



TRANSITIONING TO THE NEW  
ELEMENTAL IMPURITY  
REGULATIONS; ADVANCES IN  
ATOMIC SPECTROMETRY FOR  
USP <232>/<233> AND ICH

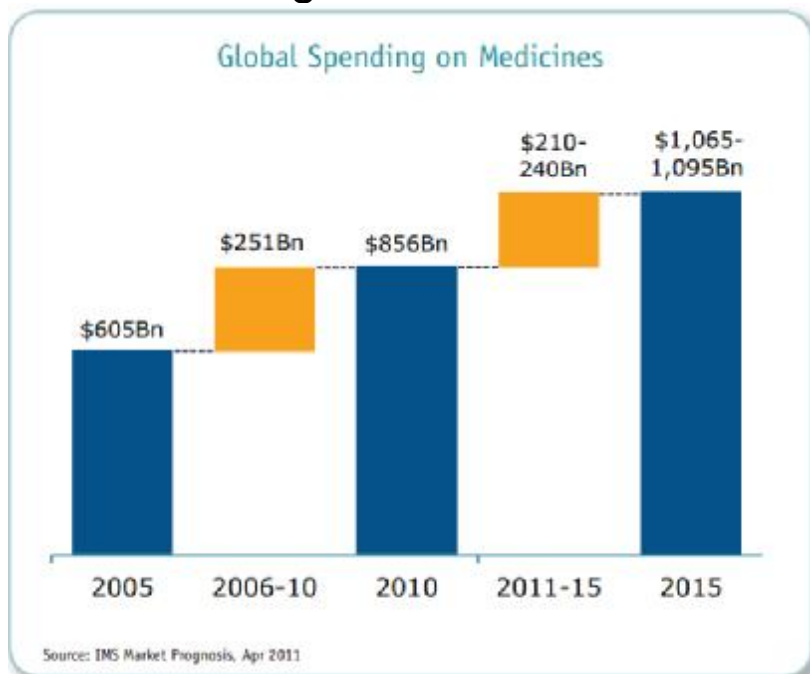
# Agenda

- What changes are coming?
- 7800/7900 and 5100 for USP
- Validation Timeline



# Trace Metal Analysis in Pharmaceuticals, Why?

- Toxicology
- Global Shift to higher consumption of medication/pharmaceutical ingredients
  - Population increase
  - Emerging Health Care
- Consumer safety
  - Small molecule therapeutics
  - Biologics



IMS Health-The Global Use of Medicines: Outlook Through 2015

Per capita pharmaceutical consumption in the non-hospital sector by country income category (by volume, 2008 in SU).

	Median per capita consumption, 2008	Multiple of median SU per capita to that of low income countries	% change in median annual per capita consumption (2000 versus 2008)
High (n=31)	1042	7.7	18.6%
Upper-middle (n=15)	515	3.8	20.4%
Lower-middle (n=19)	214	1.6	22.9%
Low (n=12)	135	1.0	29.3%

Of the 84 countries listed in Annex 1, the following were excluded from this analysis: Israel, the Netherlands, Puerto Rico (high-income), Croatia, the Russian Federation (upper-middle income) and Algeria and Ukraine (lower-middle income).

For the rate of growth in volumes between these two dates, see Annex 3. WHO-The World Medicines Situation 2011

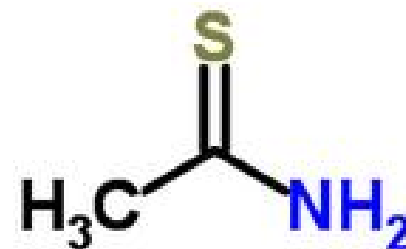
- Excipients; fillers, colors, flavors, stabilizers
- API; source (phyto-, animals, recombinant)
- Catalysts; used in API synthesis
- Production Equipment; pipes, filters, reactors
- Packaging



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# Current USP Metals Analysis Method - USP<231>

- Introduced in USP VIII (1905)
  - Consists of three Procedures (Dilution,  $\text{H}_2\text{SO}_4$  & Ashing,  $\text{H}_2\text{SO}_4/\text{HNO}_3$  &  $\text{H}_2\text{O}_2$ )
    - Sulfide precipitation
    - Visual comparison of precipitate to a 10 ppm Pb STD
- Not reproducible
  - Recovery problems
  - Sample and STD stability
  - High sample size (10 ppm L à 2g)
- Utilizes unsafe reagents
  - Thioacetamide ( $\text{H}_2\text{S}$  is a reaction product; highly toxic)
  - Not allowed in many regions
- Compendial test, does not discriminate
  - Not specific to any analyte
  - Limited number of metals will react (Cr and PGEs will not)
  - Reaction products vary in response
- Subjective results; analyst dependent
- Harsh sample treatment; ashing at  $600^\circ\text{C}$ 
  - Vaporization of volatile analyte. False Negatives (Sb, Hg)



# Comparison of USP<231> with a modern analytical technique

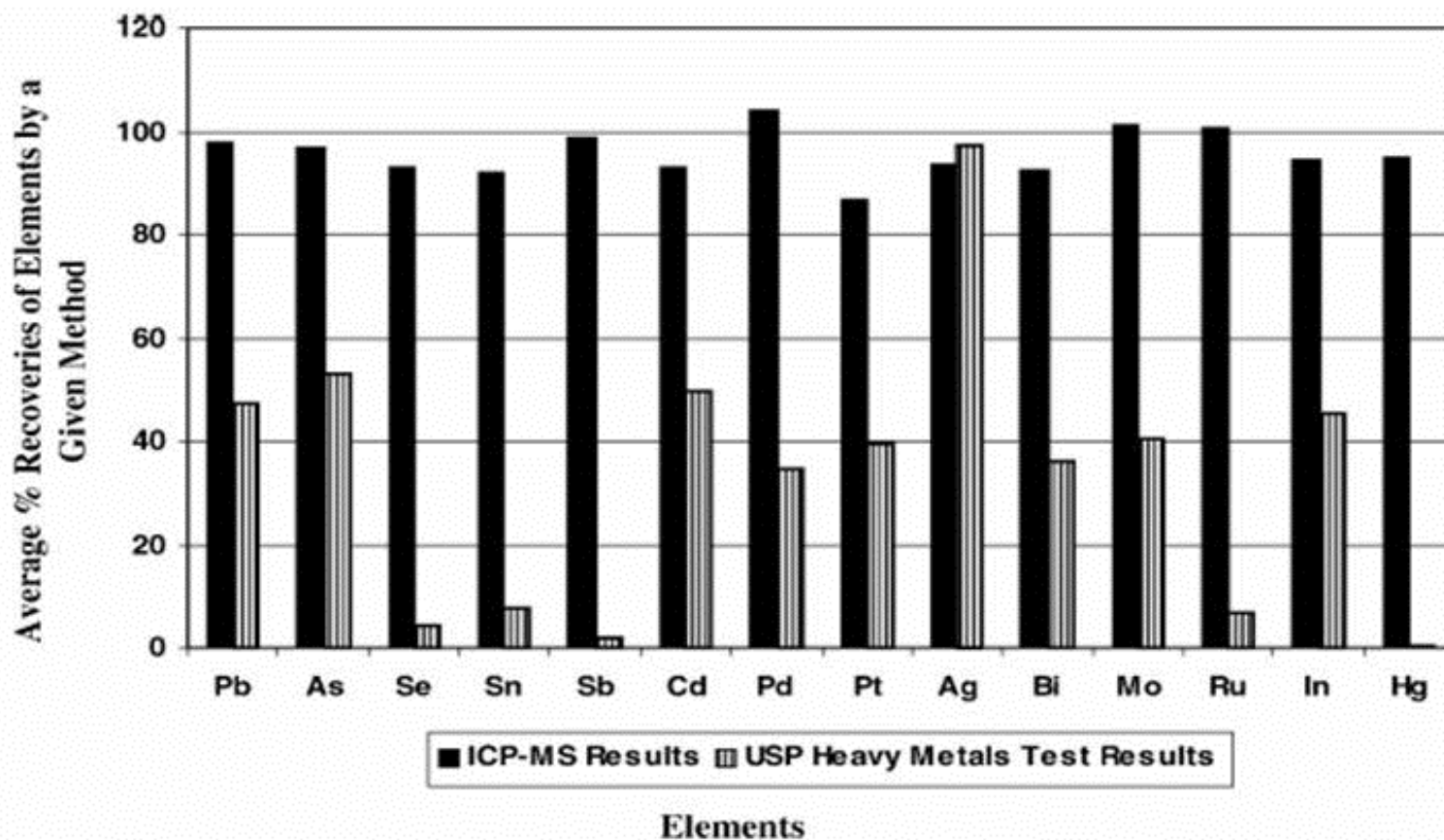


Fig. 2. Comparison of average (%) recoveries of elements: USP Heavy Metals test vs. ICP-MS Heavy Metals test.

From: A rapid ICP-MS screen for heavy metals in pharmaceutical compounds; N. Lewen, S. Mathew, M. Schenkenberger and T. Raglione, [Journal of Pharmaceutical and Biomedical Analysis](#), Volume 35, Issue 4, 29 June 2004, Pages 739-752

# USP<231> Ashing Step Leads to Loss of Volatiles

Table showing low recovery for several elements due to high temperature ashing step in USP<231> (600°C ashing leads to almost total loss of volatile analytes such as Hg and Sb). Issues of low recovery are eliminated when ICP (closed-vessel acid digestion) sample prep is used

**Table 1. Effects on Test Samples of Heating/Temperature on Volatilization of Heavy Metals Using ICP Detection**

Heavy Metal Spiked	Test Solution with 10 ppm Heavy Metal					
	Pharmacopeial Methodology				ICP Sample Preparation	
	After Hot Plate Evaporation		After 600 °C Ashing		After Acid Digestion	
	PPM	% Recovery	PPM	% Recovery	PPM	% Recovery
Silver (Ag)	5.2	52	1.8	18	9.4	94
Arsenic (As)	3.4	34	5.2	52	9.0	90
Bismuth (Bi)	10.5	105	5.4	54	9.9	99
Cadmium (Cd)	11.0	110	9.4	94	10.6	106
Copper (Cu)	10.4	104	4.8	48	10.5	105
Mercury (Hg)	5.6	56	0.6	6	10.7	107
Molybdenum (Mo)	9.5	95	4.7	47	9.8	98
Lead (Pb)	12.5	125	9.6	96	10.5	105
Antimony (Sb)	4.6	46	0.5	5	10.4	104
Tin (Sn)	7.0	70	0.3	3	10.9	109

Pharmacopeial Forum Stimuli Vol. 34(6) [Nov.–Dec. 2008]



# Timeline for USP<231> Replacement Method

- 1995:** 1<sup>st</sup> Pharmacopeial Forum (PF) “Stimuli to the Revision Process” article (K. Blake)
- 2000:** 2<sup>nd</sup> PF Stimuli article proposed ICP-MS (T. J. Wang)
- 2005:** USP heavy metals subcommittee appointed
- 2005:** ICP-MS Included in Chinese Pharmacopeia
- 2009:** ICP-MS Included in European Pharmacopeia
- 2010:** Proposals for USP<232>, <233> and <2232>
- 2012:** USP final revision to be published
- 2013:** Latest revision published
- 2013:** Final Implementation is postponed
- 2016: ICH Q3D implementation for new products only, June 2016**
- 2017: ICH Q3D implementation for existing products, (Dec ?)**
- 2018: USP <232>/<233>/<2232> becomes official January 1, 2018**

USP Completely aligned with ICH PDEs

# Heavy Metal Chapters – Current and Planned

Heavy Metals Limit Test

<231>



**Is being replaced with:**

<232>

Elemental  
Impurities  
(Limits)

<233>

Elemental  
Impurities  
(Procedures)

<232> will eventually  
replace other “metals”  
General Chapters

Lead

<251>

Arsenic

<211>

Mercury

<261>



Related method <2232>  
applies to dietary  
supplements only

<2232>

Elemental  
Impurities in  
Dietary  
Supplements

Terminology changing:  
“Heavy Metals” à “Elemental Impurities”



# Current PDEs

ICH Class	Element	Symbol	ICH (ug/day) Oral PDE	USP (ug/day) Oral PDE	EMA (ug/day) Oral PDE	ICH (ug/day) Parenteral PDE	USP (ug/day) Parenteral PDE	ICH (ug/day) Inhalation PDE	USP (ug/day) Inhalation PDE
Class 1	Arsenic	As	15	15		15	15	2	2
	Cadmium	Cd	5	5		2	2	2	2
	Mercury	Hg	30	30		3	3	1	1
	Lead	Pb	5	5		5	5	5	5
Class 2A	Cobalt	Co	50			5		3	
	Molybdenum	Mo	3000	3000	250	1500	1500	10	10
	Selenium	Se	150			80		130	
	Vanadium	V	100	100	250	10	10	1	1
Class 2B	Silver	Ag	150			10		7	
	Gold	Au	100			100		1	
	Iridium	Ir	100	100	100	10	10	1	1
	Osmium	Os	100	100	100	10	10	1	1
	Palladium	Pd	100	100	100	10	10	1	1
	Platinum	Pt	100	100	100	10	10	1	1
	Rhodium	Rh	100	100	100	10	10	1	1
	Ruthenium	Ru	100	100	100	10	10	1	1
	Thallium	Tl	8			8		8	
	Barium	Ba	1400			700		300	
	Chromium	Cr	11000	11000	250	1100	1100	3	3
	Copper	Cu	3000	3000	2500	300	300	30	30
Class 3	Lithium	Li	550			250		25	
	Nickle	Ni	200	200	250	20	20	5	5
	Antimony	Sb	1200			90		20	
	Tin	Sn	6000			600		60	
Class 4	Aluminum	Al							
	Boron	B							
	Calcium	Ca							
	Iron	Fe			13000				
	Magnesium	Mg							
	Manganese	Mn			2500				
	Potassium	K							
	Sodium	Na							
	Tungstan	W							
	Zinc	Zn			13000				



# Agilent Atomic Spectrometry Portfolio



AA

Atomic Absorption  
Spectroscopy



MP-AES

Microwave Plasma-Atomic  
Emission Spectroscopy



ICP-OES

Inductively Coupled Plasma-  
Optical Emission Spectroscopy



ICP-MS

Inductively Coupled Plasma-  
Mass-Spectrometry



ICP-QQQ

Triple Quadrupole ICP-MS



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# ICP-MS -or- ICP-OES

ICH Class	Element	Symbol	ICH (ug/day) Oral PDE	USP ug/day) Oral PDE	EMA (ug/day) Oral PDE	ICH (ug/day) Parenteral PDE	USP ug/day) Parenteral PDE	ICH (ug/day) Inhalation PDE	USP ug/day) Inhalation PDE
Class 1	Arsenic	As	15	15		15	15	2	2
	Cadmium	Cd	5	5		2	2	2	2
	Mercury	Hg	30	30		3	3	1	1
	Lead	Pb	5	5		5	5	5	5

## Solid Drug Product (requires digestion):

-Oral Target Limit for Cd is 5 ug/day

Assuming Daily Dose of 10 g/day

5 ug / 10g (500 ppb)

Typical solid sample digestion results in 200x dilution

Target Limit = 2.5 ppb (500 ppb / 200x dilution)

0.5J = 1.25 ppb, 1.5J = 3.75 ppb

## Saline Solution (can measure directly):

-Parenteral Target Limit for Cd is 2ug/day

Assuming typical administration of 2-3 L / Day

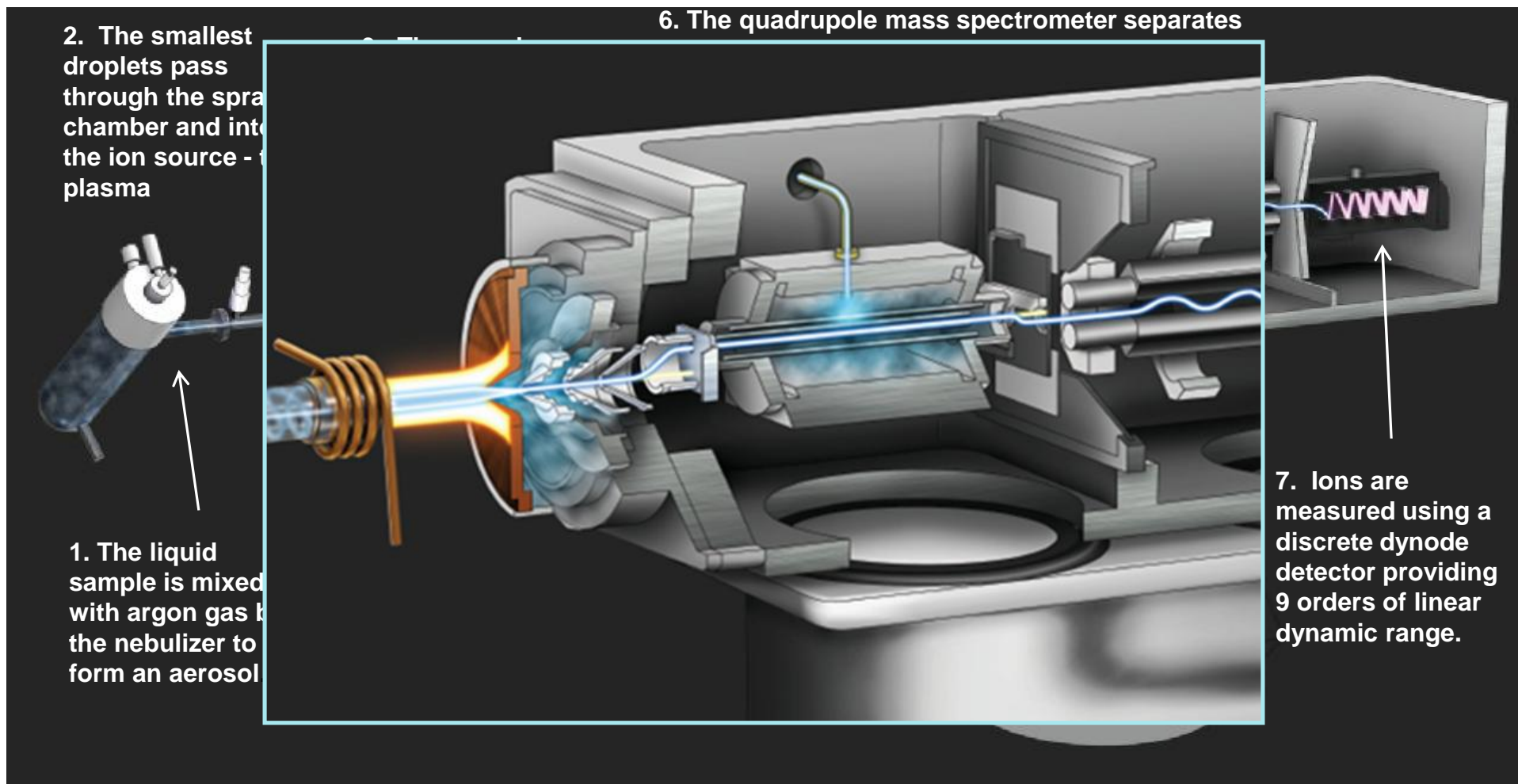
2 ug / 3L = 0.66 ug/L

0.5J = 0.33 ug/L, 1.5J = 0.99 ug/L

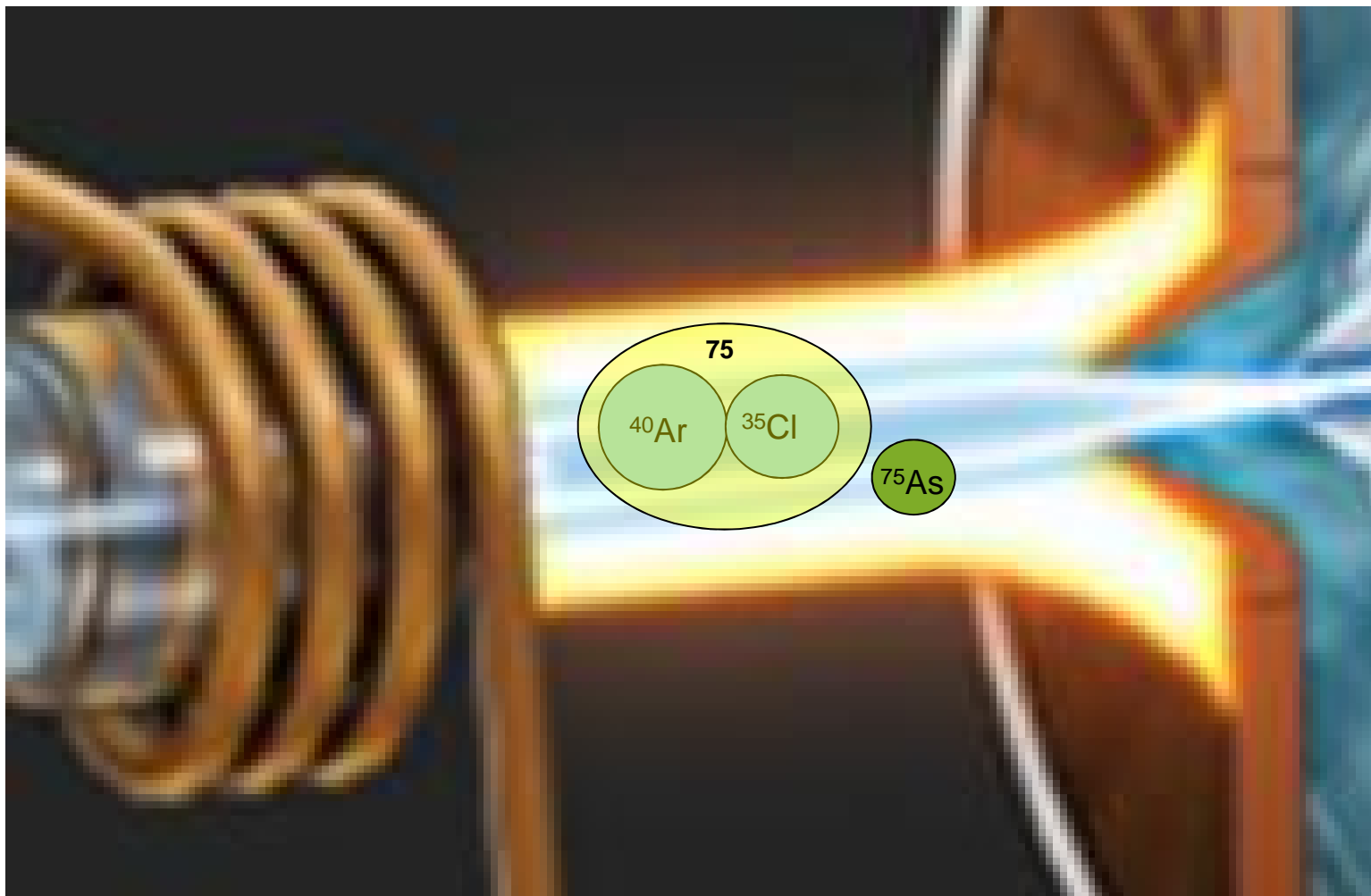
# Agilent 7900 ICP-MS – In a Class by Itself



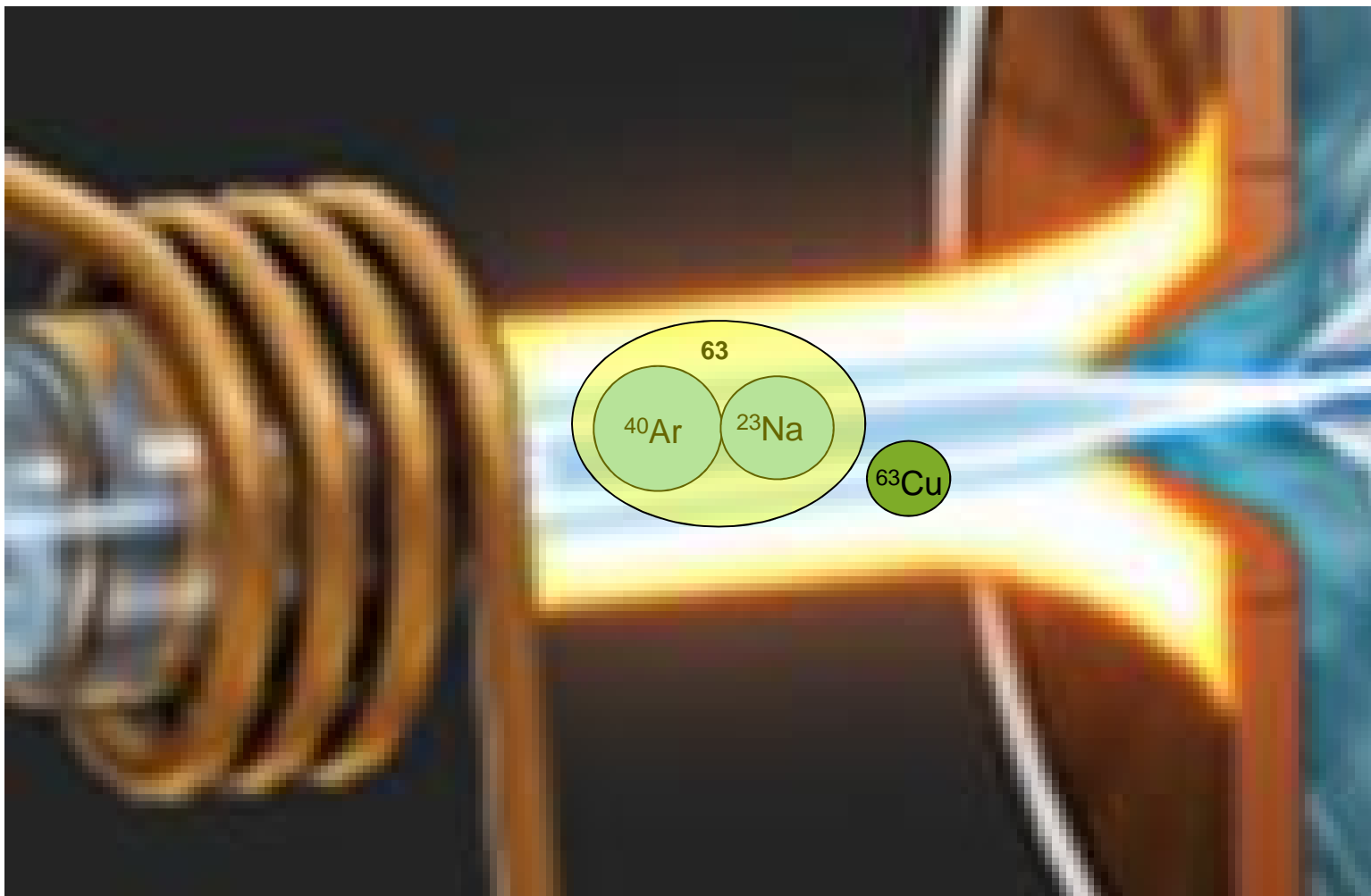
# ICPMS with Enhanced ORS<sup>4</sup> Technology



# Polyatomic Interference Formation



# Polyatomic Interference Formation





# Troublesome Region of the Periodic Table

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	L	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	A															
		L	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
		A	Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr



# 3 Key Benefits of Agilent 7900 ICP-MS For USP Applications

## 1) Matrix Tolerance



### Ultra High Matrix Introduction System (UHMI)

**Handles tough sample matrices better than any other ICP-MS. Highest total dissolved solids(TDS) capability up to 25%**

- Reduces sample prep time and error
- Better long-term stability

## 2) Interference Removal

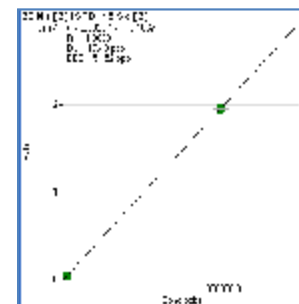


### Octopole Reaction System (ORS<sup>4</sup>) He Mode

**He Mode effectively removes common polyatomic interferences in the samples**

- Easy to use - He collision mode only
- Effective for a wide range of sample types
- Accurate measurements

## 3) Dynamic Range



### Wider Dynamic Range

**11 orders dynamic range: 0.1ppt(DL) to 10,000ppm**

- Simplifies method development
- Easy sample prep.
- Improves productivity

# Introducing the Ground-Breaking Agilent UHMI

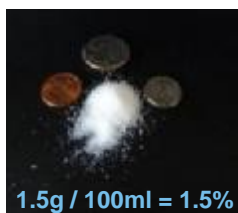
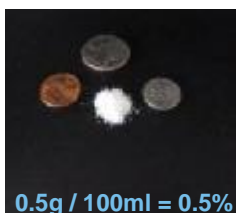
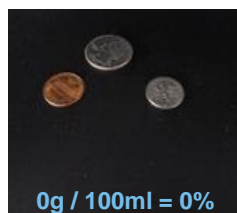


UHMI (ultra High Matrix Interface) – much more than just a simple T-piece

UHMI uses optimized gas mixing geometry and sophisticated plasma/gas-flow tuning algorithm to set reproducible conditions for predictable aerosol dilution rate

# "Big Four" Spiked into Different Salt Matrices

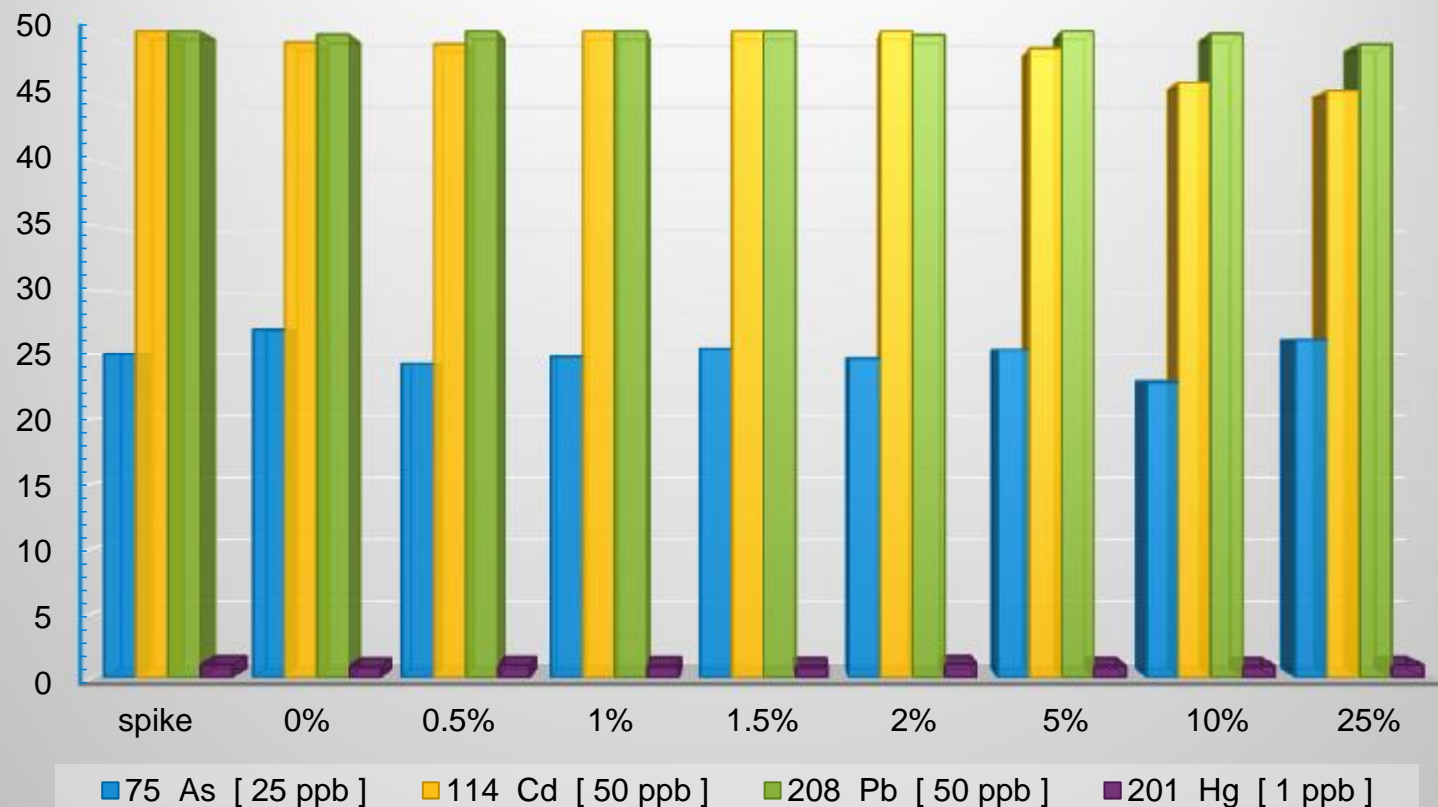
NaCl Amount	75 As [ 25 ppb ]	114 Cd [ 50 ppb ]	208 Pb [ 50 ppb ]	201 Hg [ 1 ppb ]
0%	26.9	49.2	49.7	0.85
0.5%	24.2	49.0	50.1	0.99
1%	24.8	51.5	50.2	0.93
1.5%	25.5	50.0	50.5	0.88
2%	24.6	50.0	49.7	1.03
5%	25.4	48.7	50.7	0.89
10%	22.8	46.1	49.8	0.91
25%	26.2	45.4	49.0	0.96
<b>Average</b>	<b>25.1</b>	<b>48.7</b>	<b>50.0</b>	<b>0.93</b>
<b>% Recovery</b>	<b>100%</b>	<b>97%</b>	<b>100%</b>	<b>93%</b>
<b>% RSD</b>	<b>5%</b>	<b>4%</b>	<b>1%</b>	<b>6%</b>



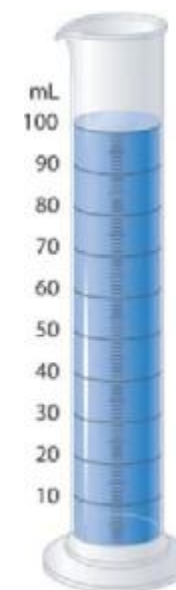
# "Big Four" Toxic Elements in Variable NaCl Matrices

25% TDS is 125x the recommended maximum for typical ICP-MS

**Spike Recovery at  
0, 0.5, 1, 1.5, 2, 5, 10 and 25% NaCl**

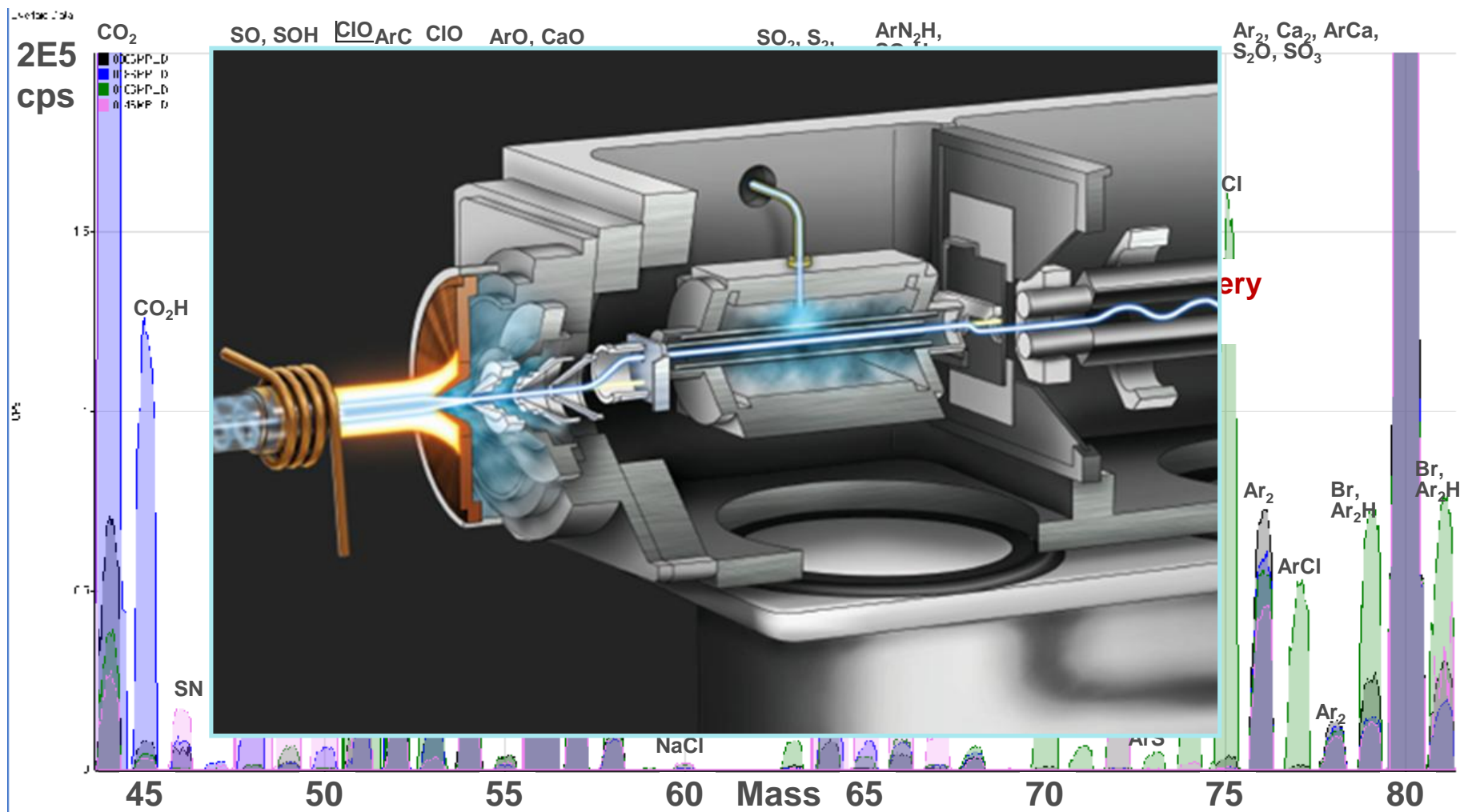


25g / 100ml = 25%



# Polyatomic Interferences in No Gas Mode

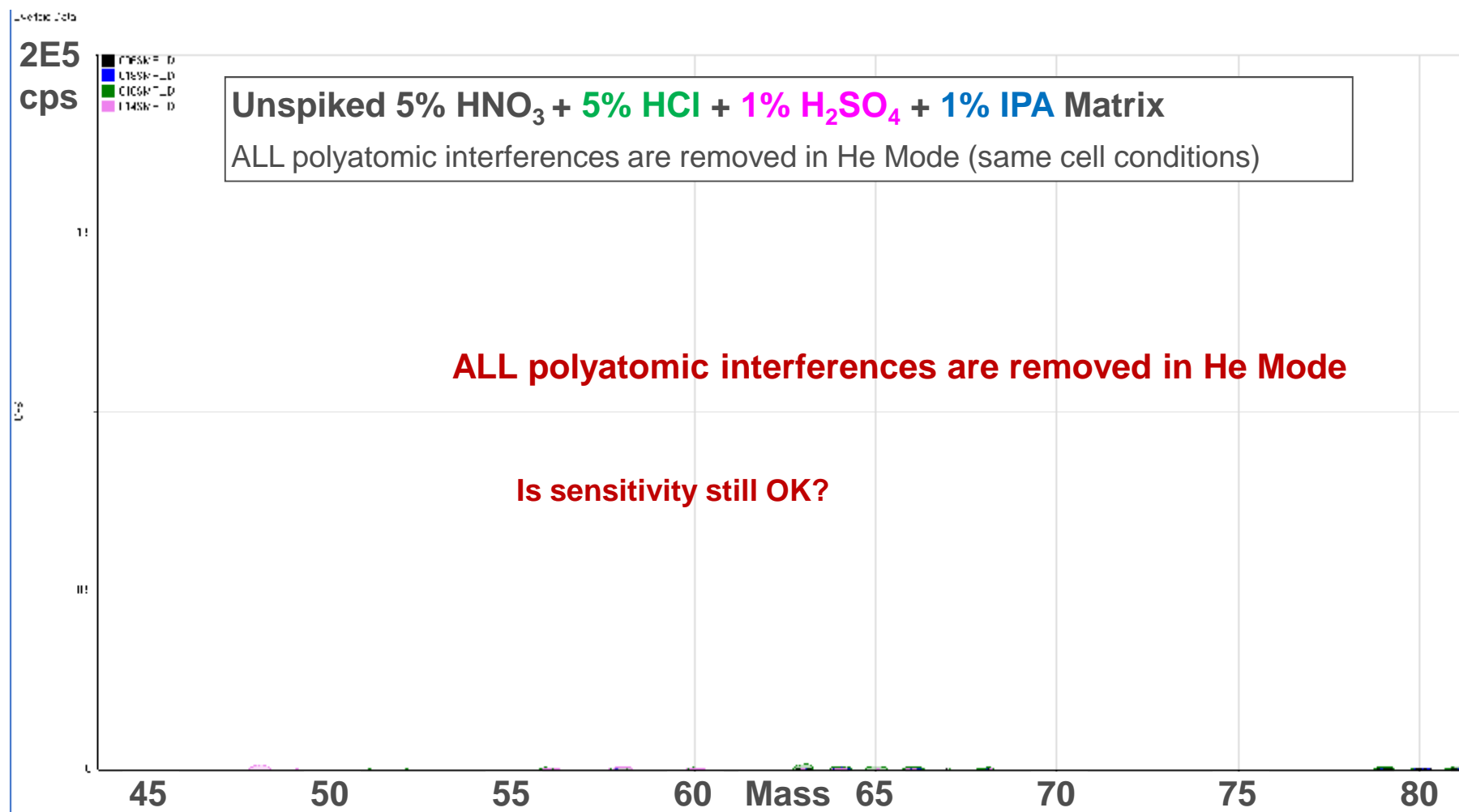
Color of spectrum indicates which matrix gave each interfering peak



No Gas Mode

# Polyatomic Interferences in He Mode

Color of spectrum indicates which matrix gave each interfering peak

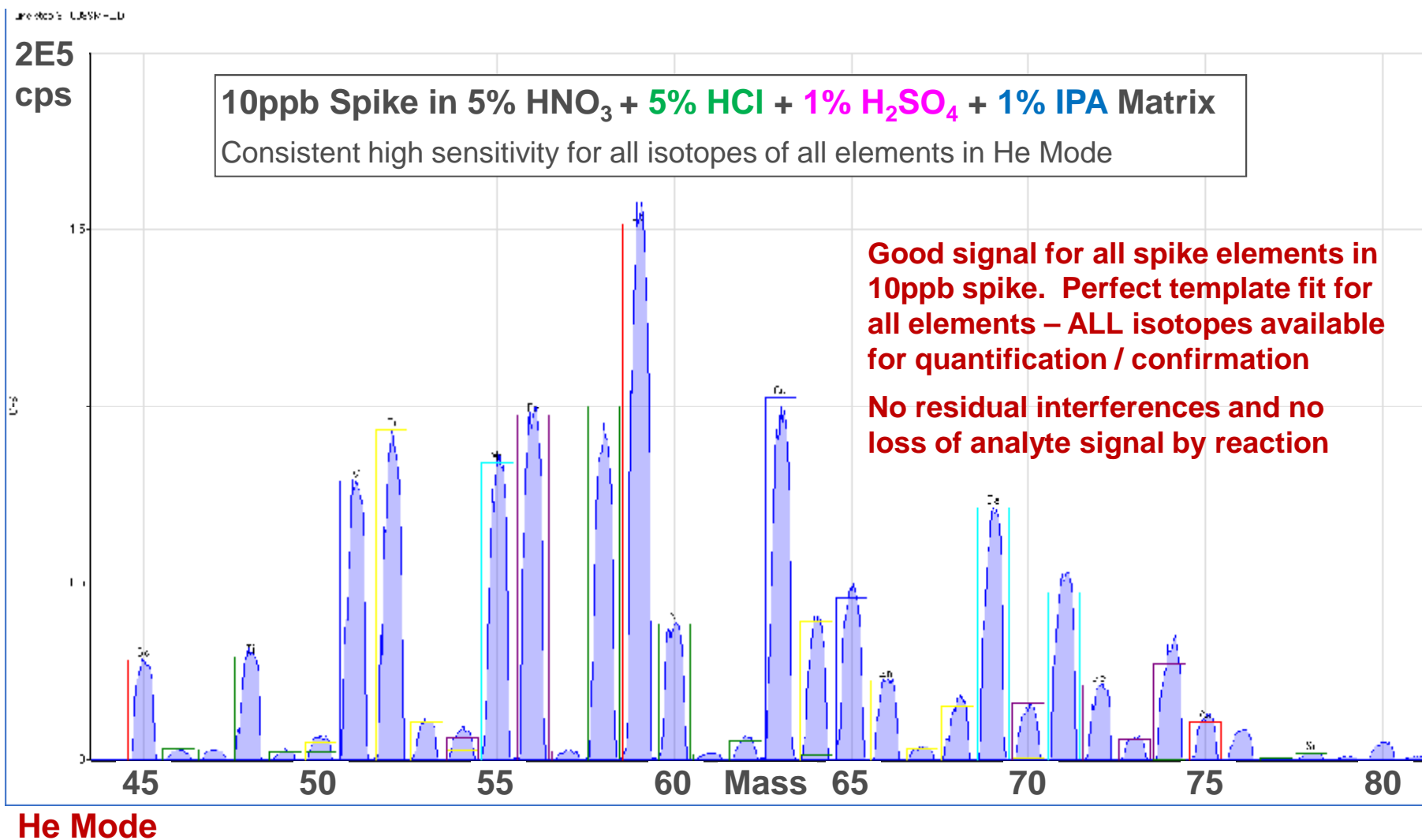


**He Mode**



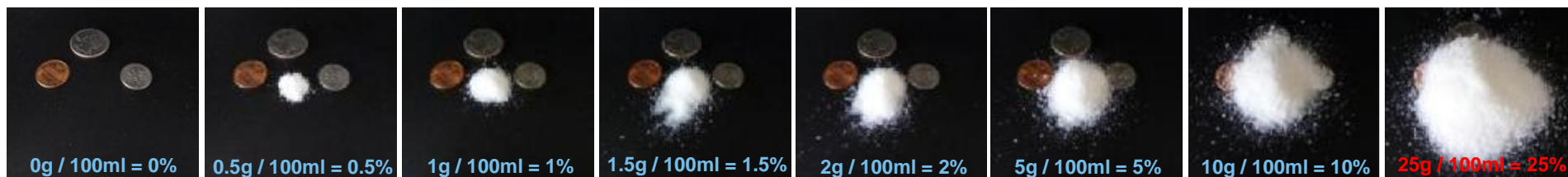
# Matrix Mix with Spike (10ppb) in He Mode

Consistent sensitivity and perfect template match for all elements



# Interfered Elements Spiked into Different Salt Matrices

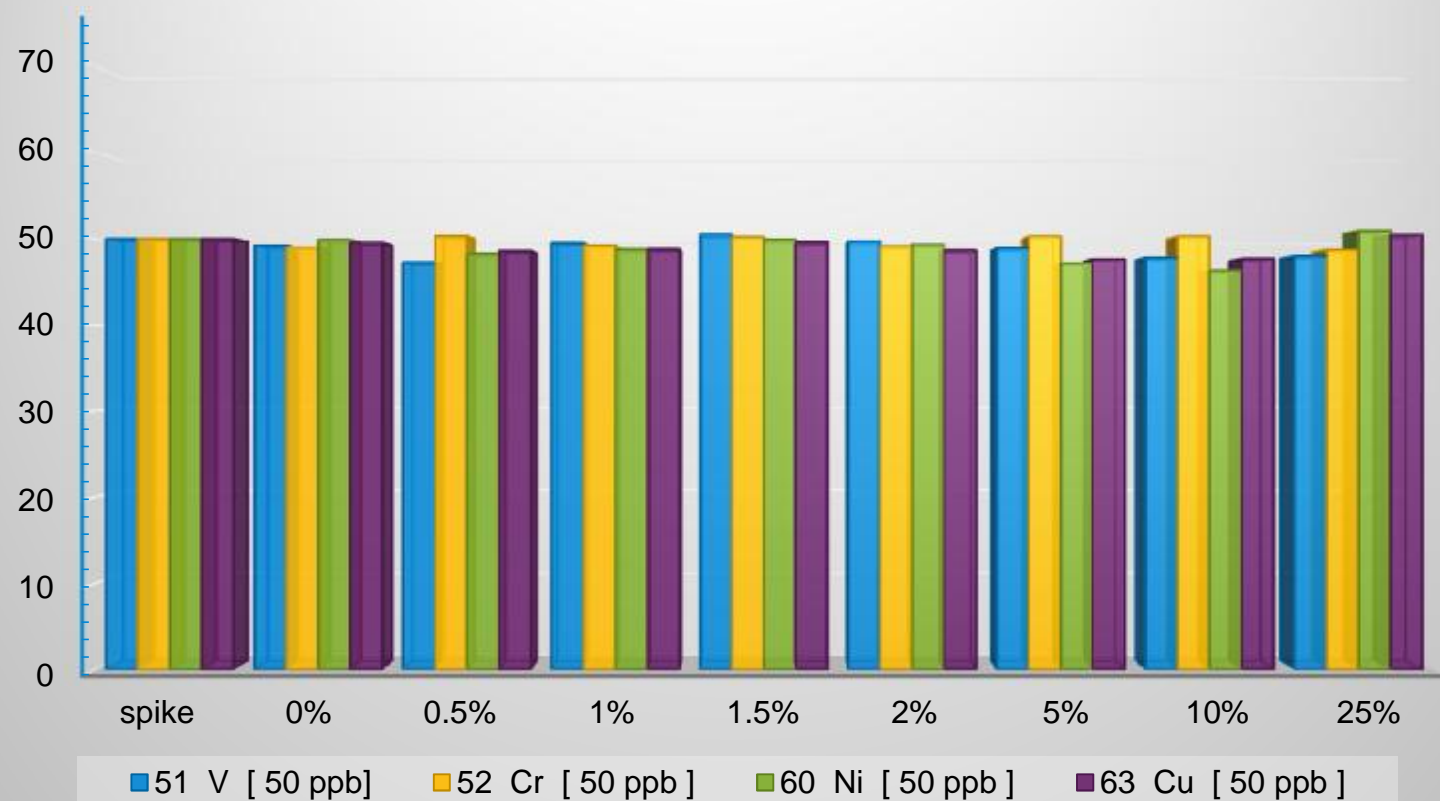
NaCl Amount	51 V [ 50 ppb ]	52 Cr [ 50 ppb ]	60 Ni [ 50 ppb ]	63 Cu [ 50 ppb ]
0%	49.2	49.1	49.9	49.6
0.5%	47.3	50.3	48.3	48.6
1%	49.5	49.3	48.8	48.8
1.5%	50.5	50.3	49.9	49.6
2%	49.7	49.1	49.4	48.7
5%	48.9	50.3	47.2	47.7
10%	47.8	50.3	46.3	47.7
25%	48.0	48.7	50.9	50.5
<b>Average</b>	<b>48.9</b>	<b>49.7</b>	<b>48.8</b>	<b>48.9</b>
<b>% Recovery</b>	<b>98%</b>	<b>99%</b>	<b>98%</b>	<b>98%</b>
<b>% RSD</b>	<b>2%</b>	<b>1%</b>	<b>3%</b>	<b>2%</b>



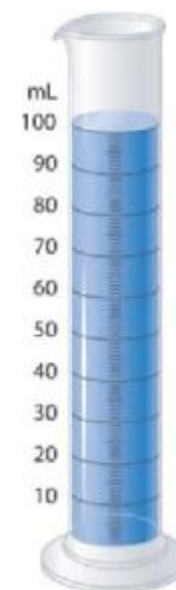
# Interfered Elements in Variable NaCl Matrices

V-51 (ClO), Cr-52 (ClOH), Ni-60 (NaCl) and Cu-63 (ArNa)

**Spike Recovery at  
0, 0.5, 1, 1.5, 2, 5, 10 and 25% NaCl**



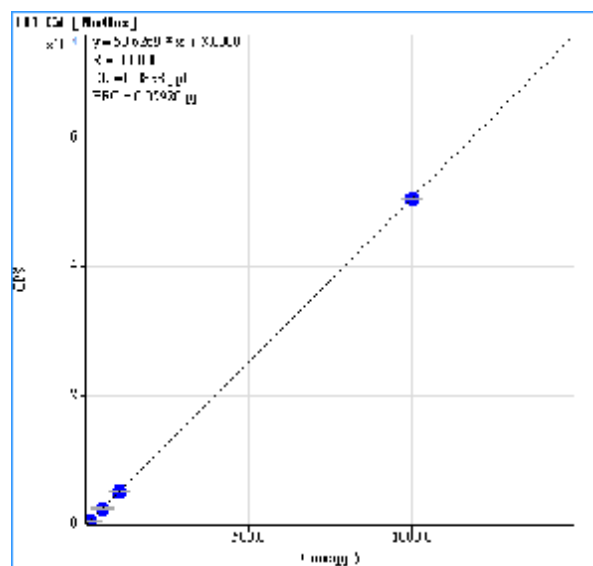
**25g / 100ml = 25%**



# Far Wider Dynamic Range Than Any Other ICP-MS

## 11 orders - low and high level calibrations in a single run

Cd (1ppt - 1ppb) and Na (100ppb - 10,000ppm (1%)) in the same run

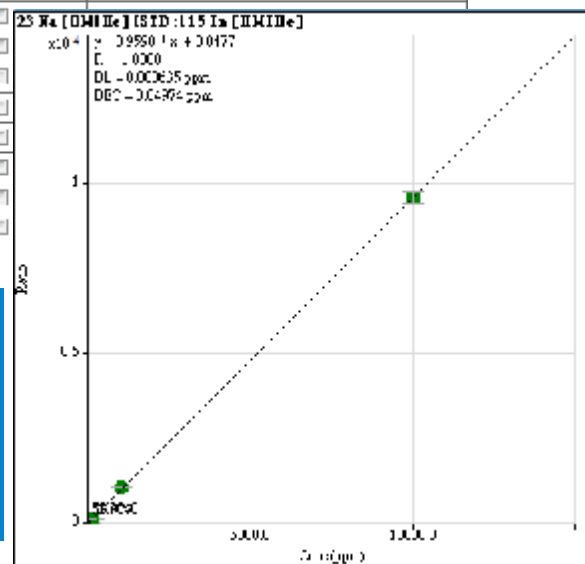


Current Sample	Conc	Conc	Ratio	Det	Conc. STD
1234567890	1000.00	506.000	0	0.0	

Level	Conc.	Calc. Conc.	CR%	Ratio	Det	Conc. STD
1	0.1	0.100	0.0	0.0	0.0	0.0
2	1.0	1.000	0.0	0.0	0.0	0.0
3	10.00	10.090	0.090	0	0.0	0.0
4	100.00	46.081	256.00	0	0.0	0.0
5	1000.00	1000.00	0.000	0	0.0	0.0
6	10000.0	10000.0	0.000	0	0.0	0.0

Both calibrations are linear.  
Total concentration range covered from Cd blank (BEC of <0.1ppt) to Na top standard (1%) is 11 orders



Current Sample	Conc	Conc	Ratio	Det	Conc. STD
1234567890	1000.00	506.000	0	0.0	

Level	Conc.	Calc. Conc.	CR%	Ratio	Det	Conc. STD
1	0.1	0.100	0.0	0.0	0.0	0.0
2	1.0	1.000	0.0	0.0	0.0	0.0
3	10.00	10.090	0.090	0	0.0	0.0
4	100.00	100.00	0.000	0	0.0	0.0
5	1000.00	99.024	400.000	0	0.0	0.0
6	10000.0	10000.0	0.000	0	0.0	0.0
7	100000.0	100000.0	0.000	0	0.0	0.0
8						
9						
10						
11						
12						
13						
14						

Concentration range (11 orders) and upper measurement limit (>1%) are at least 10x better than any other ICP-MS



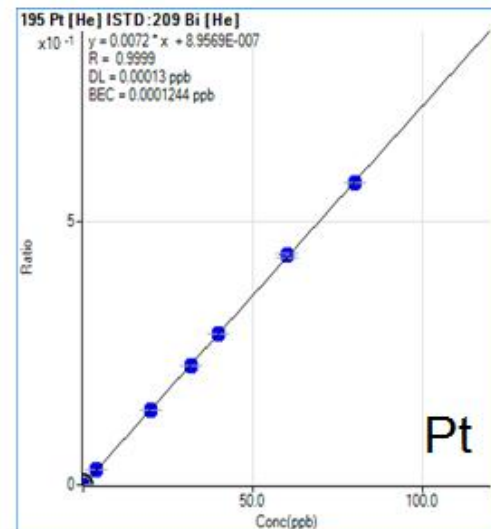
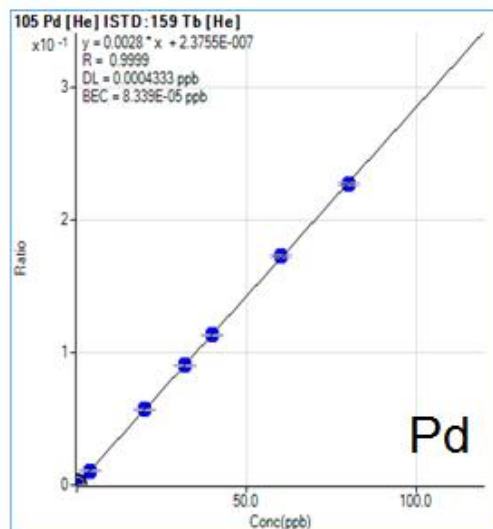
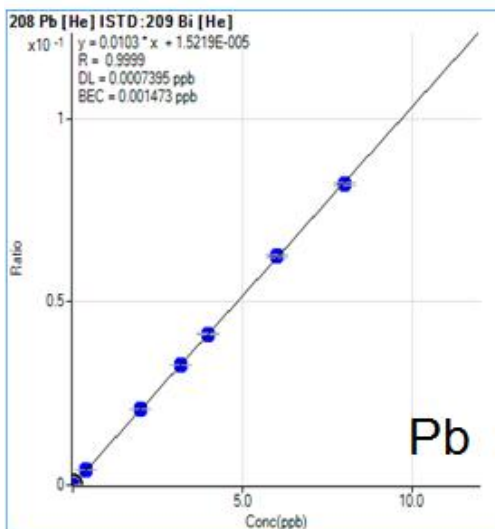
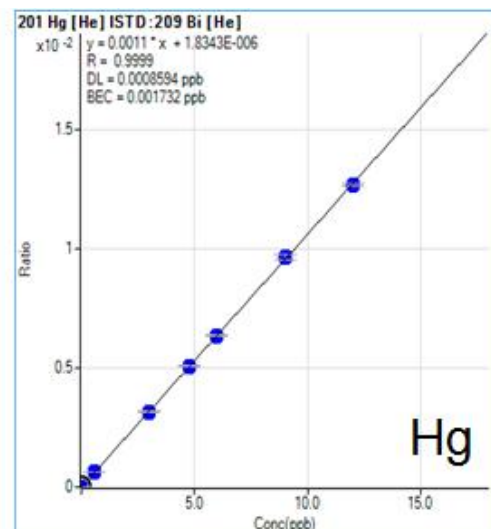
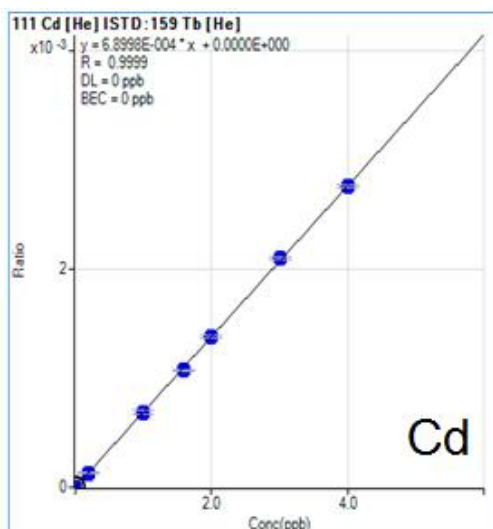
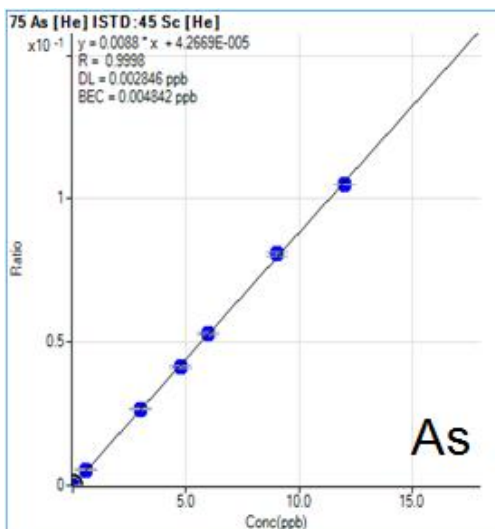
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Agilent Restricted

March 21, 2016

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# Example Calibrations; 0.1J to 2J



# Agilent Atomic Spectrometry Portfolio



AA

Atomic Absorption  
Spectroscopy



MP-AES

Microwave Plasma-Atomic  
Emission Spectroscopy



ICP-OES

Inductively Coupled Plasma-  
Optical Emission Spectroscopy



ICP-MS

Inductively Coupled Plasma-  
Mass-Spectrometry



ICP-QQQ

Triple Quadrupole ICP-MS



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# Agilent ICP-OES

## 5100 SVDV with Dichroic Spectral Combiner (DSC)

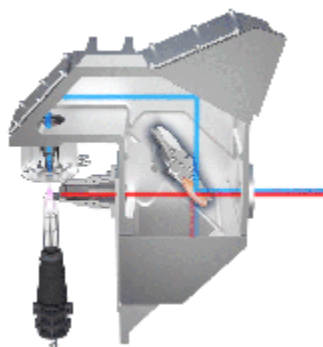
- Vertical torch
  - Excellent matrix tolerance (>25%)
- Synchronous axial and radial view
  - reduction of interferences
  - increased linear range
  - highest throughput
- VistaChip II detector
  - Full, continuous wavelength coverage
  - Elimination of interferences
  - Qualifier wavelengths
- ICP Expert 7 Software
  - FBC Fitted Background Correction
  - FACT spectral deconvolution





# ICP-OES Agilent 5100: Benefits for USP <232> <233>

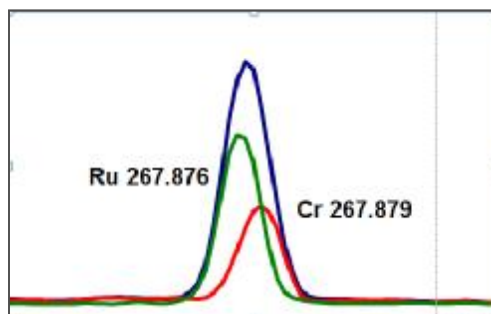
## 1) Matrix tolerance



Vertical Torch with Synchronous  
Axial and Radial Viewing

**Able to analyze high total  
dissolved solids ( > 25%)**

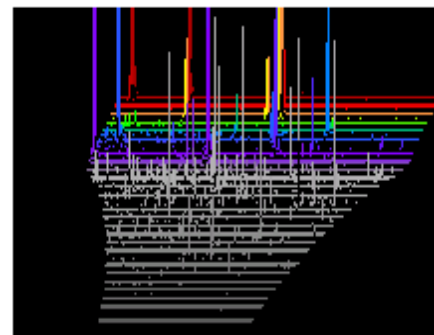
## 2) Interference removal



Background Correction and  
Interference Removal

**FBC Fitted Background Correction  
FACT Spectral Deconvolution**

## 3) Dynamic range



**Wide Dynamic Range**

Full complete wavelength coverage  
VistaChip II detector



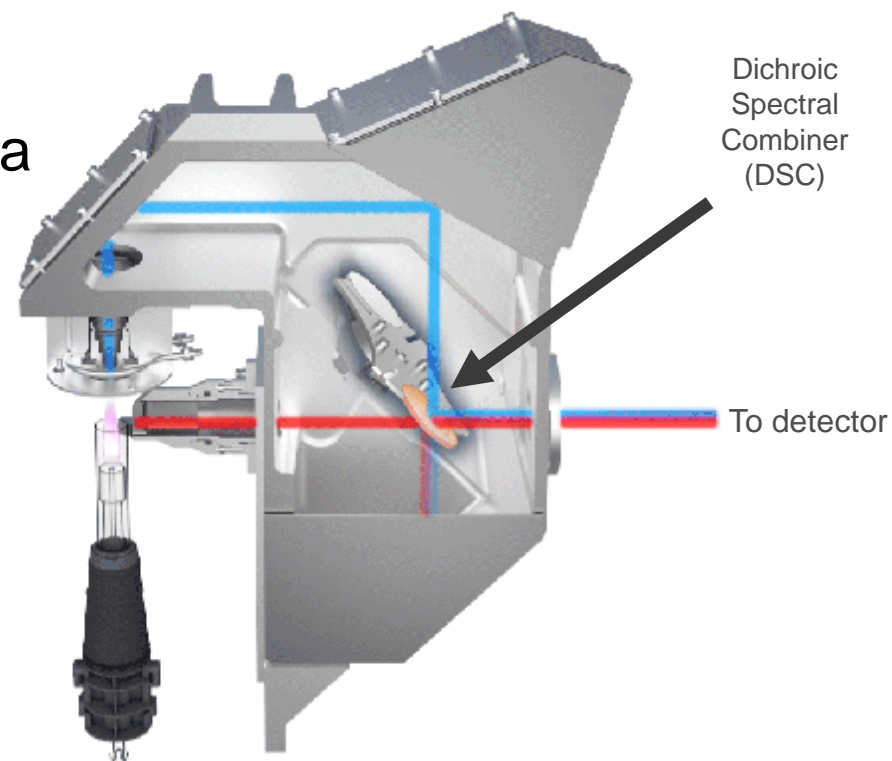
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# Agilent 5100 ICP-OES

## SVDV ICP-OES

Patented DSC technology for next generation ICP-OES.  
Provides DV without limitations.

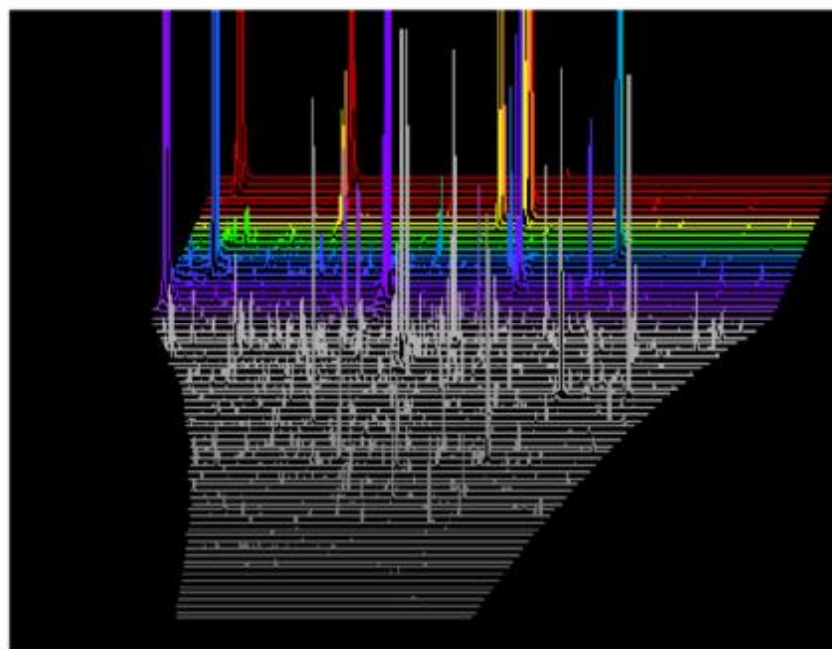
- Synchronous reading of the plasma for both radial and axial.
- Vertical torch provides high matrix capability



# Agilent 5100 ICP-OES

Full complete wavelength coverage

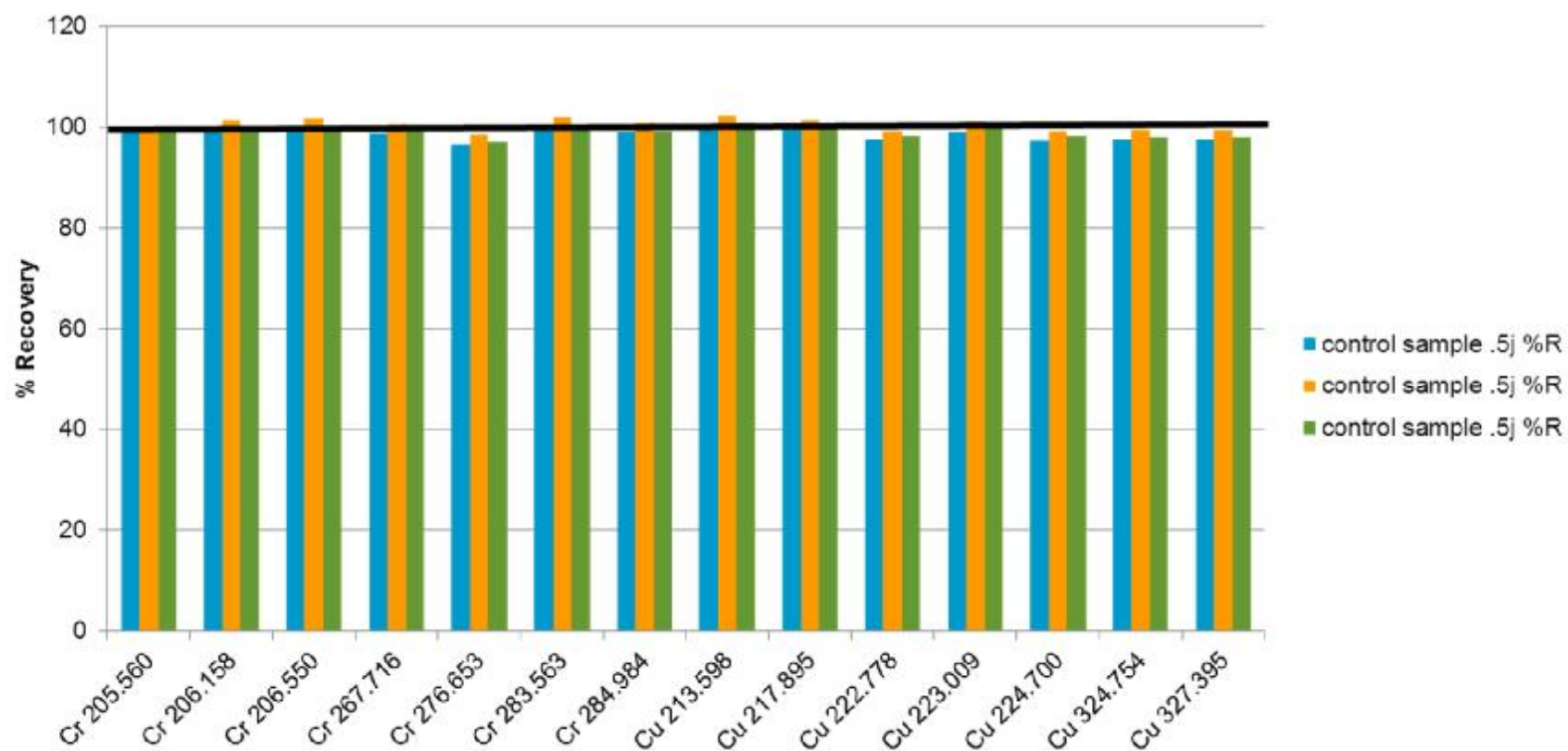
- VistaChip II CCD detector



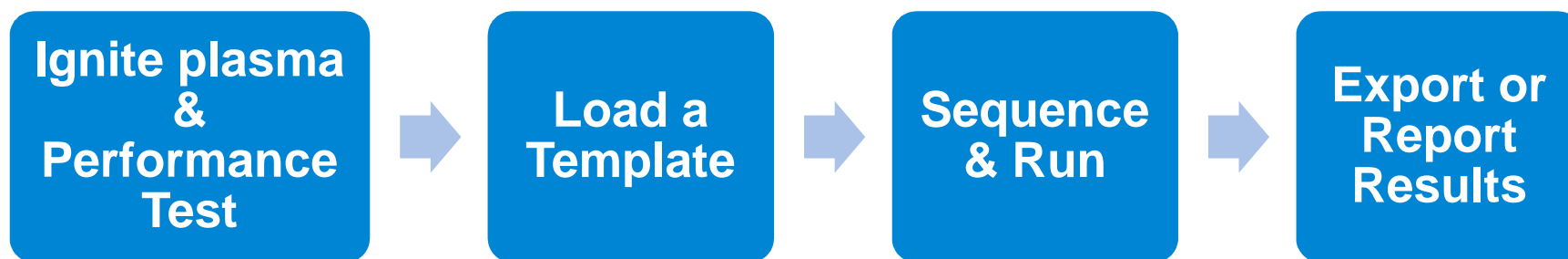
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# Agilent 5100 ICP-OES

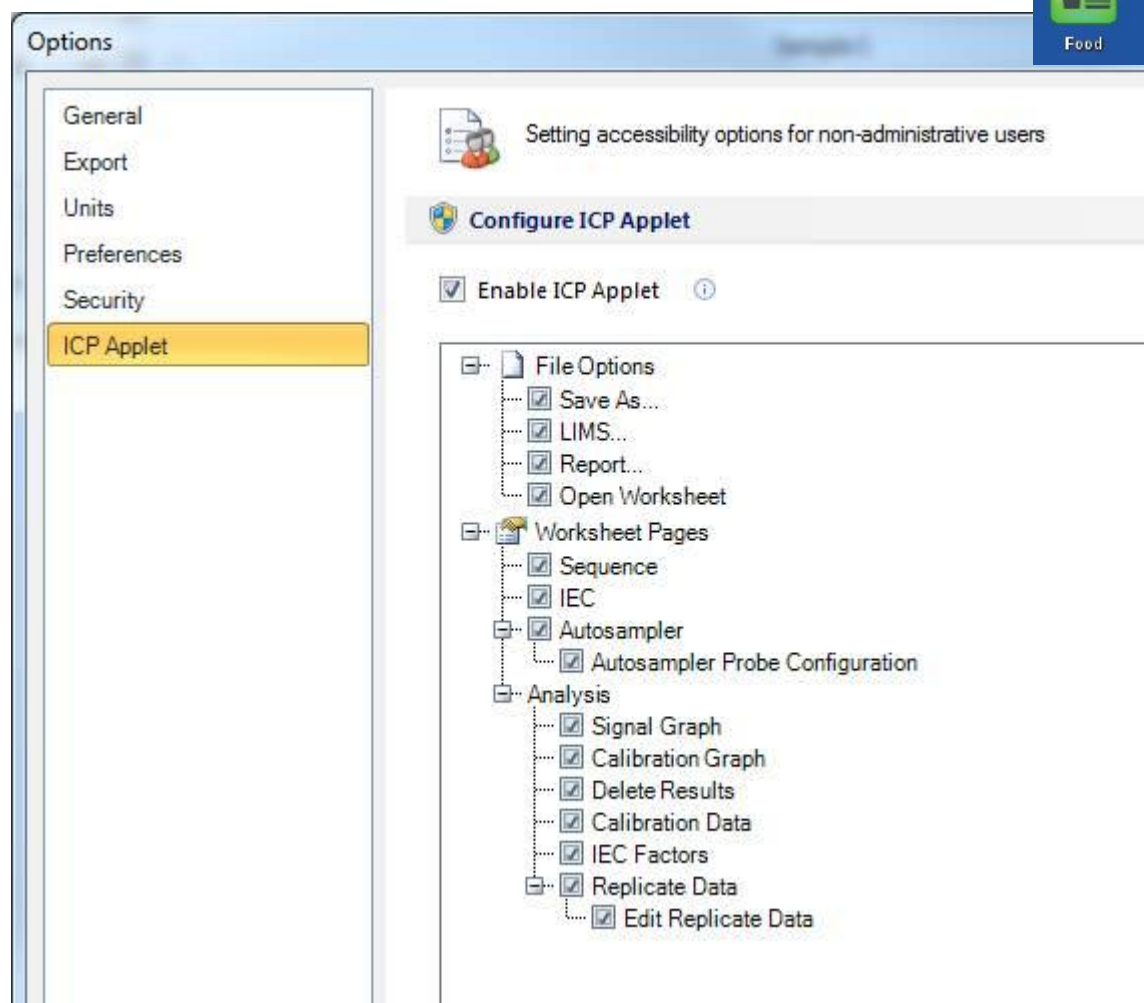
## Results Confirmation Capability



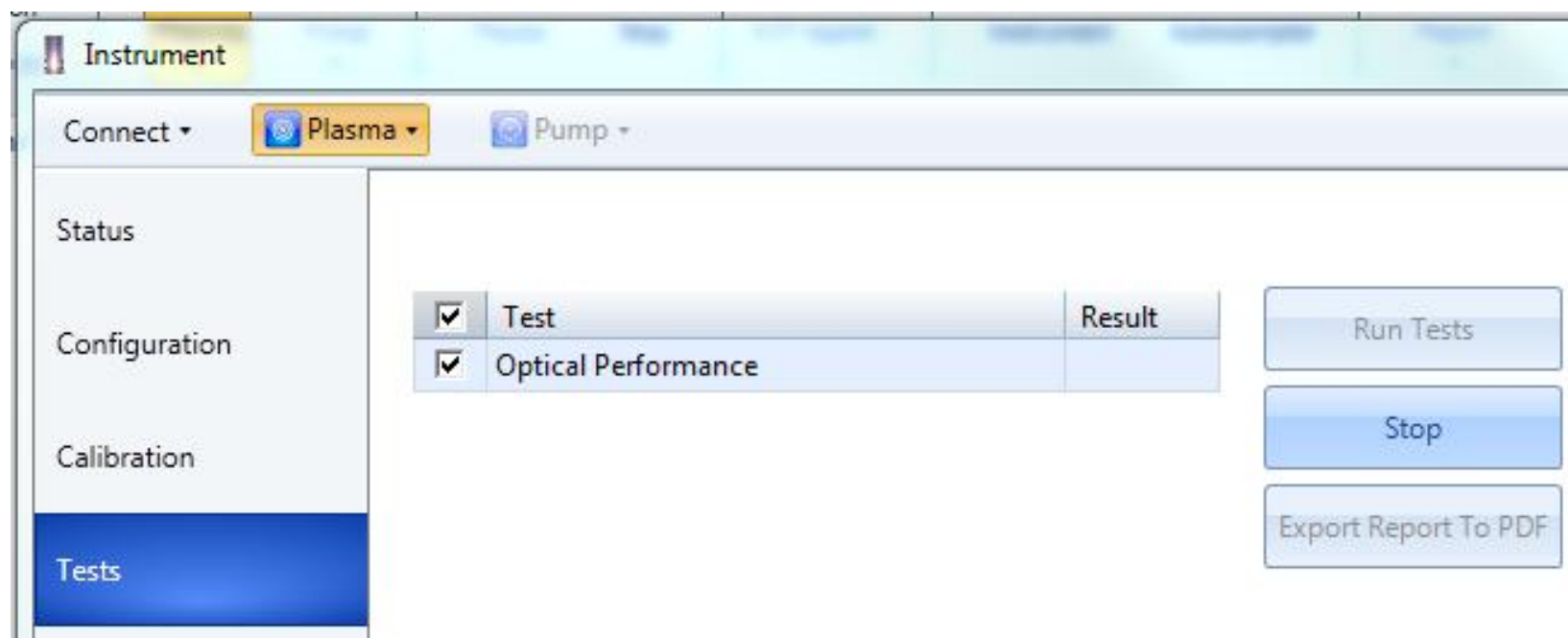
# Complete Workflow Solution; 5100 ICP-OES



# Workflow Solutions; Method Applets

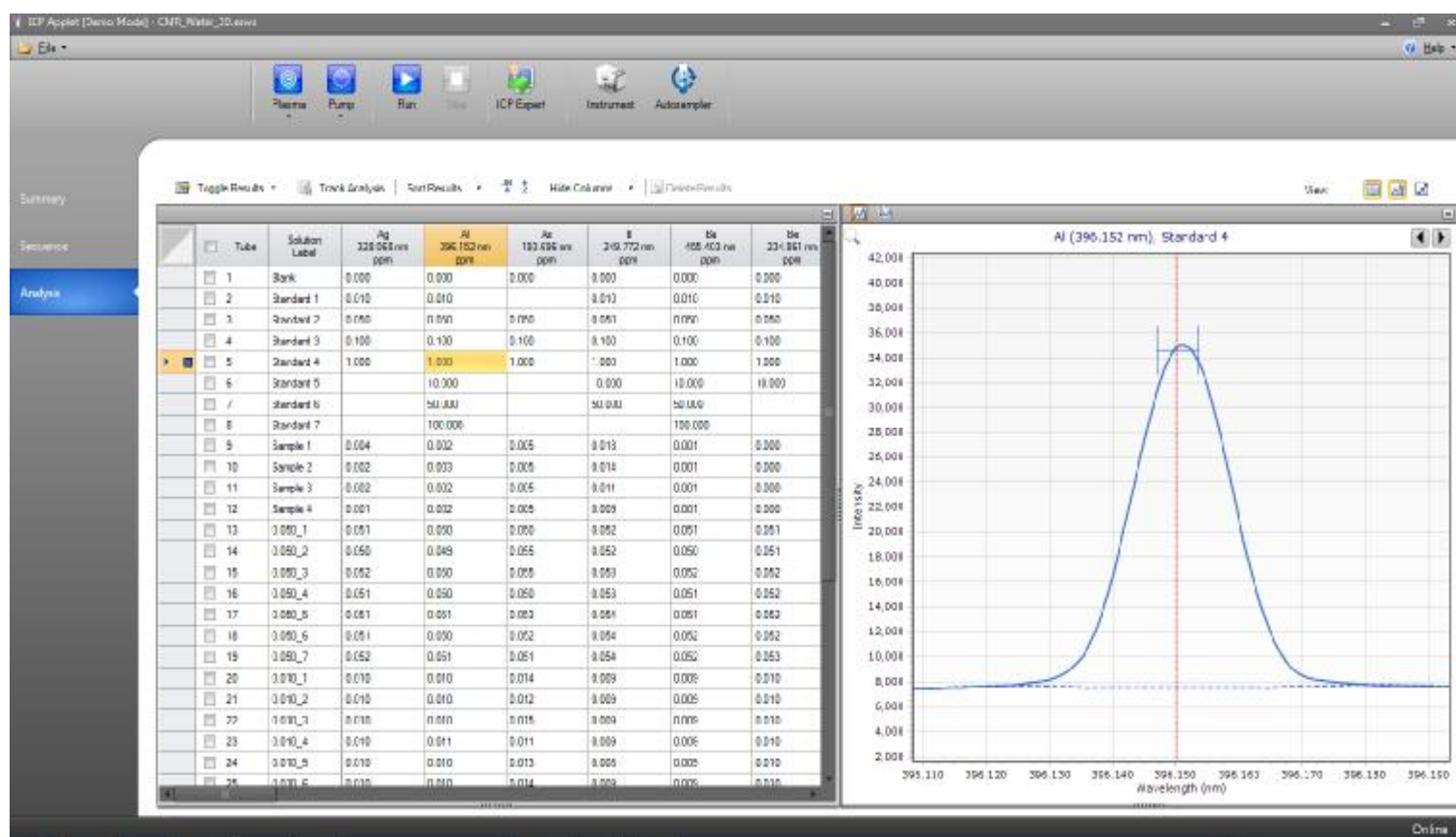


# Workflow Solutions; Method Automation





# Workflow Solutions; Sample Analysis / Data Correction



# Agilent Atomic Spectrometry Portfolio



AA

Atomic Absorption  
Spectroscopy



MP-AES

Microwave Plasma-Atomic  
Emission Spectroscopy



ICP-OES

Inductively Coupled Plasma-  
Optical Emission Spectroscopy



ICP-MS

Inductively Coupled Plasma-  
Mass-Spectrometry



ICP-QQQ

Triple Quadrupole ICP-MS



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# The Future of Pharmacopeia Testing For Metal Impurities

Agilent Atomic Products are the new Gold Standard for metals testing in pharmaceutical materials.

With the Agilent 7900 ICP-MS and 5100 ICP-OES, labs will be ready for USP<232>/<233> Methods which are replacing USP<231>



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# Thank You!

