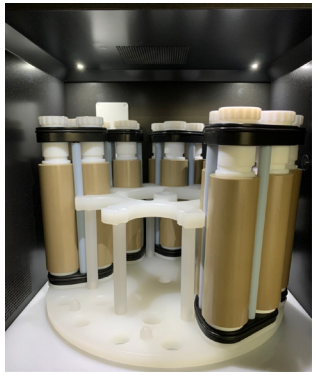




Seal the vessel



Place the vessel in the microwave



Adjust the final volume to 50 ml with ultrapure water

Analysis by iCAP RQ ICP-MS

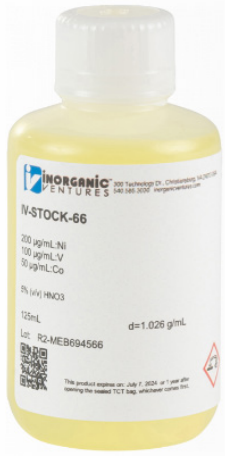
Calibration solution preparation

- Standard solutions at concentrations of blank, 0.5J and 2J
- Ga, In and Tl internal standards at 10 µg/L, added online via a T-piece
- Rinse solution : 2% HNO_3

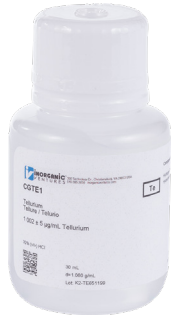
Criteria

- Accuracy test : Matrix spike recoveries for each repeat of all samples at the 0.8J spike
  - Acceptance criteria for test are recoveries of between 80 and 150%
- Precision test : ≤ 20%

USP<232>/ICH Q3D Class 1 Oral



USP<232>/ICH Q3D Class 2A Oral



Tl – Internal Standard

Ga - Internal Standard

In - Internal Standard

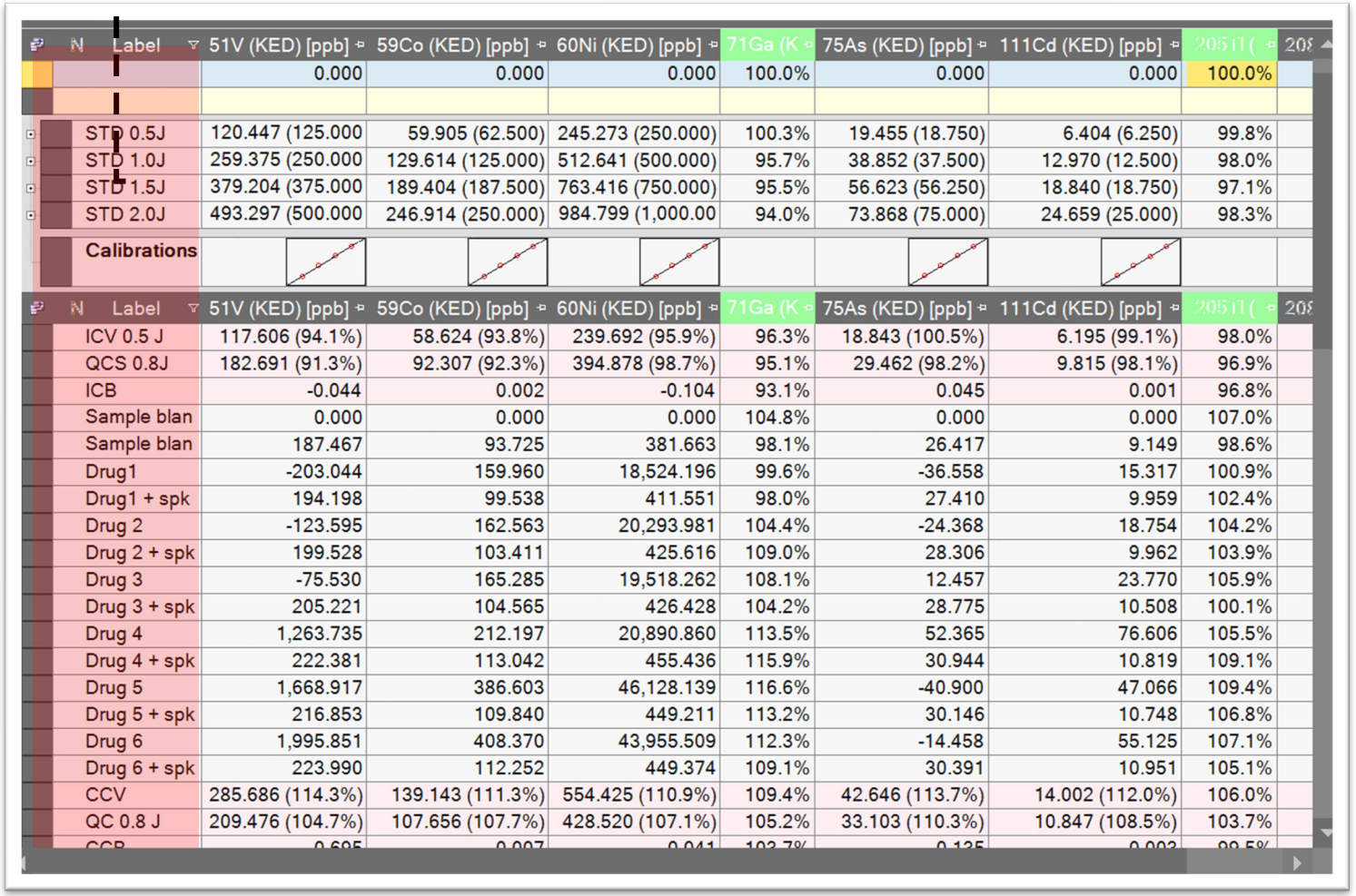
Condition of iCAP RQ ICP-MS

- **KED (Kinetic energy discrimination)** : Technique to reduce polyatomic ion interferences derived from the plasma or vacuum interface in collision cell ICP-MS.

	Element	Isotope	Mode
Class 1A	Cd	111	KED
	Pb	208	KED
	As	75	KED
	Hg	200	KED
Class 2A	Co	59	KED
	V	51	KED
	Ni	60	KED
Internal std.	Ga	71	KED
	In	115	KED
	Tl	205	KED

iCAP RQ ICP-MS	
Nebulizer	PFA-ST nebulizer
Peristaltic pump tubing	Sample tube: PVC tube, - ID 0.508mm,orange/yellow
	IS tube: PVC, - ID 0.254 mm, orange/blue
	Drain tube: Silicon tube - ID 1.295 mm gray/gray
Sample Cone	Ni Sample cone
Skimmer cone	Ni Skimmer cone
KED	He gas

Sequential for analysis

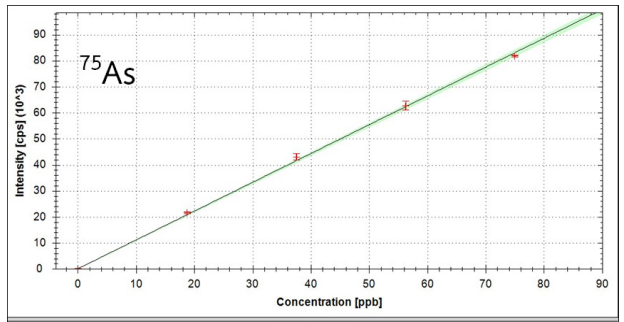


N	Label	51V (KED) [ppb]	59Co (KED) [ppb]	60Ni (KED) [ppb]	71Ga (K	75As (KED) [ppb]	111Cd (KED) [ppb]	205Tl (	208
		0.000	0.000	0.000	100.0%	0.000	0.000	100.0%	
	STD 0.5J	120.447 (125.000	59.905 (62.500)	245.273 (250.000)	100.3%	19.455 (18.750)	6.404 (6.250)	99.8%	
	STD 1.0J	259.375 (250.000	129.614 (125.000)	512.641 (500.000)	95.7%	38.852 (37.500)	12.970 (12.500)	98.0%	
	STD 1.5J	379.204 (375.000	189.404 (187.500)	763.416 (750.000)	95.5%	56.623 (56.250)	18.840 (18.750)	97.1%	
	STD 2.0J	493.297 (500.000	246.914 (250.000)	984.799 (1,000.00	94.0%	73.868 (75.000)	24.659 (25.000)	98.3%	
	Calibrations								
N	Label	51V (KED) [ppb]	59Co (KED) [ppb]	60Ni (KED) [ppb]	71Ga (K	75As (KED) [ppb]	111Cd (KED) [ppb]	205Tl (	208
	ICV 0.5 J	117.606 (94.1%)	58.624 (93.8%)	239.692 (95.9%)	96.3%	18.843 (100.5%)	6.195 (99.1%)	98.0%	
	QCS 0.8J	182.691 (91.3%)	92.307 (92.3%)	394.878 (98.7%)	95.1%	29.462 (98.2%)	9.815 (98.1%)	96.9%	
	ICB	-0.044	0.002	-0.104	93.1%	0.045	0.001	96.8%	
	Sample blan	0.000	0.000	0.000	104.8%	0.000	0.000	107.0%	
	Sample blan	187.467	93.725	381.663	98.1%	26.417	9.149	98.6%	
	Drug1	-203.044	159.960	18,524.196	99.6%	-36.558	15.317	100.9%	
	Drug1 + spk	194.198	99.538	411.551	98.0%	27.410	9.959	102.4%	
	Drug 2	-123.595	162.563	20,293.981	104.4%	-24.368	18.754	104.2%	
	Drug 2 + spk	199.528	103.411	425.616	109.0%	28.306	9.962	103.9%	
	Drug 3	-75.530	165.285	19,518.262	108.1%	12.457	23.770	105.9%	
	Drug 3 + spk	205.221	104.565	426.428	104.2%	28.775	10.508	100.1%	
	Drug 4	1,263.735	212.197	20,890.860	113.5%	52.365	76.606	105.5%	
	Drug 4 + spk	222.381	113.042	455.436	115.9%	30.944	10.819	109.1%	
	Drug 5	1,668.917	386.603	46,128.139	116.6%	-40.900	47.066	109.4%	
	Drug 5 + spk	216.853	109.840	449.211	113.2%	30.146	10.748	106.8%	
	Drug 6	1,995.851	408.370	43,955.509	112.3%	-14.458	55.125	107.1%	
	Drug 6 + spk	223.990	112.252	449.374	109.1%	30.391	10.951	105.1%	
	CCV	285.686 (114.3%)	139.143 (111.3%)	554.425 (110.9%)	109.4%	42.646 (113.7%)	14.002 (112.0%)	106.0%	
	QC 0.8 J	209.476 (104.7%)	107.656 (107.7%)	428.520 (107.1%)	105.2%	33.103 (110.3%)	10.847 (108.5%)	103.7%	
	CCB	0.695	0.007	0.041	103.7%	0.125	0.003	99.5%	

No.	Analysis
1	Standard Blank
2-5	Standard solution (0.5J - 2J)
6	ICV-Standard check (0.5J)
7	QCS Standard check (0.8J)
8	ICB-Standard Blank
9	Sample blank
10	Sample blank + spike
11-20	Sample 1, Sample 1 + spiked, ...
21	CCV-Standard check (1.0J)
22	QCS Standard check (0.8J)
23	CCB-Standard Blank

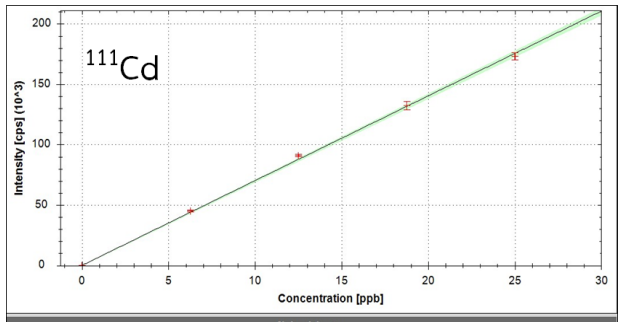
Results - Calibration curve

Linear calibrations with low (sub ng.ml^{-1}) blanks were obtained for all elements.



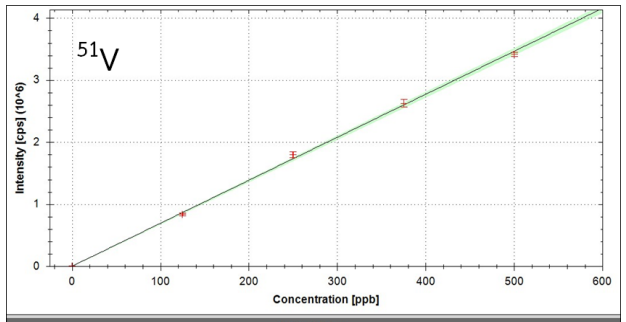
f(x) = b*x + a

Parameter	Value	Confidence Delta at 90%	StdErr	Rel. StdErr [%]
b	1,106.626	+/-15.986	10.427	0.942
a	65.334	+/-0.000	0.000	0.000
R²	0.999			
BEC	0.059 ppb			
IDL(LOD)	0.013 ppb			



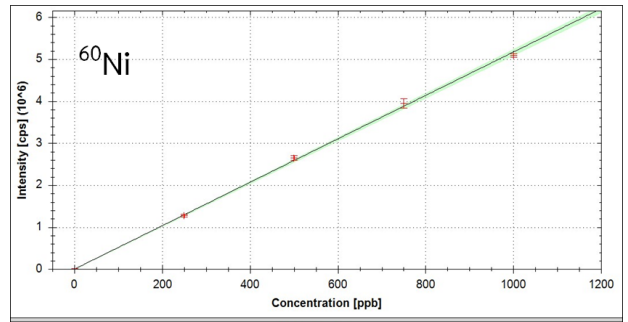
f(x) = b*x + a

Parameter	Value	Confidence Delta at 90%	StdErr	Rel. StdErr [%]
b	7,021.518	+/-97.367	63.506	0.904
a	0.000	+/-0.000	0.000	NaN
R²	0.999			
BEC	0.000 ppb			
IDL(LOD)	0.005 ppb			



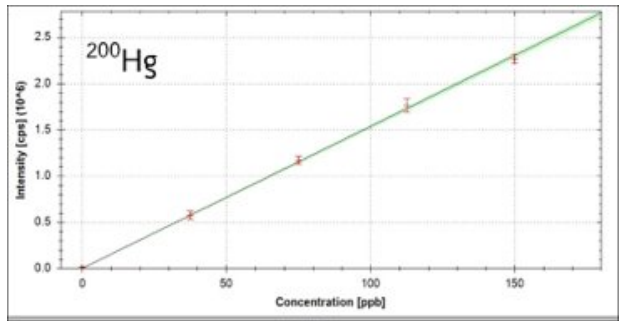
f(x) = b*x + a

Parameter	Value	Confidence Delta at 90%	StdErr	Rel. StdErr [%]
b	6,930.506	+/-102.313	66.732	0.963
a	0.000	+/-0.000	0.000	NaN
R²	0.999			
BEC	0.000 ppb			
IDL(LOD)	0.048 ppb			



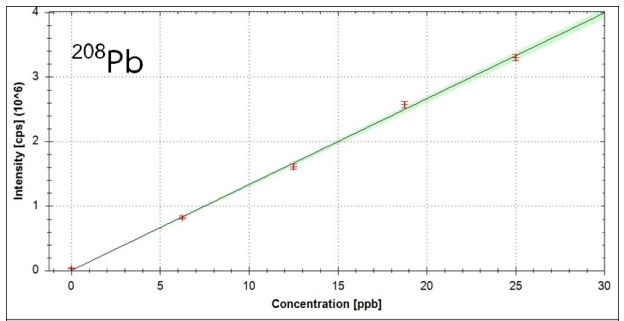
f(x) = b*x + a

Parameter	Value	Confidence Delta at 90%	StdErr	Rel. StdErr [%]
b	5,171.093	+/-71.867	46.874	0.906
a	0.000	+/-0.000	0.000	NaN
R²	0.999			
BEC	0.000 ppb			
IDL(LOD)	0.039 ppb			



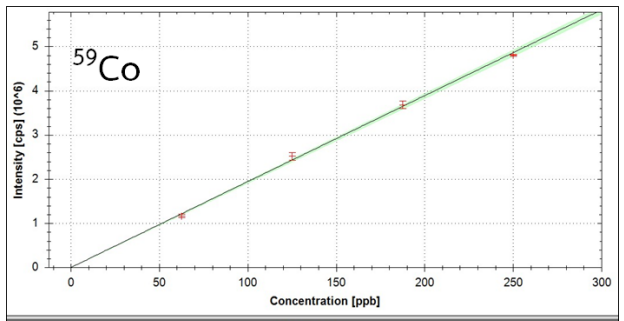
f(x) = b*x + a

Parameter	Value	Confidence Delta at 90%	StdErr	Rel. StdErr [%]
b	15,355.264	+/-202.421	132.025	0.860
a	0.000	+/-0.000	0.000	NaN
R²	0.999			
BEC	0.000 ppb			
IDL(LOD)	0.079 ppb			



f(x) = b*x + a

Parameter	Value	Confidence Delta at 90%	StdErr	Rel. StdErr [%]
b	133,082.476	+/-2,336.215	1,523.751	1.145
a	0.000	+/-0.000	0.000	NaN
R²	0.998			
BEC	0.000 ppb			
IDL(LOD)	0.020 ppb			

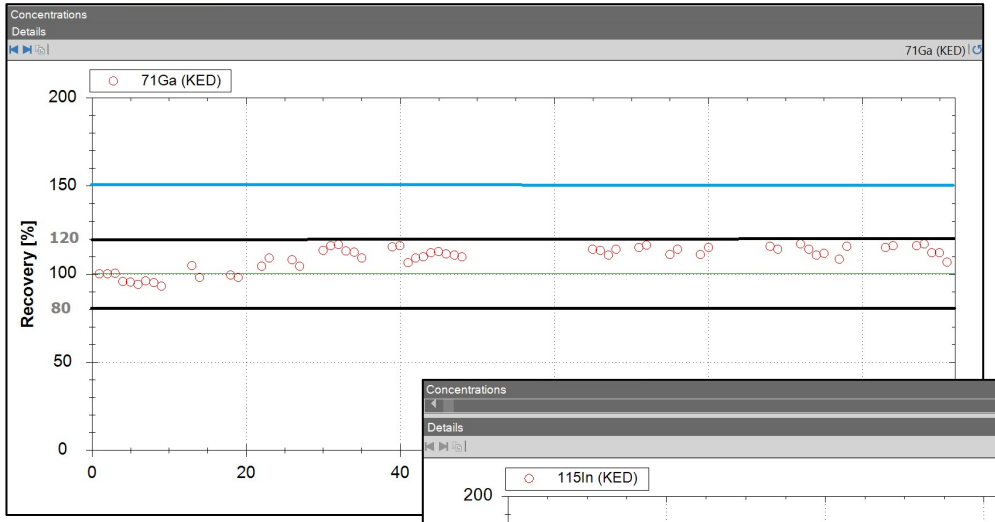


f(x) = b*x + a

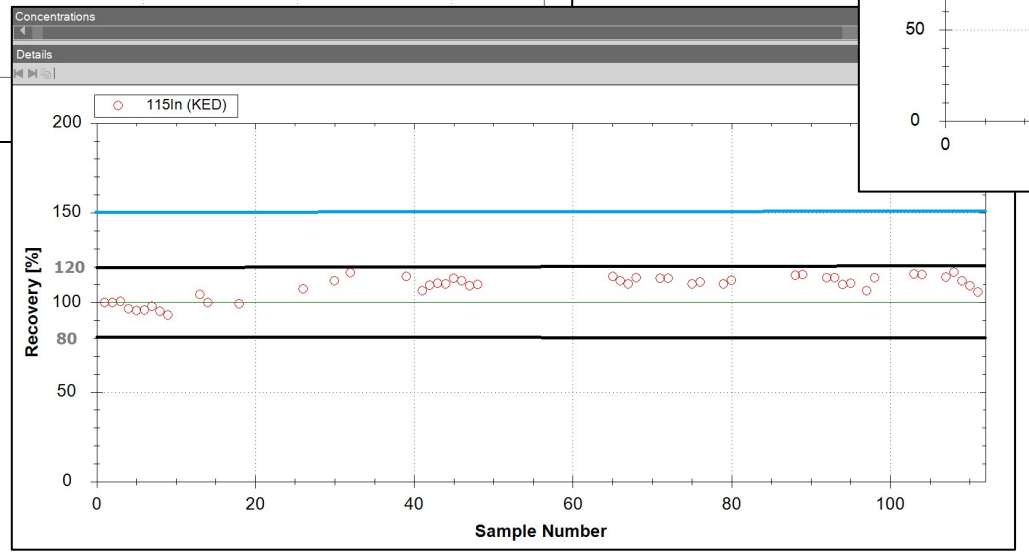
Parameter	Value	Confidence Delta at 90%	StdErr	Rel. StdErr [%]
b	19,424.552	+/-279.177	182.088	0.937
a	0.000	+/-0.000	0.000	NaN
R²	0.999			
BEC	0.000 ppb			
IDL(LOD)	0.004 ppb			

Results – Internal Standards

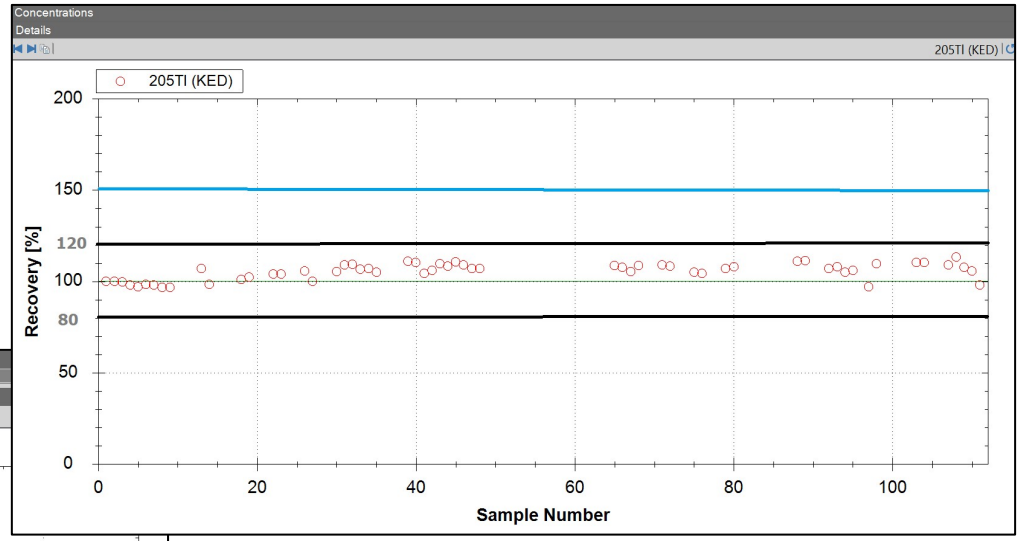
- Acceptance criteria for test are recoveries of between 80 and 150%



71Ga



115In



205 Tl

Results - Raw data from Qtegra

Label	71Ga (KED)	75As (KED) [ppb]	111Cd (KED) [ppb]	115In (KED)	200Hg (KED) [ppb	205Tl (KED	208Pb (KED) [ppb]
	100.0%	0.000	0.000	100.0%	0.000	100.0%	0.000
ICV 0.5 J	96.3%	18.843 (100.5%)	6.195 (99.1%)	97.7%	37.305 (99.5%)	98.0%	5.935 (95.0%)
QCS 0.8J	95.1%	29.462 (98.2%)	9.815 (98.1%)	95.0%	58.540 (97.6%)	96.9%	9.214 (92.1%)
ICB	93.1%	0.045	0.001	93.2%	1.888	96.8%	-0.007
Sample blan	104.8%	0.000	0.000	104.5%	0.000	107.0%	0.000
Sample blan	98.1%	26.417	9.149	99.9%	58.578	98.6%	9.573
Drug1	99.6%	-36.558	15.317	99.3%	4,273.238	100.9%	963.175
Drug1 + spk	98.0%	27.410	9.959	186.1%	72.139	102.4%	9.746
Drug 2	104.4%	-24.368	18.754	104.2%	1,882.429	104.2%	342.885
Drug 2 + spk	109.0%	28.306	9.962	196.4%	70.678	103.9%	9.785
Drug 3	108.1%	12.457	23.770	107.6%	1,281.099	105.9%	3,115.101
Drug 3 + spk	104.2%	28.775	10.508	197.7%	69.115	100.1%	10.081
Drug 4	113.5%	52.365	76.606	112.1%	2,261.651	105.5%	272.913
Drug 4 + spk	115.9%	30.944	10.819	212.1%	77.193	109.1%	9.664
Drug 5	116.6%	-40.900	47.066	116.6%	4,231.559	109.4%	242.519
Drug 5 + spk	113.2%	30.146	10.748	205.5%	77.402	106.8%	10.237
Drug 6	112.3%	-14.458	55.125	111.8%	6,490.754	107.1%	225.278
Drug 6 + spk	109.1%	30.391	10.951	209.3%	84.358	105.1%	10.362
CCV	109.4%	42.646 (113.7%)	14.002 (112.0%)	108.7%	71.082 (94.8%)	106.0%	13.375 (107.0%)
QC 0.8 J	105.2%	33.103 (110.3%)	10.847 (108.5%)	106.0%	55.678 (92.8%)	103.7%	10.073 (100.7%)
CCB	103.7%	0.135	0.003	103.9%	2.136	99.5%	0.014
Drug 7	106.5%	21.432	15.007	106.4%	1,230.087	104.5%	70.000
Drug 7 + spk	109.1%	29.664	10.248	109.7%	57.503	106.0%	10.240
Drug 8	109.9%	-14.860	41.497	110.8%	3,808.253	109.7%	147.870
Drug 8 + spk	111.9%	29.710	10.418	110.3%	54.915	108.5%	10.870
Drug 9	112.6%	35.771	32.685	113.5%	3,103.980	110.7%	313.152
Drug 9 + spk	111.4%	29.628	10.451	112.1%	55.317	109.1%	10.442
Drug 10	110.6%	161.583	91.696	109.2%	5,013.468	107.1%	337.012
Drug 10 + sp	109.7%	28.450	10.017	110.0%	56.611	106.9%	10.160

Concentrate calculation of Drug

Result of the concentration of the Antihypertensives medicine group

Element	Concentration (μg/ml)														
	Drug A-1	Drug A-2	Drug A-3	Drug A-4	Drug A-5	Drug A-6	Drug A-7	Drug A-8	Drug A-9	Drug A-10	Drug A-11	Drug A-12	Drug A-13	Drug A-14	Drug A-15
Cd	0.0257	0.0198	ND	0.0494	0.0417	ND	ND	ND	ND	ND	ND	0.0516	0.0359	0.0060	ND
Pb	ND	ND	2.4557	ND	ND	ND	0.2965	ND	ND	ND	ND	ND	ND	ND	ND
As	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hg	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Co	ND	ND	0.1635	0.2094	ND	ND	0.1572	0.3834	0.4040	ND	0.1598	0.6990	0.3512	0.0456	0.0371
V	1.5584	ND	ND	ND	ND	1.0672	ND	ND	ND	1.5000	ND	ND	1.4884	ND	ND
Ni	ND	1.0775	20.6538	22.0288	ND	1.7826	19.7826	48.4305	46.2400	2.4360	21.4305	48.4869	3.4996	1.0417	0.9338

ND = Not Detection < MDL

Concentrate calculation of Drug

Result of the concentration of the Hypolipidemic medicine group

Element	Concentration (μg/ml)			
	Drug B-1	Drug B-2	Drug B-3	Drug B-4
Cd	ND	0.0912	0.1427	0.0169
Pb	ND	ND	ND	ND
As	ND	ND	ND	ND
Hg	ND	ND	ND	ND
Co	ND	ND	0.0416	ND
V	1.0983	ND	ND	ND
Ni	0.9948	1.4711	0.3628	3.4493

ND = Not Detection < MDL

Result of the concentration of the Antidiabetic medicine group

Element	Concentration (μg/ml)			
	Drug C-1	Drug C-2	Drug C-3	Drug C-4
Cd	0.0560	0.0160	ND	0.0450
Pb	ND	ND	ND	ND
As	ND	ND	ND	ND
Hg	ND	ND	ND	ND
Co	ND	0.0719	0.1187	ND
V	3.0680	1.1062	ND	ND
Ni	6.2760	2.6478	10.8867	ND

Results – QC analysis

Limit of detection (LOD) ; It is the minimum amount of substance analyzed in any samples that can be detected

Background equivalent concentration (BEC) ; It is defined as the analyte concentration that produces a net signal equal to the background

Method detection limit (MDL) ; It is the minimum concentration of the substance to be analyzed, which can be measured by that test method.

Isotope	LOD (ng/ml)	BEC (ng/ml)	MDL (ng/ml)
^{51}V	0.0477	0.5618	0.8966
^{59}Co	0.0039	0.0201	0.0264
^{60}Ni	0.0390	1.7122	0.2606
^{75}As	0.0128	0.0590	0.0751
^{111}Cd	0.0054	0.0190	0.0152
^{200}Hg	0.0790	1.0088	1.3824
^{208}Pb	0.0213	0.2751	0.2428

%Recovery of matrix spike

Result of the recovery of the Antihypertensives medicine group

Element	%Recovery of matrix spike														
	Drug A-1	Drug A-2	Drug A-3	Drug A-4	Drug A-5	Drug A-6	Drug A-7	Drug A-8	Drug A-9	Drug A-10	Drug A-11	Drug A-12	Drug A-13	Drug A-14	Drug A-15
Cd	100.59	106.19	104.96	107.80	98.81	103.68	99.51	107.36	109.37	105.72	99.52	107.60	99.94	104.01	99.05
Pb	102.87	103.61	84.99	95.26	93.19	102.48	92.62	101.76	103.06	104.35	96.11	100.84	100.76	108.10	97.91
As	98.13	103.96	95.80	102.95	94.06	101.95	91.33	100.42	101.21	101.77	94.29	98.39	94.60	98.95	94.46
Hg	93.69	86.74	114.11	126.75	88.06	86.04	116.65	127.24	137.89	90.41	116.21	127.10	92.27	88.95	92.53
Co	105.89	113.43	104.48	112.94	102.67	109.30	99.46	109.74	112.15	111.94	103.33	108.68	106.34	112.33	102.68
V	103.93	109.69	102.48	110.70	101.54	103.06	97.01	108.06	111.58	107.53	99.65	108.19	103.33	108.12	102.00
Ni	107.04	109.50	103.89	110.96	103.71	109.46	100.33	109.17	109.35	108.26	103.60	106.26	106.61	109.91	106.23

%Recovery of matrix spike

Result of the recovery of the Hypolipidemic medicine group

Element	%Recovery of matrix spike			
	Drug B-1	Drug B-2	Drug B-3	Drug B-4
Cd	104.04	103.38	99.26	99.56
Pb	104.67	99.59	93.40	98.56
As	99.83	103.39	99.31	98.48
Hg	92.49	92.49	92.49	92.49
Co	108.43	111.92	104.63	104.15
V	105.65	110.47	105.43	101.98
Ni	103.89	109.25	108.42	109.34

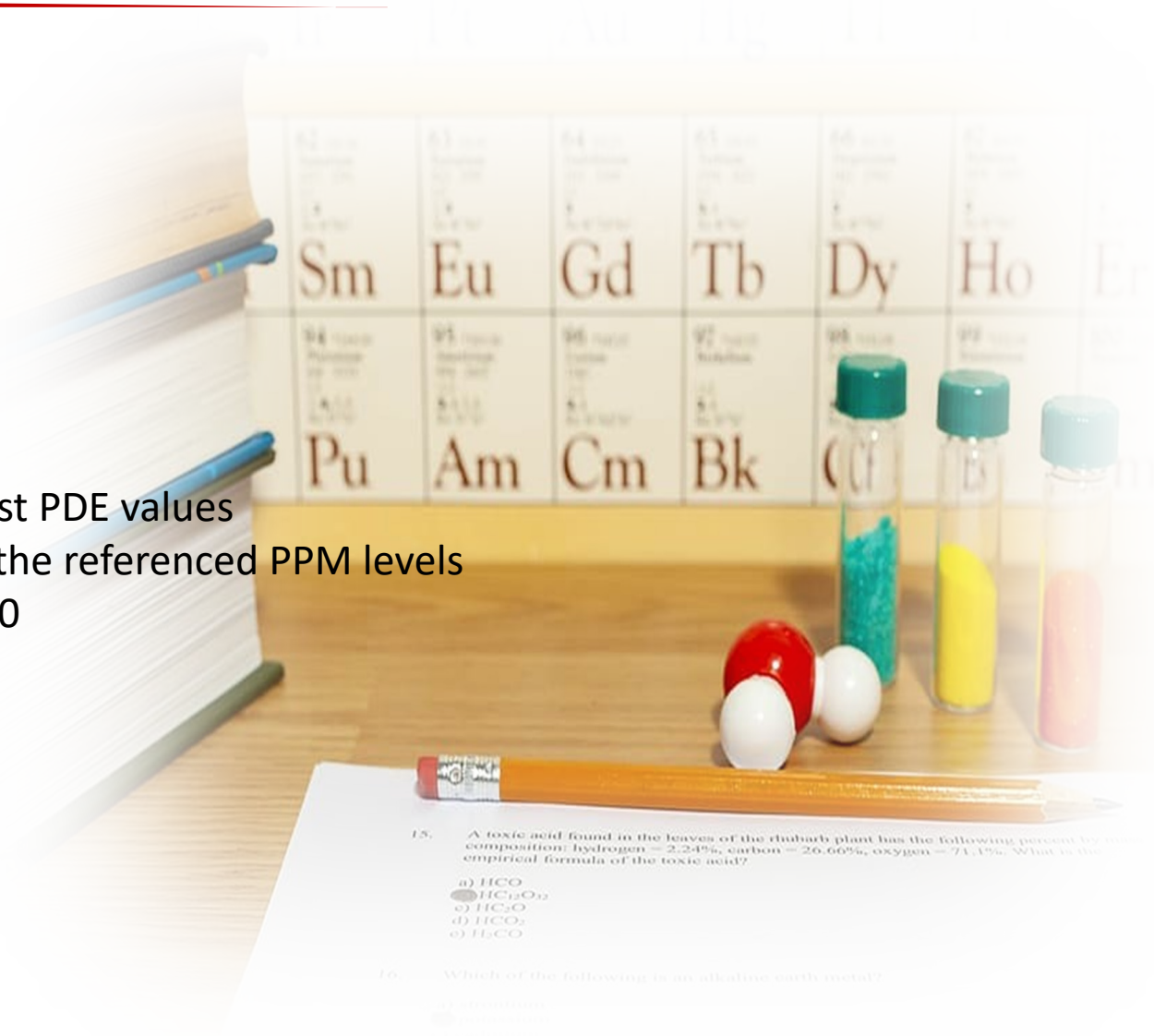
Result of the recovery of the Antidiabetic medicine group

Element	%Recovery of matrix spike			
	Drug C-1	Drug C-2	Drug C-3	Drug C-4
Cd	100.46	104.79	102.33	104.15
Pb	99.93	104.64	101.68	106.48
As	97.29	102.25	98.70	102.36
Hg	87.19	93.56	93.74	89.51
Co	104.86	110.67	109.95	109.83
V	103.45	105.30	105.91	107.68
Ni	86.89	95.56	94.32	91.33

Conclusion

Drug Product Testing:

- ✓ Test the drug product and compare against PDE values in “USP <232> and USP <233>”
- ✓ Add all contribution from excipients and compare against PDE values
- ✓ Testing each component material and compare against the referenced PPM levels
- ✓ Acceptance criteria for test are recoveries of between 80 and 150%
- ✓ %RSD < 20%



Question

Thank You

Q & A