ICP-MS for ICH and USP<232>/<233>

Elemental impurity in pharmaceuticals

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Agilent
Trusted Answers

Pharmaceutical Impurities

What are Pharmaceutical Impurities?

Unwanted chemicals that remain with active pharmaceutical ingredients (API) or drug product formulations.

Sources of Impurities

Starting materials, intermediates, reagents, solvents, catalysts, and reaction by-products.

Why do they need to be analyzed/controlled?

The amount of various impurities found in drug substances will determine the ultimate **safety** of the final pharmaceutical product.

Existing Elemental Impurities Test

USP <231>

- USP <231> is a test for “heavy metals”
- Test indicates the total content of metal impurities using a colored sulfide precipitate
  - Over 100 years old (circa 1905)
  - Compared to 0.001% (10 ppm) Lead standar
  - Sample ignition and ashing at 600 °C
  - Addition of H2S
  - Visual (subjective) comparison of color of metal sulfide precipitates

Trigger for Development of a New Method:

USP<231> Ashing Step Leads to Loss of Volatiles

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, Sn and Sb).

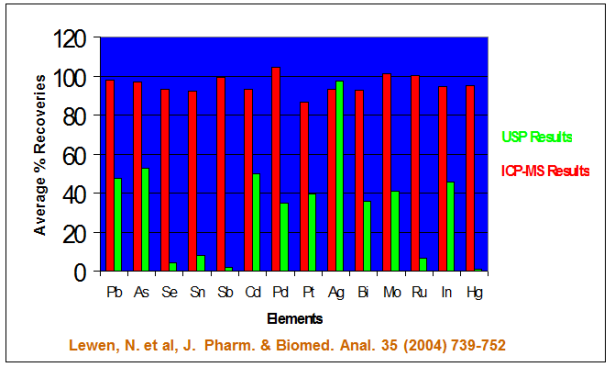
Table 1. Effects on Test Samples of Heating/Temperature on Volatilization of Heavy Metals Using ICP Detection

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]

Alternative (ICP) Sample Prep Preserves Volatiles

Issue of low recoveries is eliminated when ICP (closed-vessel acid digestion) sample prep is used



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Overview of USP

Heavy Metals Chapters (current and proposed)

Heavy Metals Limit Test

<231>

100 year old colorimetric method for total “Heavy Metals”

Is being replaced with

<232>	**<233>**	**<2232>**
Elemental Impurities (Limits)	Elemental Impurities (Procedures)	Elemental Impurities in Dietary Supplements

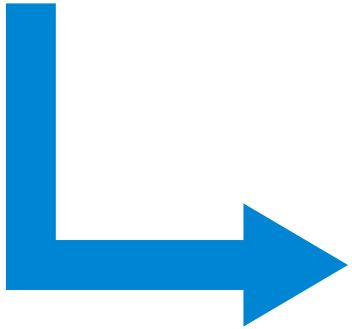
Terminology changing:

“**Heavy Metals**” → “**Elemental Impurities**”

Elemental Impurities – Latest Method Updates

February 2017 – final harmonization between USP & ICH

Elements, concentrations, route of administration, risk assessment



Instrumental analytical methods

AA, ICP-OES & ICP-MS

Validation criteria

ICH Q2 (R1) & USP<1225>

January 1, 2018 – **Pharma companies must comply with Elemental Impurities Analysis**

Harmonized PDE Levels – Same for USP and ICH

Permitted Daily Exposures (PDE)

ICH/USP Class	Element	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalational PDE (µg/day)
Class 1	Cd - Cadmium	5	2	2
	Pb - Lead	5	5	5
	As - Arsenic (inorganic)	15	15	2
	Hg - Mercury (inorganic)	30	3	1
Class 2A	Co - Cobalt	50	5	3
	V - Vanadium	100	10	1
	Ni - Nickel	200	20	5
Class 2B	Tl - Thallium	8	8	8
	Au - Gold	100	100	1
	Pd - Palladium	100	10	1
	Ir - Iridium	100	10	1
	Os - Osmium	100	10	1
	Rh - Rhodium	100	10	1
	Ru - Ruthenium	100	10	1
	Se - Selenium	150	80	130
	Ag - Silver	150	10	7
	Pt - Platinum	100	10	1
Class 3	Li - Lithium	550	250	25
	Sb - Antimony	1200	90	20
	Ba - Barium	1400	700	300
	Mo - Molybdenum	3000	1500	10
	Cu - Copper	3000	300	30
	Sn - Tin	6000	600	60
	Cr - Chromium	11000	1100	3

- PDE: Permissible Daily Exposure. Defined in the USP <232> for each element.
- Different values are defined depending on pathways to take the drug.

  Oral, Parenteral, and Inhalational
- Unit: µg / day

Drugs intended for **inhalational** or **parental (injectable)** administration have **much lower limits** that drugs taken orally.

What Improvements Will USP<232>/ICH Q3D Offer

New list of analytes and much lower limits

- List of elements that are controlled in drug products is based on **patient safety**, not method capability
- Limits based on **toxicological risk**
- Limits are modified depending on intended **route of administration**

Sample Preparation methods ensure no loss of volatiles

- Recommended sample digestion procedures include **closed-vessel microwave digestion**

Quantitative and specific analytical methods

- Recommended analytical (instrumental) procedures are **ICP-OES and ICP-MS**
- Quantitative analysis of individual analytes
  - Subjective, colorimetric test that gives a result for total metals will no longer be acceptable

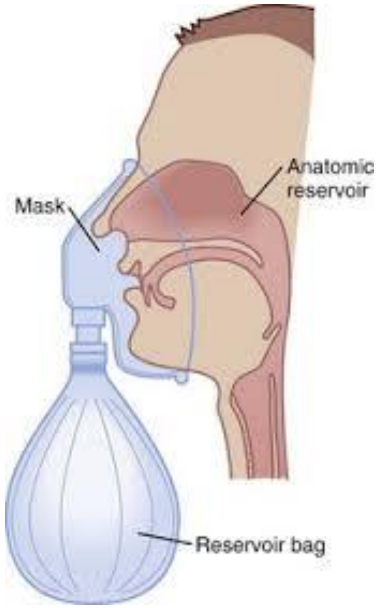
Elemental Impurities - Procedure

- Characterize your Material
- Which Impurities Do *You* Need to Analyze?
- Determine ‘J’
- Sample/Standard Preparation
- Instrumental Technique to be Used
  - ICP-MS
  - ICP-OES
- Validation Procedure
  - Limit Test
  - Quantitative Test

Procedure for USP/ICH Analysis

Characterizing your material

- **Drug product**
  - Oral
  - Parenteral
  - Inhalational



- **Drug components**
  - API
  - Excipient
  - Raw material
  - …

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  - ICP-OES
- Validation Procedure
  - Limit Test
  - Quantitative Test

Procedure for USP/ICH Analysis

Determining Which Impurities to Analyze

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Procedure for USP/ICH Analysis

Determining Which Impurities to Analyze

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			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Class 1 & 2A must be analyzed for Oral, Parenteral and Inhalational Materials

Procedure for USP/ICH Analysis

Determining Which Impurities to Analyze

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Li, Sb and Cu must be analyzed for parenteral materials

Procedure for USP/ICH Analysis

Determining Which Impurities to Analyze

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Class 3 elements must be analyzed for inhalational materials

Procedure for USP/ICH Analysis

Confirm PDE Limits for Your Material

Element	Class	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

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)
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

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- Characterize your Material
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  - ICP-MS
  - ICP-OES
- Validation Procedure
  - Limit Test
  - Quantitative Test

Procedure for USP/ICH Analysis

J Value Calculations

- USP 233 uses the J value as an important Figure of Merit;

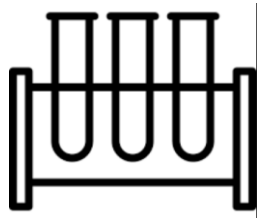
$$J = \frac{PDE}{Maximum\ Daily\ Dose\ x\ Dilution\ Factor}$$

ORAL DOSAGE ROUTE

Element	Conc. µg/day
Cd	5
Pb	5
As	15
Hg	30
Co	50
V	100
Ni	200

MAXIMUM DAILY DOSE

SAMPLE PREPARATION



Permitted Daily Exposures (PDE) and J Value

Example

- A drug package insert

- Soluble non-ionic iron preparation -

Ferromia® Tablets 50mg

2. Product description

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
FERROMIA Tablets 50 mg	Film-coated tablets	S 301			White
	S301	Diameter (mm) 10.3	Weight (mg) 550	Thickness (mm) 5.0	

DOSAGE AND ADMINISTRATION

FERROMIA Tablets 50 mg:

The usual adult dosage for oral use is 100-200 mg as elemental iron (2-4 tablets) daily in one or two divided doses after meals.

The dosage may be adjusted depending on the patient's age and symptoms.

- Sample preparation: Assume, 1 tablet is digested and diluted to 100ml.
  - Way of intake: Oral
  - Max. Daily Dose: 4 tablets x 0.55g = 2.2 g
  - Total Dilution : 100g / (0.55g x 1 tablet) = 181.8

$$J = \frac{PDE}{Total\ Dil. \times Max.\ Daily\ Dose}$$

Element	A: Oral Daily Dose PDE (µg/day)	B. Total Dil	C. Max. Daily Dose (g)	J (µg/g, ppm)
Cd	5	181.8	2.2	0.0125
Pb	5	181.8	2.2	0.0125
Inorganic As	15	181.8	2.2	0.0375
Inorganic Hg	30	181.8	2.2	0.0750
Ir,Os,Pd,Pt,Rh,Ru	100	181.8	2.2	0.250
Cr	11000	181.8	2.2	7.50
Mo	3000	181.8	2.2	7.50
Ni	200	181.8	2.2	0.500
V	100	181.8	2.2	0.250
Cu	3000	181.8	2.2	7.50

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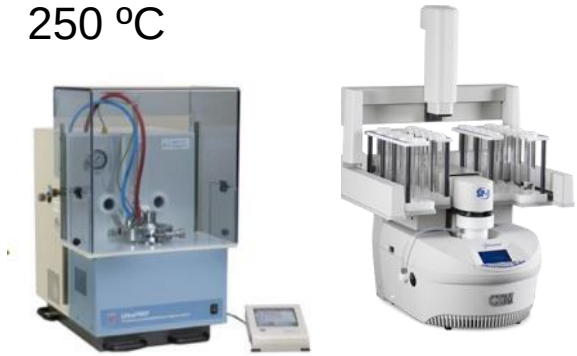
Procedure for USP/ICH Analysis

Sample Preparation Procedures

Options

Neat	Aqueous	Organic	Digestion
Sample ready for analysis as is, undiluted	Dilution/ solubilization in an acidic solvent	Dilution/ solubilization in an organic solvent	MW digestion Glass/quartz/PFA 4:1 HNO_3:HCl 250 ºC



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Which instrument is the best for USP<232>,<233>

Choosing ICP-MS or ICP-OES

Decision will typically come down to DL

ICP-OES

- Mainly oral dose medicines – PDE limits are higher
- Large sample volume available (e.g. bulk excipients); no dilution

ICP-MS

- All dosage forms: Parenteral, inhalational, or oral administration
- Small sample amounts available (e.g. APIs); large dilution needed
- Speciation for As/Hg

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Validation Procedure

Limit Test

- System suitability must be evaluated prior to any sample analysis (at “J”, accounting for dilution)
- **Limit of Detection**
  - Standard Solution - SRM for the target elements at the target concentration (“J”) for each
  - Spike 1 - Actual sample spiked with SRM at the target concentration (“J”)
  - Spike 2 - Actual sample spiked with SRM at 80% of J
  - Acceptance:
    - ✓ Average of triplicate measurements of Spike 1 is within +/- 15% of triplicate measurements of Standard Solution.
    - ✓ Spike 2 solution < Standard solution
- **Precision**
  - Six (N=6) samples of material under test spiked with SRM for the target analytes
  - Acceptance: Relative standard deviation (%RSD) – 20% 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, including other Target Elements and matrix components.

Validation Procedure

Quantitative Test

- **Accuracy**
  - Standard Solution - 3 replicate SRM solutions containing 50%-150% J of the target analytes
  - Test Samples - 3 replicate samples under test spiked with SRM at 50%-150% J
  - Acceptance - 70%-150% spike recovery at each concentration
- **Precision**
  - Test Samples - Six samples spiked with target analytes at J
  - Acceptance - Standard deviation, 20 %RSD
- **Intermediate precision**
  - Repeatability Test - Repeat analysis (choose one of the following)
    - On a different day
    - With a different instrument
    - With a different analyst
  - Acceptance – 25 %RSD for each target analyte
- **Specificity**
  - False-positive and false-negative check (interference check)

Agilent ICP-MS Family

An optimized solution for any ICP-MS application

7850	7900	8900 ICP-QQQ

More typical applications → More demanding or unusual applications

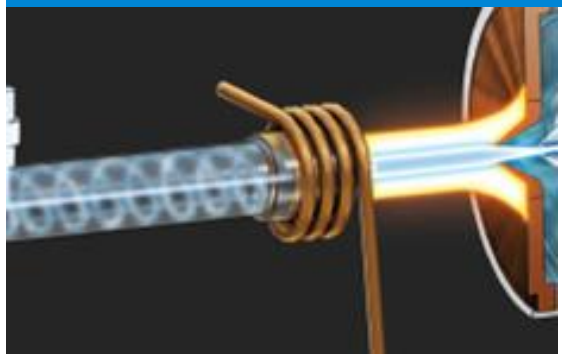
Agilent's ICP-MS

Keys to high quality unequivocal data

Handle varied, challenging samples

Simplify preparation and measurement of a wide range of different sample types

Robust Plasma



Superior sensitivity across all masses

Consistently achieve the required DLs for all critical, regulated trace analytes

Confidence in results

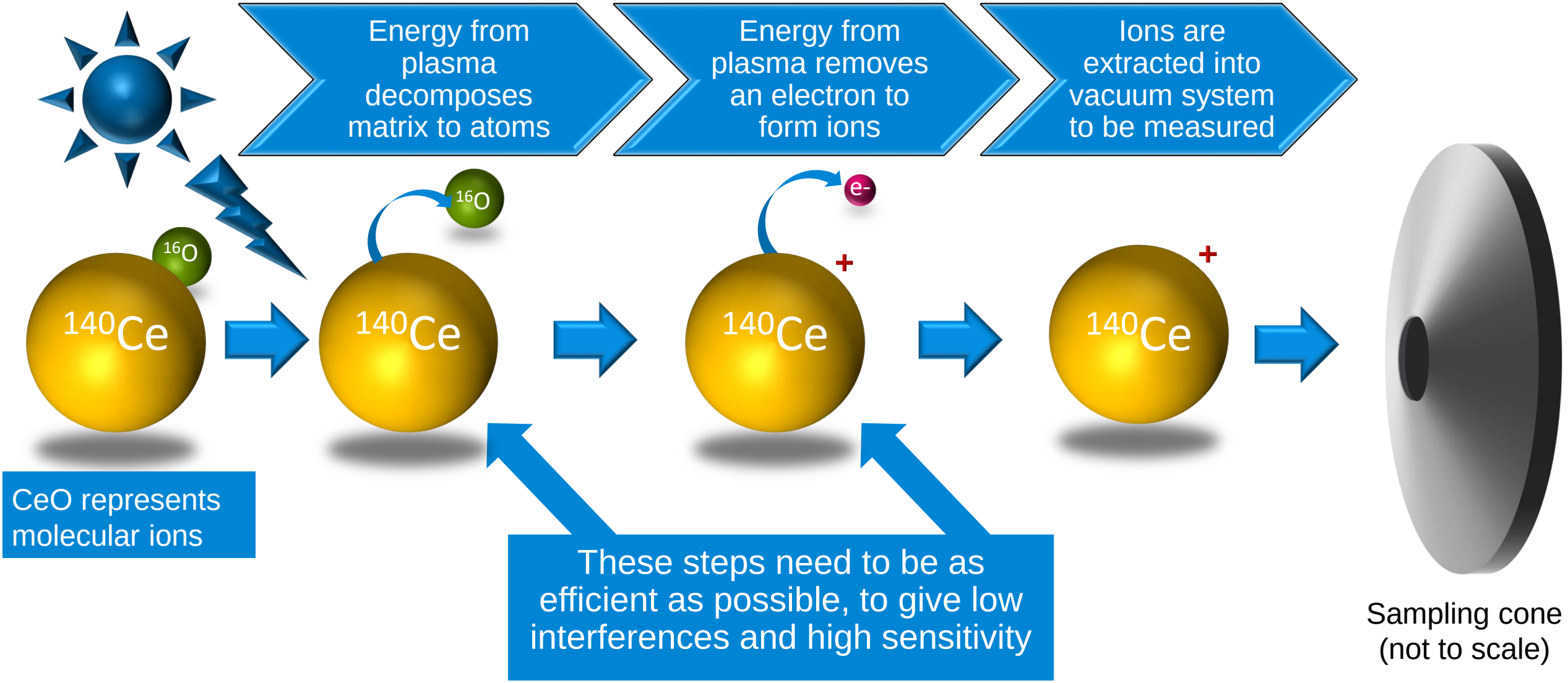
Provide reliable, accurate, verifiable results the first time every time

Required analytical range

Measure majors and traces in a single analytical run

Robust ICP-MS Plasma

CeO^+ to Ce^+ Ratio (Oxide Ratio) is Critical Parameter for ICP-MS



Robust ICP-MS Plasma

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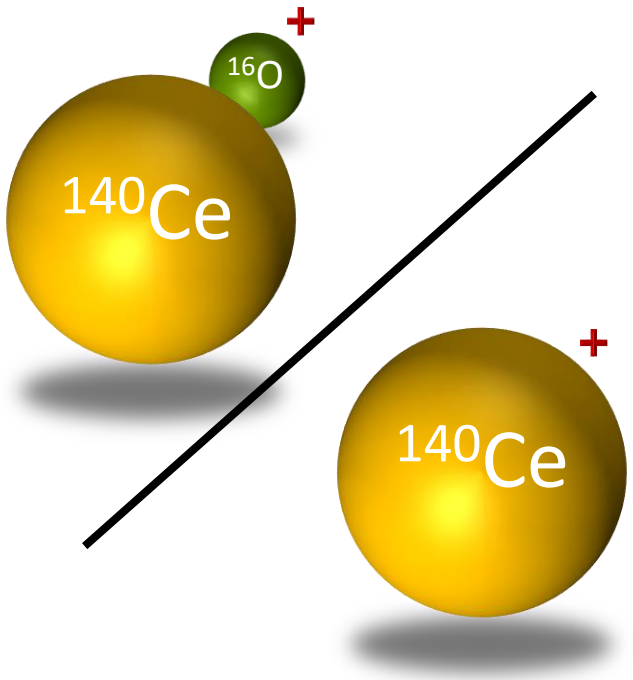
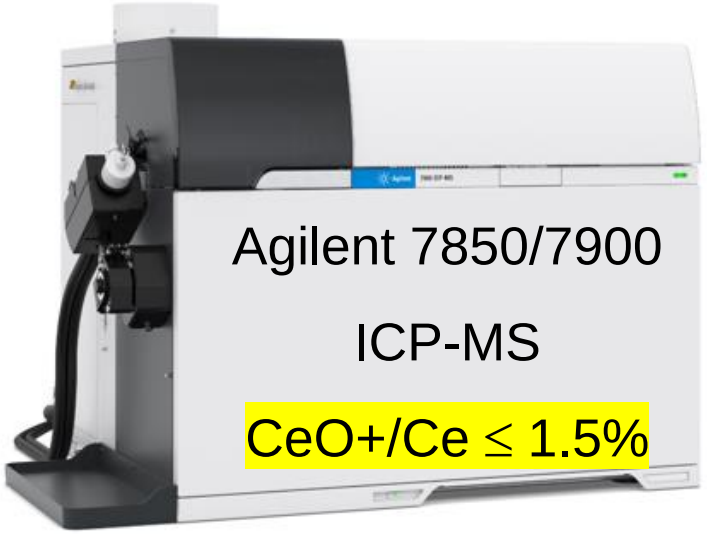


$$= \quad CeO^+/Ce^+$$

Mass 156/140

Plasma
robustness ratio



Low CeO/Ce ratio indicates
robust plasma = better matrix tolerance

Agilent's ICP-MS

Keys to high quality unequivocal data

Handle varied, challenging samples

Simplify preparation and measurement of a wide range of different sample types

Superior sensitivity across all masses

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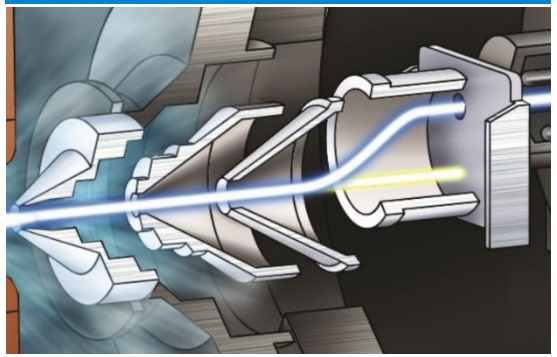
High Ion Transmission



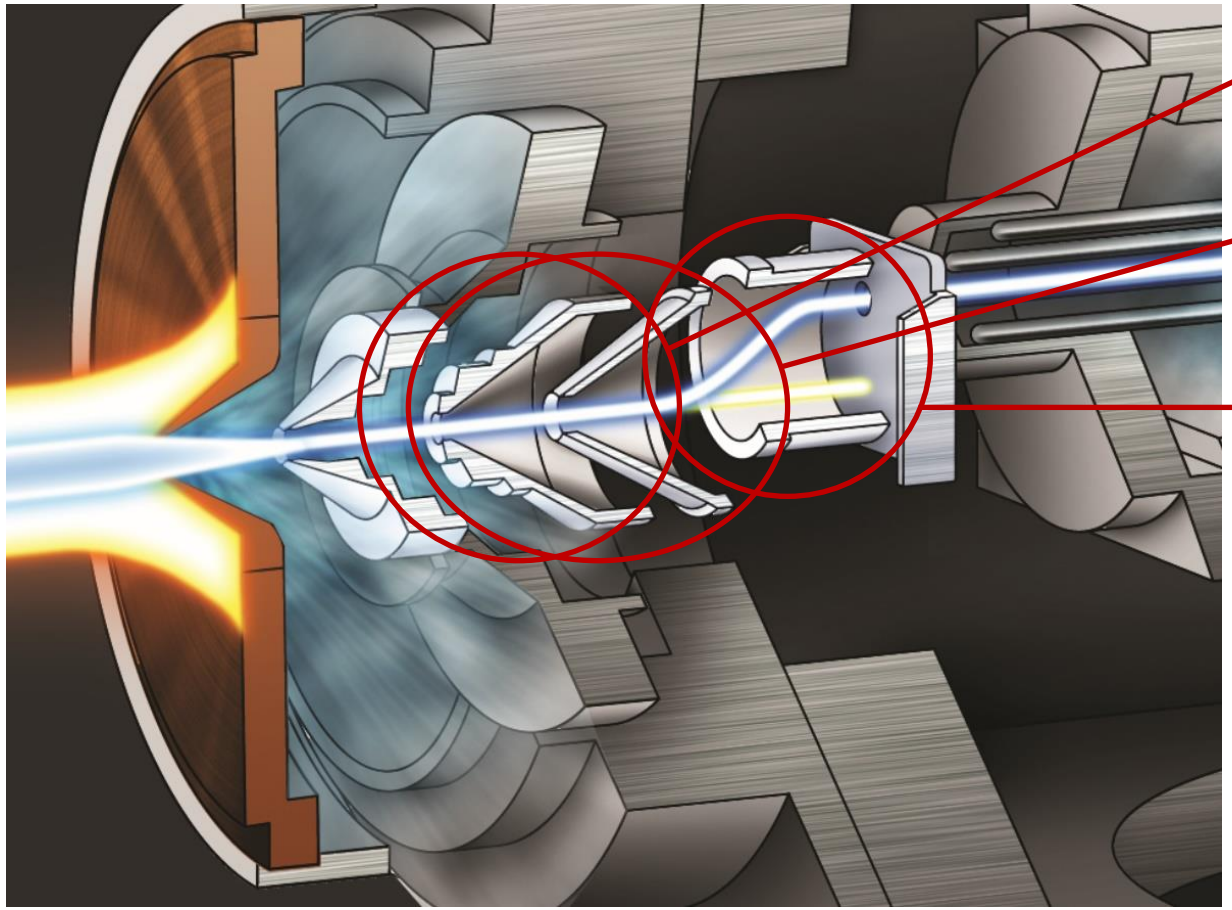
Confidence in results

Provide reliable, accurate, verifiable results the first time every time

Required analytical range

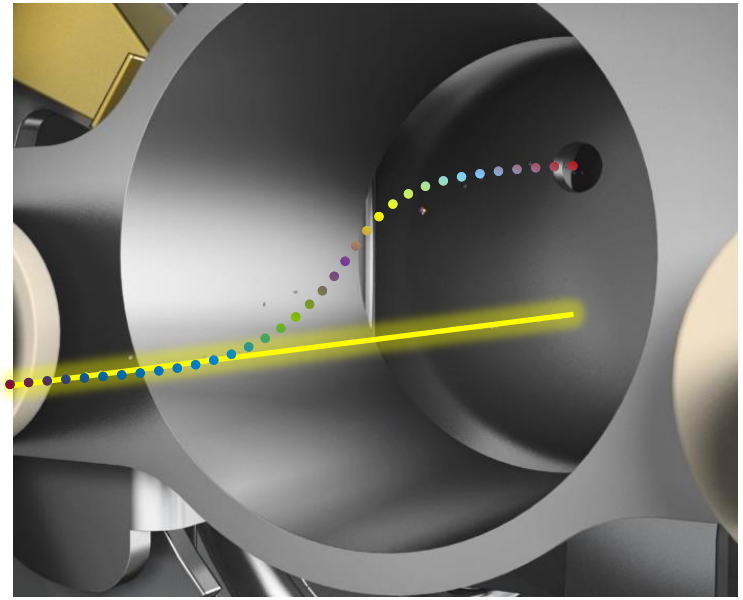
Measure majors and traces in a single analytical run

Key to Superior Sensitivity For All Masses
Agilent ICP-MS Off-Axis Lens Assembly



1. **Extract** the maximum number of ions from the interface, using low voltage for stability
2. **Focus all masses** efficiently to provide superior sensitivity for all elements
3. **Separate ions** from photons and neutrals

Low voltage deflection minimizes mass bias



The Agilent Off-Axis lens assembly uniquely provides high sensitivity and low background **across all masses**

Analytical Requirements in the Inorganic Laboratory

Keys to high quality unequivocal data

Handle varied, challenging samples

Simplify preparation and measurement of a wide range of different sample types

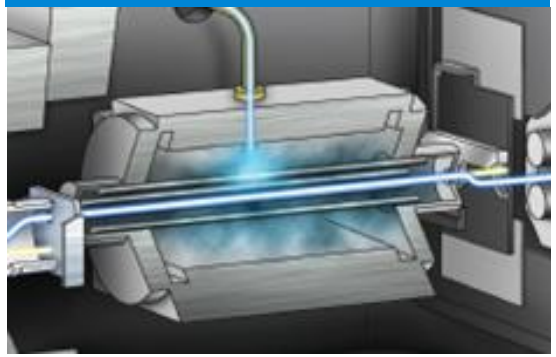
Superior sensitivity across all masses

Consistently achieve the required DLs for all critical, regulated trace analytes

Confidence in results

Provide reliable, accurate, verifiable results the first time every time

Interference Management



Required analytical range

Measure majors and traces in a single analytical run

Challenging for ICP-MS analysis

Polyatomic Interferences

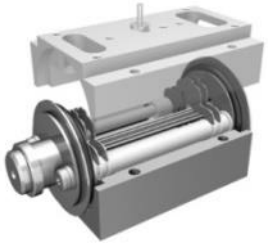
Overlap of a molecular ion on the analyte of interest

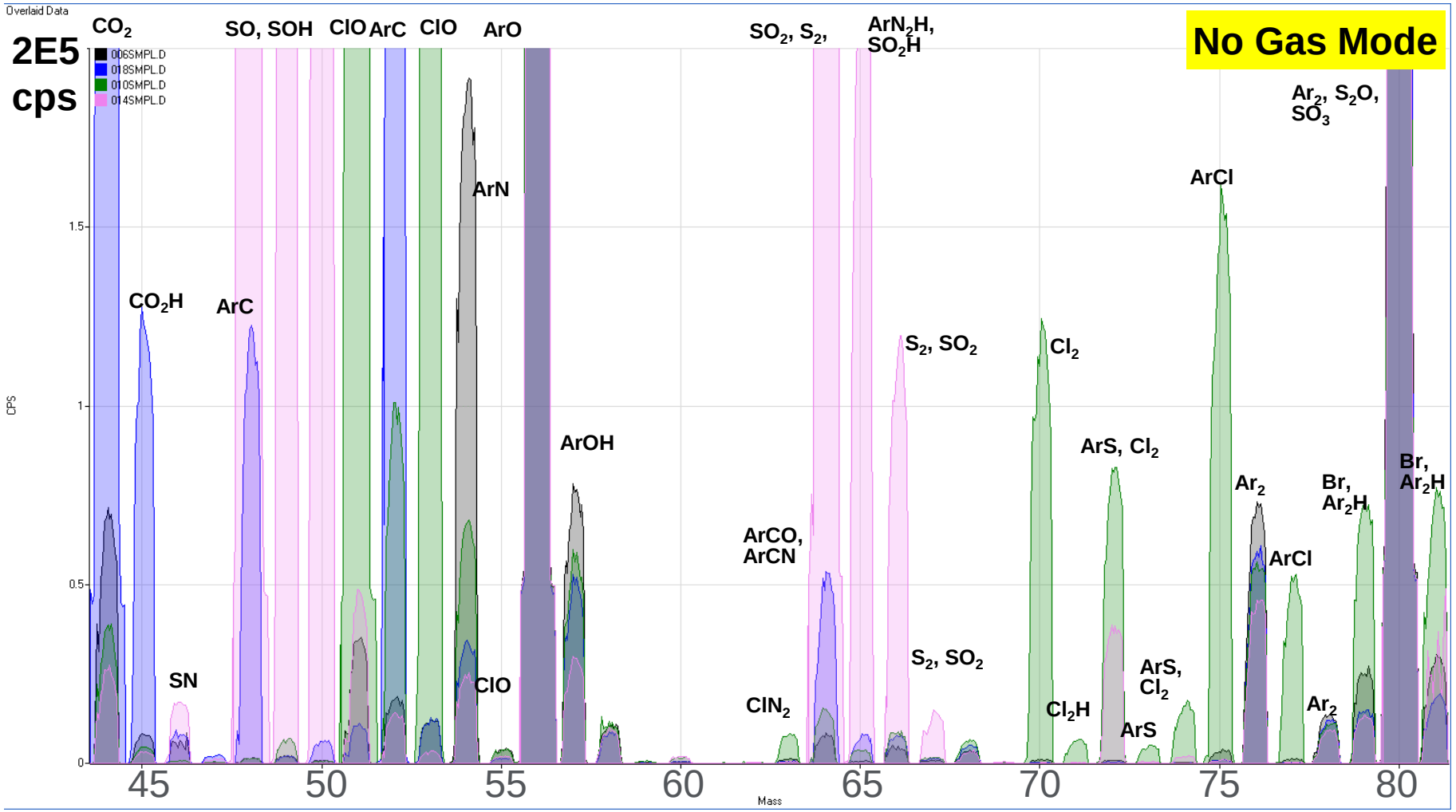
- Polyatomics are nearly always composed of just two elements, e.g. ArO^+, S_2^+
- Some depend on the matrix, others depend on the solvent or water, and others originate from plasma gases

EXAMPLE POLYATOMIC INTERFERENCES			
Mass	Analyte	Likely Cause	Favorable Conditions
28	Si	CO	only high [C] sample
28	Si	N_2	Most aq. amples
39	K	ArH	any sample
40	Ca	Ar	any sample
44	Ca	CO_2	only high [C] sample
44	Ca	SiO	only high [Si] sample
51	V	ClO	only high [Cl] sample
56	Fe	ArO	most aq. Samples
64	Cu	S_2	only high [S] sample
75	As	ArCl	only high [Cl] sample
78	Se	Ar_2	any sample

He Mode For Multiple Analytes in Complex Matrices

ORS separates analyte ions from interfering ions





Background spectra in various matrices:

5% HNO_3

5% HCl

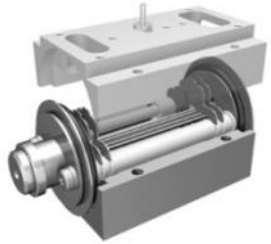
1% IPA

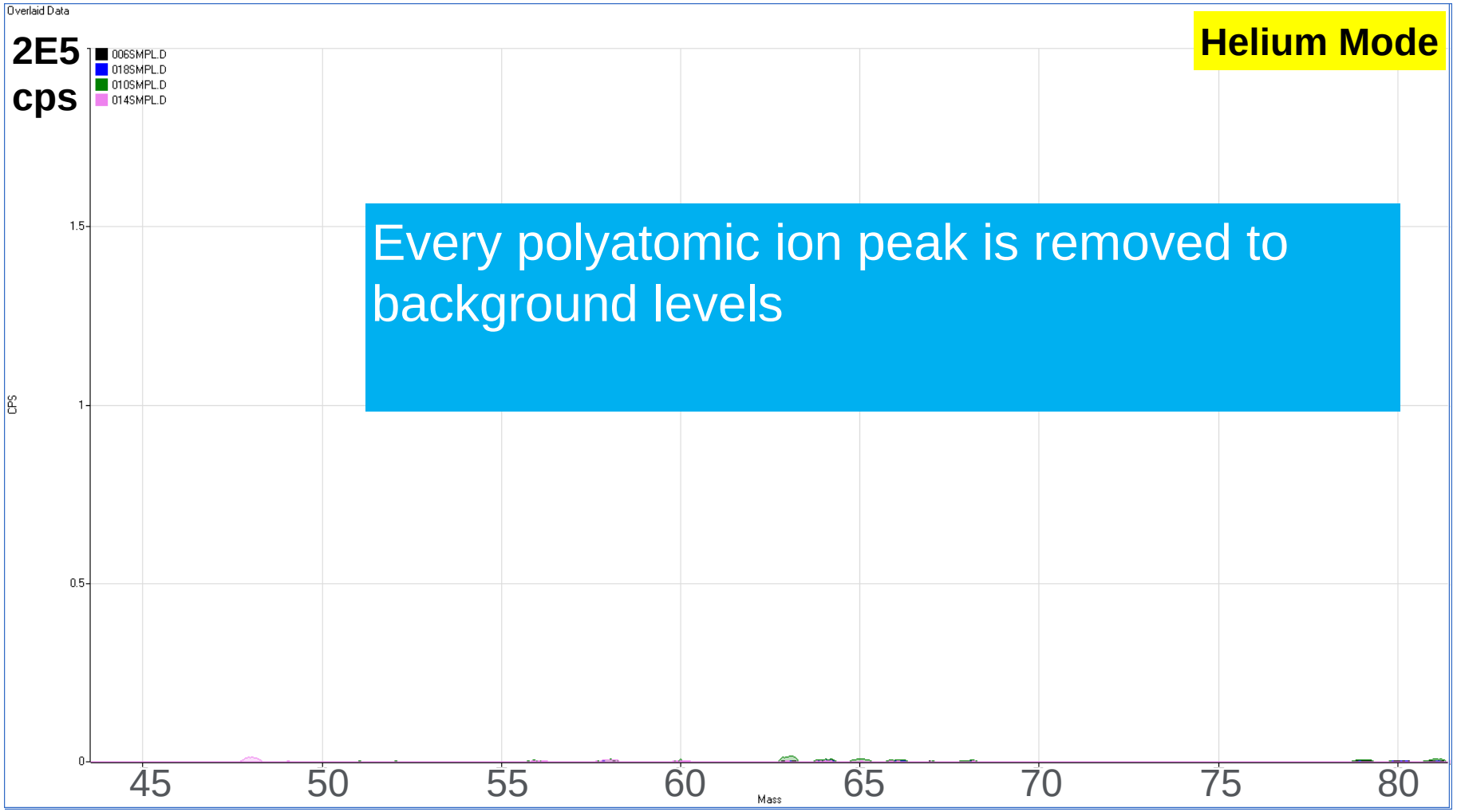
1% H_2SO_4

ALL peaks due to **polyatomic ion** interferences. Overlap all 1st row transition elements

He Cell Mode Removes Common Polyatomic Ions

Main cause of interferences in ICP-MS





Background spectra in same matrices:

5% HNO_3

5% HCl

1% IPA

1% H_2SO_4

ALL **polyatomic ion** interferences filtered out by He cell gas

Analytical Requirements in the Inorganic Laboratory

Keys to high quality unequivocal data

Handle varied, challenging samples

Simplify preparation and measurement of a wide range of different sample types

Superior sensitivity across all masses

Consistently achieve the required DLs for all critical, regulated trace analytes

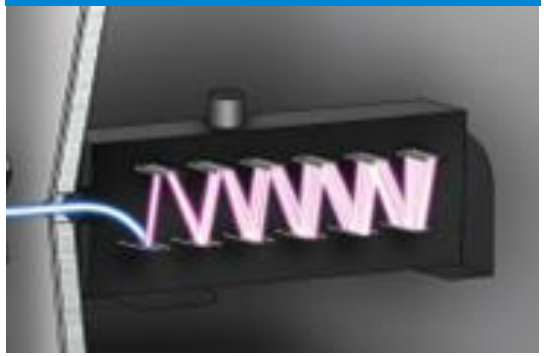
Confidence in results

Provide reliable, accurate, verifiable results the first time every time

Required analytical range

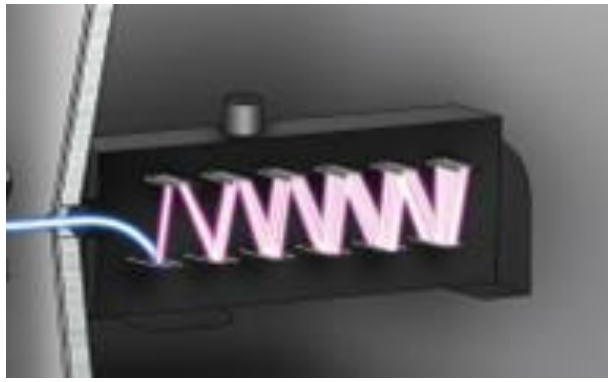
Measure majors and traces in a single analytical run

Wide Dynamic Range



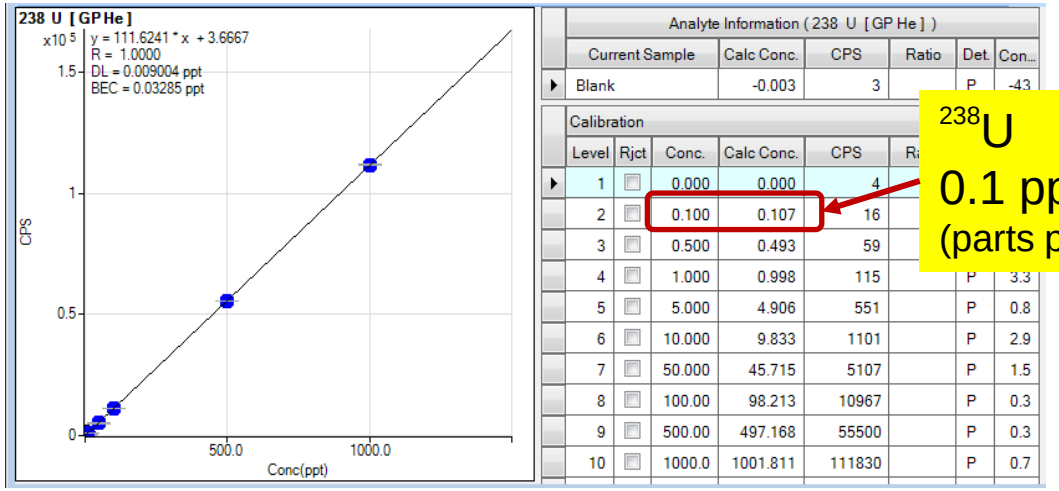
Agilent ICP-MS Detector Linear Range Gives Wide Analytical Range

10-11 orders of dynamic range

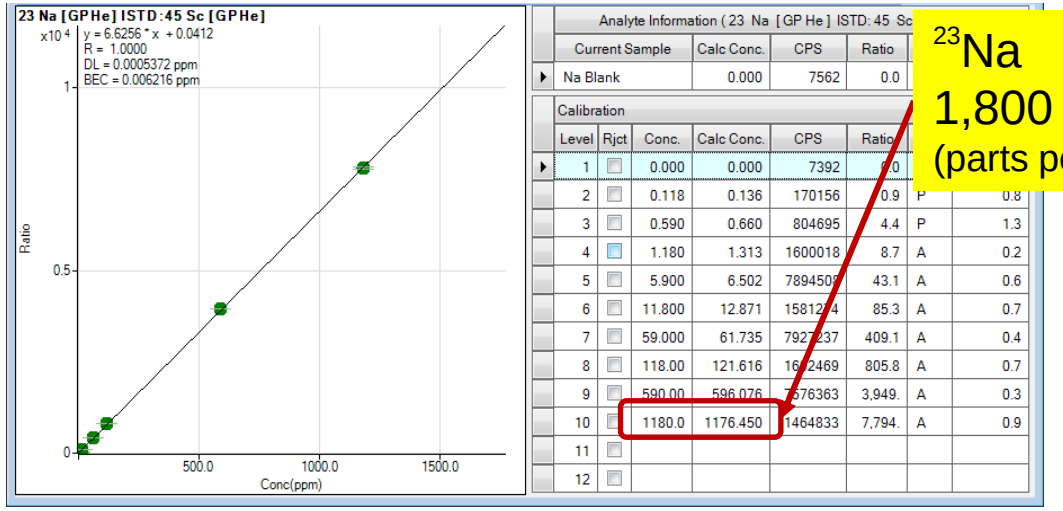


Can detect a trace element like uranium down to 0.1 ppt (0.0000001 ppm) and a major element such as sodium in 1:10 seawater at 1,800 ppm – in the same run!

On size scale, that's the same as being able to accurately measure the length of an ant and the diameter of the earth – on the same instrument!



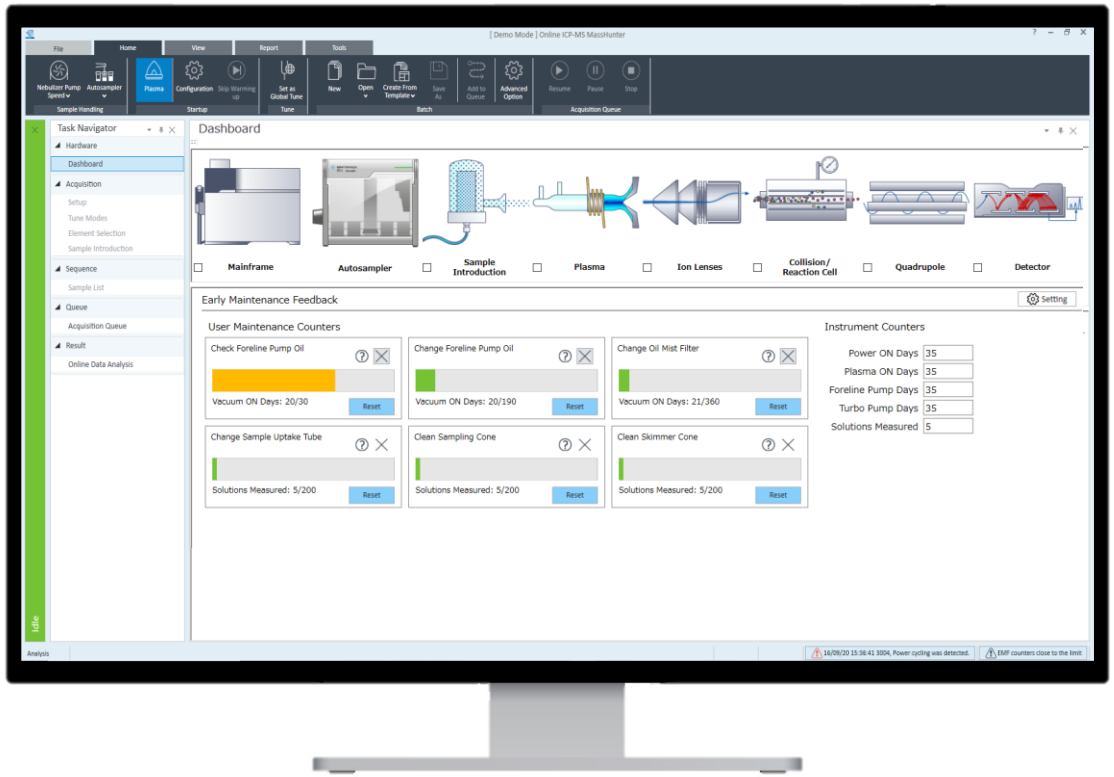
^{238}U
0.1 ppt
(parts per trillion)



^{23}Na
1,800 ppm
(parts per million)

Agilent

Uses Latest Revision of ICP-MS MassHunter

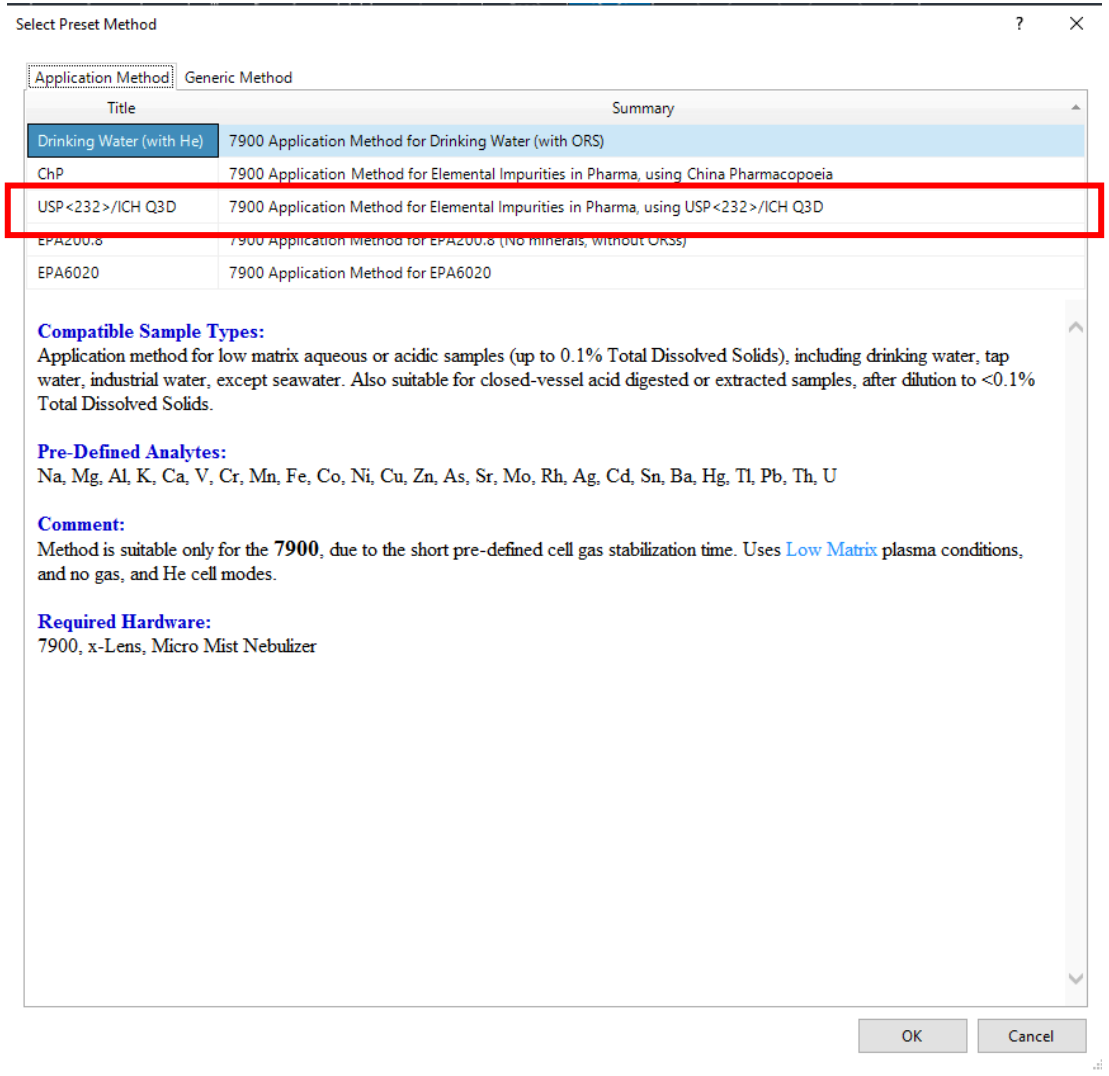


ICP-MS MassHunter 5.1:

- Completely new User Interface and Workflow
- New productivity tools
- New Smart ICP-MS monitors and checks
- Improved ICP Go option
- New, interactive Help & Learning Center

New Method Setup and Ease of Use Tools

Guided method development tools and templates included as standard



- **Preset Methods** for regulated analysis
- **Method Wizard** – guided method development for everything else
- **Predefined report templates** – for many enviro & pharma apps

The method setup tools assist operators regardless of knowledge or experience

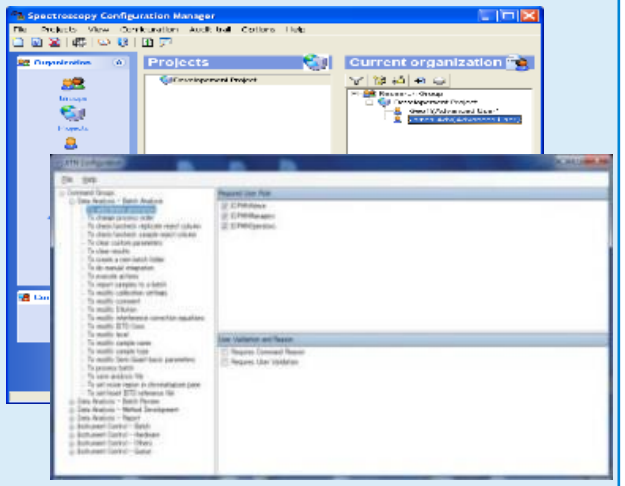
21 CFR Part 11, EU Annex 11

Application software

Control the instrument for data acquisition and processing

MassHunter software

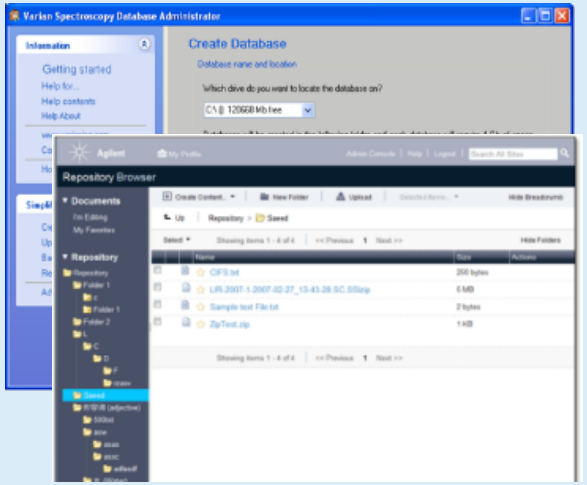
Access Control



Manage groups, projects, users and user profiles

User Access Control (UAC)

Data Management



Administration of databases and data

SDA or OpenLAB

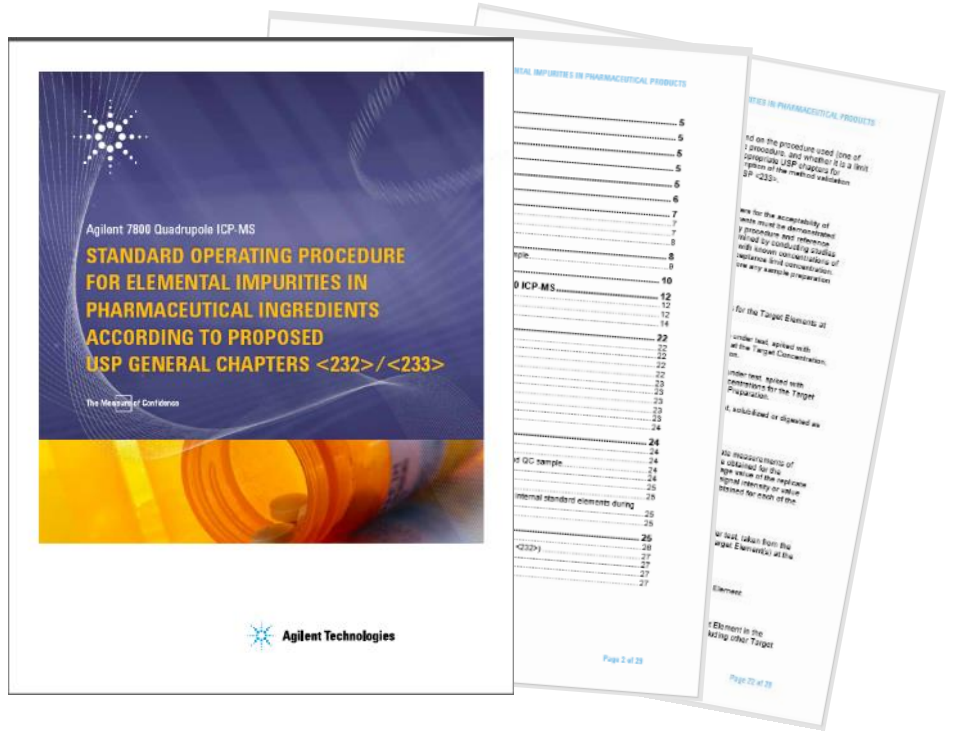
SOP for Pharma Analysis using Agilent ICP-MS

Standard Operating Procedure template for Elemental Impurity analysis is included with the Solution-Ready Agilent ICP-MS

SOP includes:

- Method summary and analyte list
- Sample preparation details
- Calibration and interferences
- Pre-set Method parameters
- Method validation and reports
- Troubleshooting guide

Method template, reports and supporting documentation included.



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Trusted Answers