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HUMAN HEALTH | ENVIRONMENTAL HEALTH

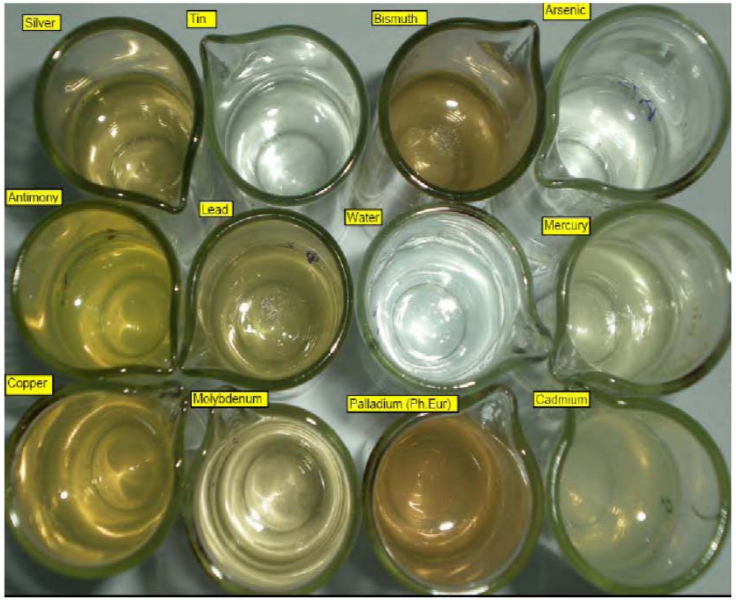
Pharma and ICPMS

Riccardo MAGARINI, Sr. Inorg. Specialist
PerkinElmer (Italia)
riccardo.magarini@perkinelmer.com

Budapest 2016, October 17th

Replacement for USP <231> Heavy Metals

- USP <231> methodology for trace metals is old and has been the subject of recent discussion, stimuli articles and workshop



- USP <232> & <233> became official on Dec 2, 2012 and conformance will be required by Jan. 2018

USP <232> at a glance

- Specifies limits for elemental impurities in drug products
- Include catalysts and environmental contaminants
  - Natural
  - Intentional
  - Inadvertent contamination
- A risk-based control strategy may be appropriate
- Elemental impurity levels present in drug substances and excipients must be known and reported
- At a minimum As, Cd, Pb, and Hg (the USP big four) have to be determined
- Dietary supplements are addressed in <2232>

ICH Elemental Impurities Limits (Currently Proposed)

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ICH Q3D Step 4 Permitted Daily Exposures for Elemental Impurities in Drug Products

Element	USP <232>	Class	Oral Daily Dose PDE[a] (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalational Daily Dose PDE (µg/day)
Cd	Yes	1	5	2	2
Pb	Yes	1	5	5	5
As[b]	Yes	1	15	15	2
Hg[b]	Yes	1	30	3	1
Co	No	2A	50	5	3
V	Yes	2A	100	10	1
Ni	Yes	2A	200	20	5
Tl	No	2B	8	8	8
Au	No	2B	100	100	1
Pd	Yes	2B	100	10	1
Ir	Yes	2B	100	10	1
Os	Yes	2B	100	10	1
Rh	Yes	2B	100	10	1
Ru	Yes	2B	100	10	1
Se	No	2B	150	80	130
Ag	No	2B	150	10	7
Pt	Yes	2B	100	10	1
Li	No	3	550	250	25
Sb	Yes	3	1200	90	20
Ba	No	3	1400	700	300
Mo	Yes	3	3000	1500	10
Cu	Yes	3	3000	300	30
Sn	No	3	6000	600	60
Cr	Yes	3	11000	1100	3

[a]PDE = Permissible daily exposure based on a 50-kg person.

[b]See Speciation section of USP <232>.

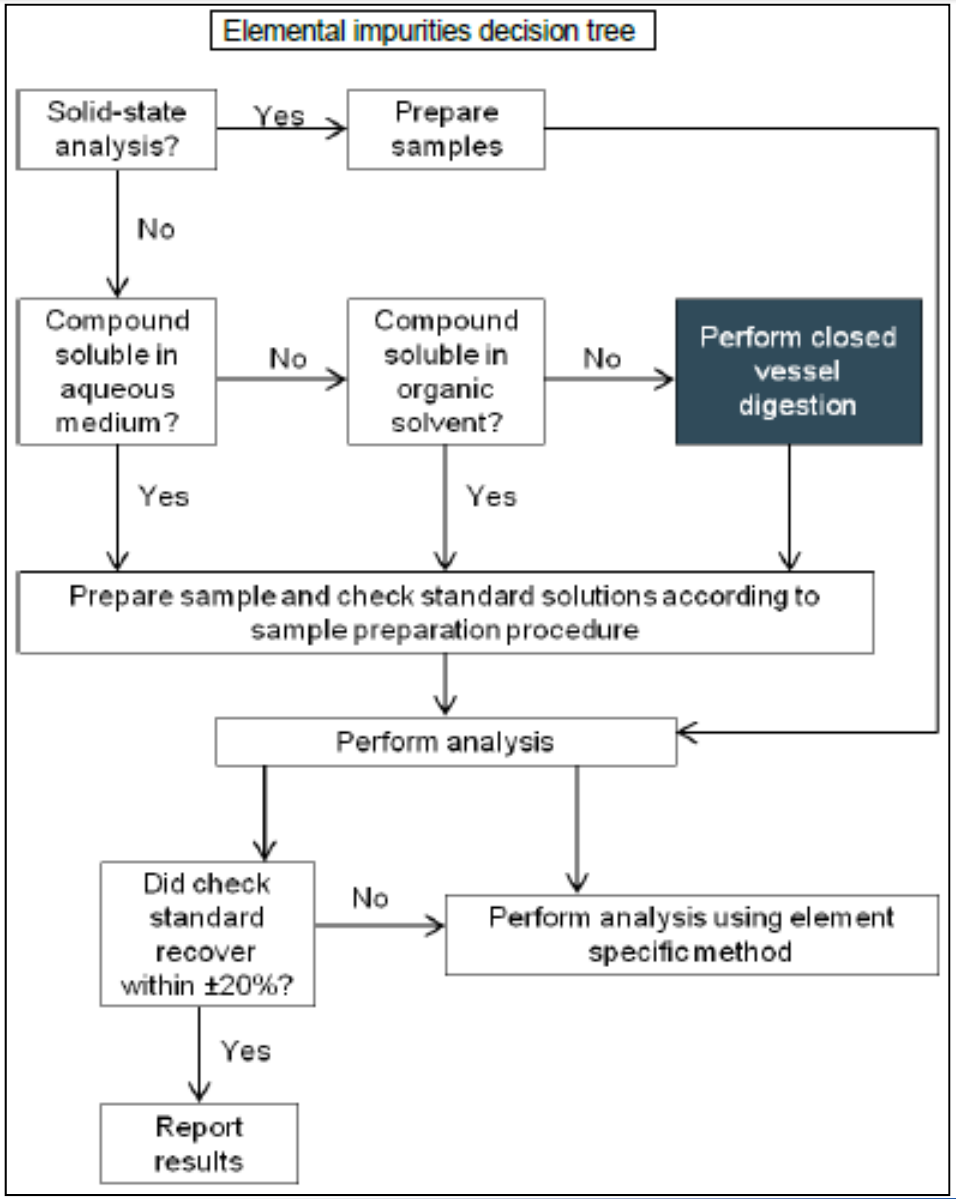
USP <233> Elemental Impurities - Procedures

- Sample preparation suggestions

- Four choices
  - 1) Analyze Neat, undiluted if sample is in suitable form.
  - 2) Dilute in Acidified Aqueous solution if soluble in water.
  - 3) Dilute in an appropriate Organic solvent.
  - 4) Closed vessel digestion for insoluble samples.

<233> Sample Preparation

- Neat
  - suitable for liquids
- Direct aqueous solution
  - sample soluble in aqueous solvent
- Direct organic solution
  - sample soluble in organic solvent
- Indirect solution
  - sample is not soluble neither in aqueous nor in organic solvent, closed-vessel procedure using concentrated acids is recommended



USP <233> and the «J» value

- The «J» value is … “The concentration (w/w) of the element(s) of interest at the *Target Limit* , appropriately diluted to the working range of the instrument”

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

Element	Oral Daily Dose PDE (µg/day)
Cadmium	25

$$J = \frac{25\ ug/day}{\frac{1g}{day}\ x\ \frac{1g}{0.5L}}$$

$$J = 50\ ug/L$$

USP <233> Elemental Impurities - Procedures

- Quantitative Validation Summary

Parameter	Test	Acceptance Criteria
Accuracy	Comparison of spike sample with standards at 0.5 J, 1.0J, 1.5J	80-150% recovery
Precision (Repeatability)	Analysis of 6 individual sample preps spiked at 1.0J	RSD<20% (n=6)
Precision (Intermediate Precision)	Repeatability test performed by: separate analyst, different system, different day (only one required)	RSD<25% (n=12)
Specificity (False Negative)	None	Accuracy and Precision Met
Specificity (False Positive)	Demonstrate lack of response when other elements are present	Not specified
LOQ	None	Accuracy Met

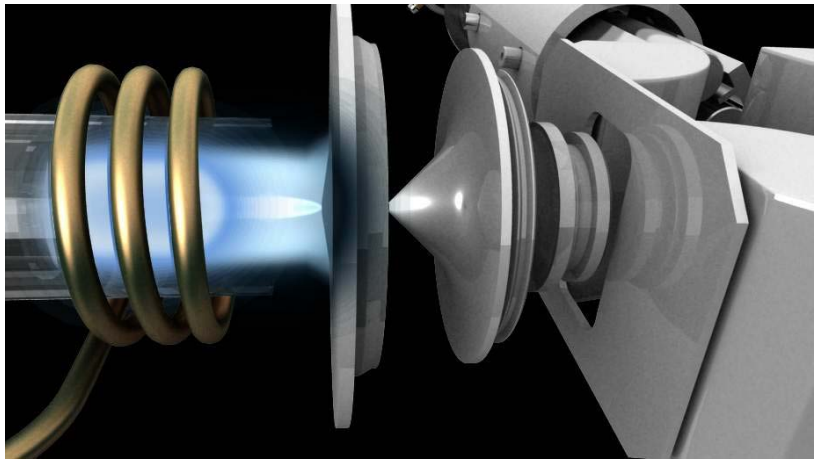
USP Analyses by NexION ICP-MS

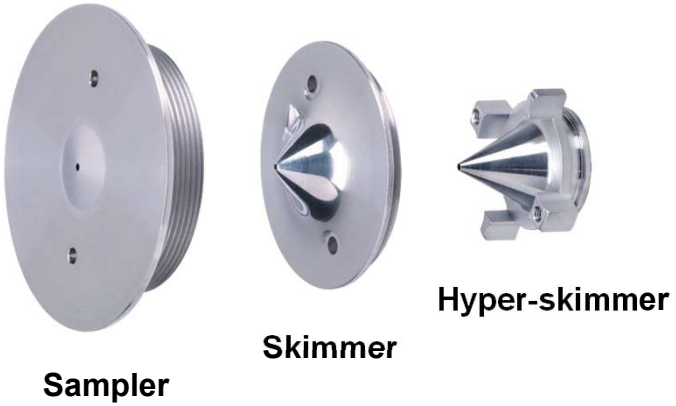
- Ability to determine most of the elements in the periodic table
- Wide dynamic range
  - Part-per-billion to part-per-million
- Can determine As, Cd, Hg and Pb at required levels
- Determine high level elements using Extended Dynamic Range (EDR)
- Requires One Sample Prep and One Method

- 3-Modes of Spectral Interferences Reduction
  - Standard Mode with Correction Equations
  - KED Collision (He) mechanism reduce polyatomics
  - DRC Reaction mechanism based on specific chemistry
- Fully 21 CFR Part 11 compliant IQ /OQ document generation

NexION 350 – A Closer look

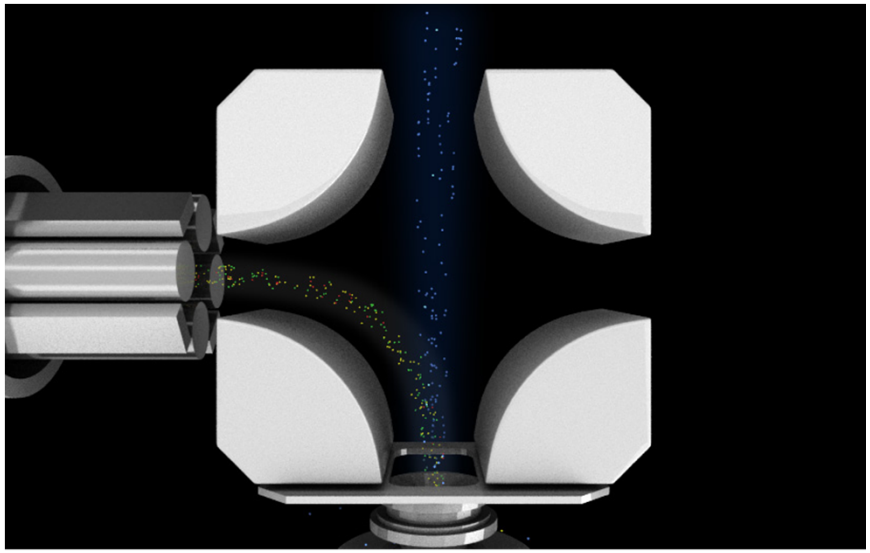
- Matrix Tolerance
  - Three very large aperture cones (1.1, 0.9, 1.0 mm) which means it is very hard to block them by sample deposits.
  - Free running RF generator which means it is the fastest RF generator to compensate for changes in the matrix.





NexION 350 – A Closer look

- Low Maintenance
  - Three very large aperture cones (1.1, 0.9, 1.0 mm) which means it is very hard to block them by sample deposits.
  - Quadrupole Ion deflector means only the ions get into the heart of the instrument



NexION 350 – A Closer look

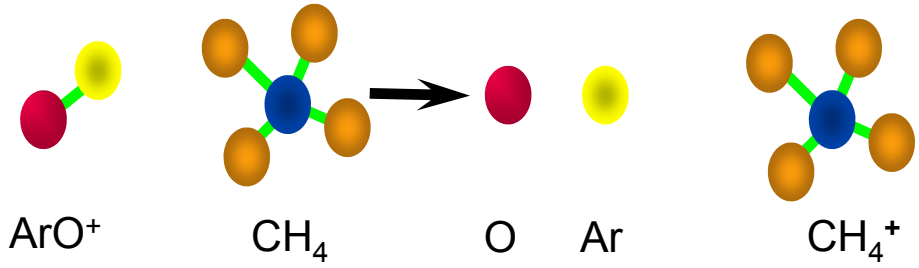
- Low Maintenance

	Cones	Ion Lens	Collision/ Reaction Cell	Main Filtering Quadrupole
Typical ICP-MS	Daily - weekly	3-6 months	6 months	1-3 years
NexION 350	weekly	None	Never	Never

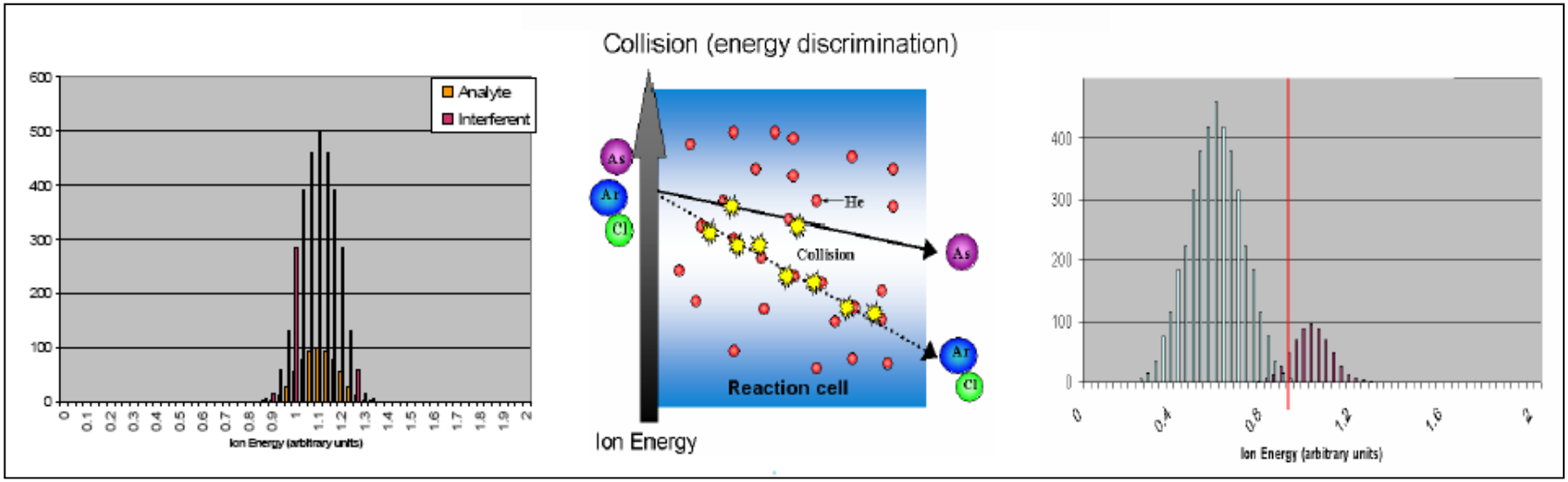
- Elimination of interference
  - Equations for low level interferences
  - **Collision** (KED) mode for medium level interferences
    - Non-complex interferences reduction, or no sensitivity problems
    - Collision gas (He) at 3 to 5 mL/min
  - **Reaction** (DRC) mode for high level interferences or mass overlapping
    - Specific interferences reduction and/or need for sensitivity
    - Reactive gases (O_2, CH_4, NH_3 …) at 0.3 – 1 mL/min

Collisions /Reactions Cells

- Reaction - specific reduction of an interference by chemical reaction.

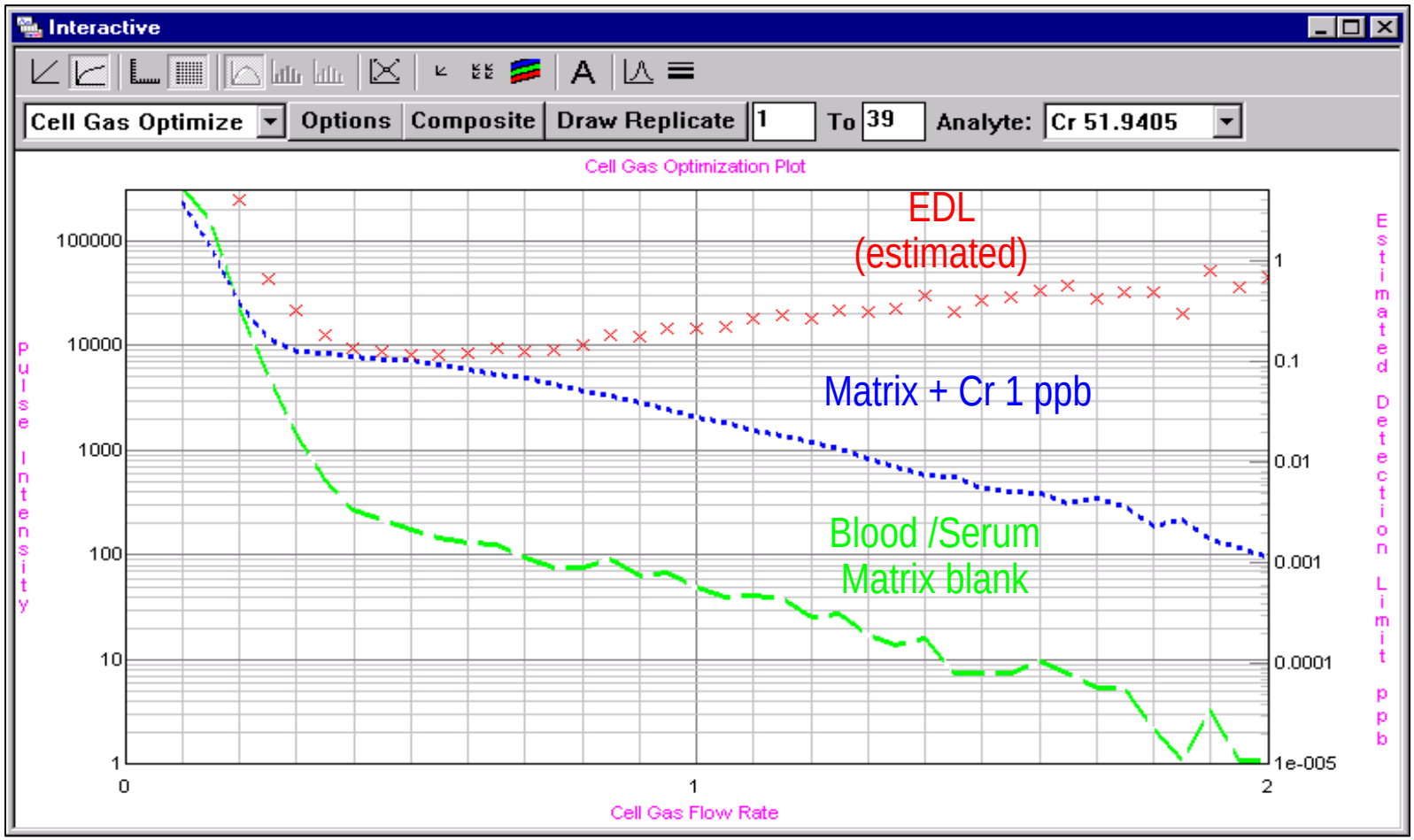


- Collision - reduction of energies of polyatomic ions.



KED and He Gas Flow Optimization

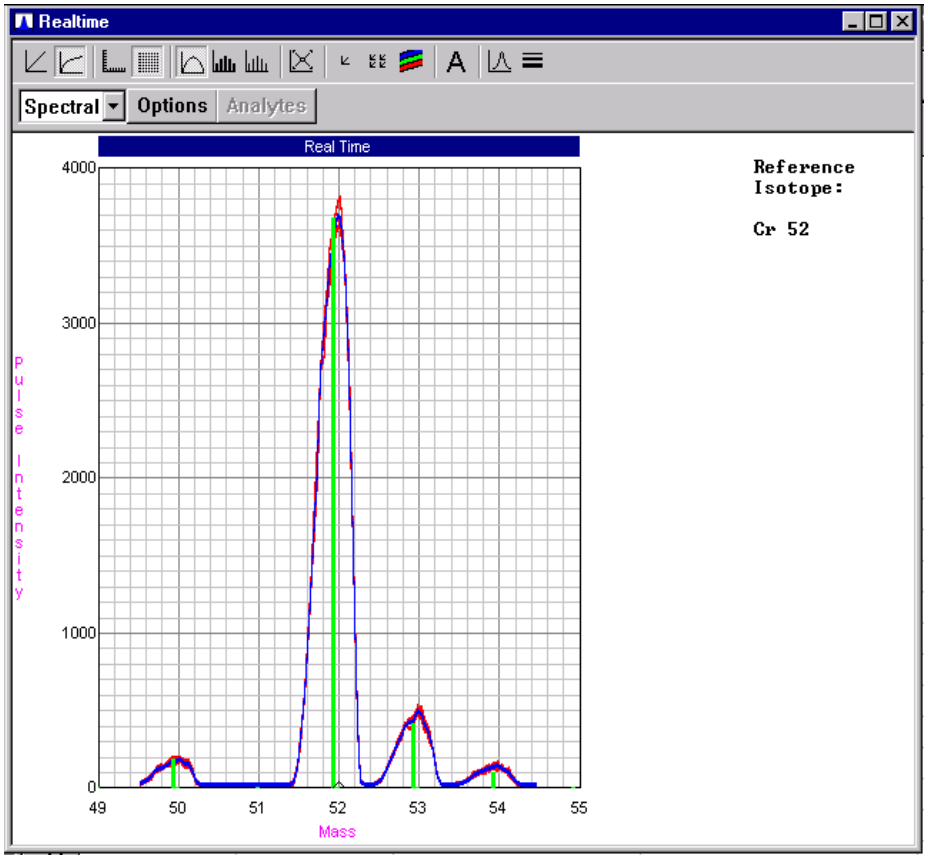
52Cr with NH3 reaction gas (blood /serum matrix)



EDL = Estimated Detection Limit in undiluted blood (1 s. integration, 15x dil.)

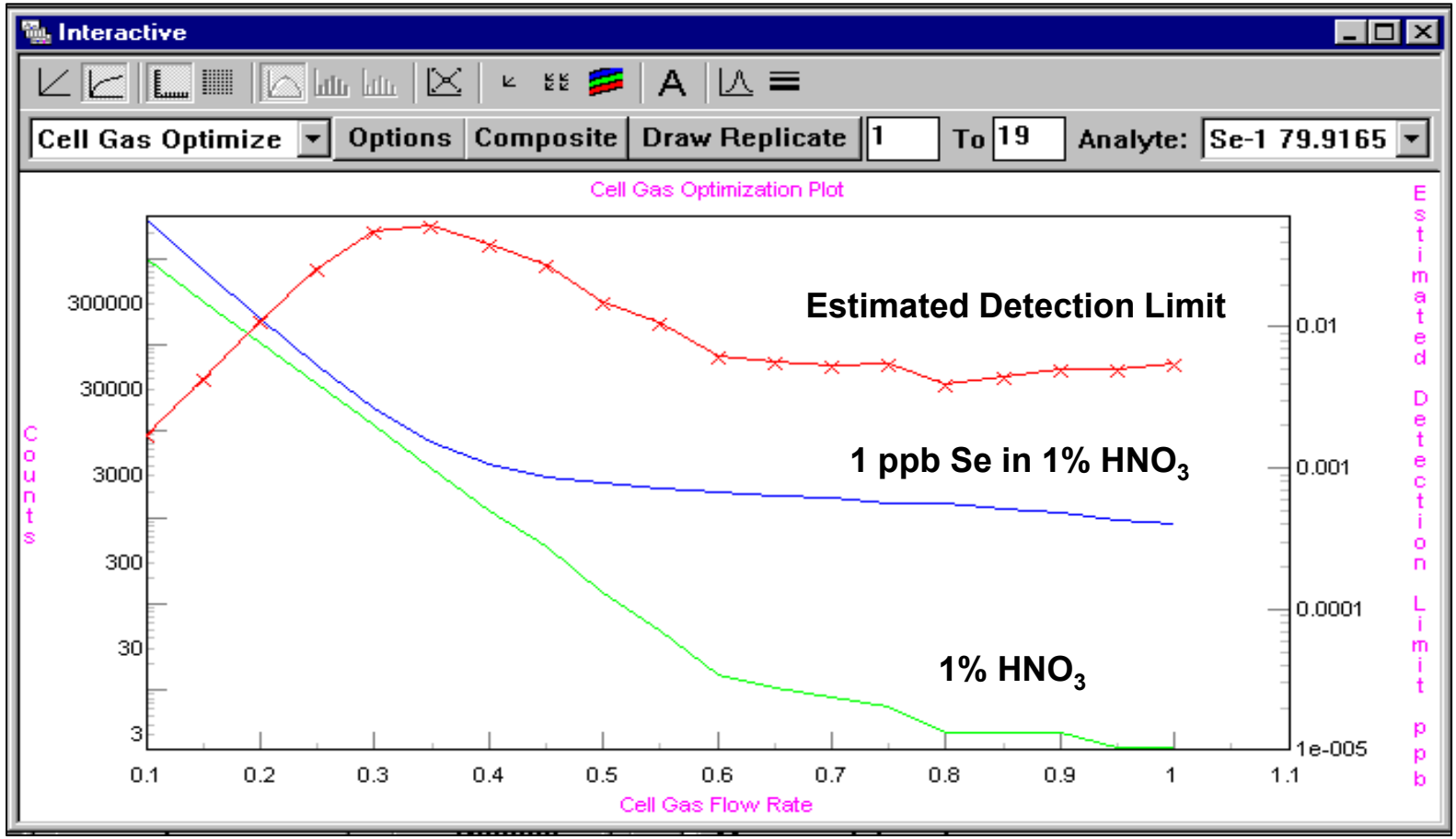
Cr in Blood

- 1ppb Cr in synthetic blood matrix with butanol etc.,
- NH_3 reaction gas, a=0, q=0.7
- Complete removal of ArC and ClO
- Isotopic fingerprint confirms the removal of interferences

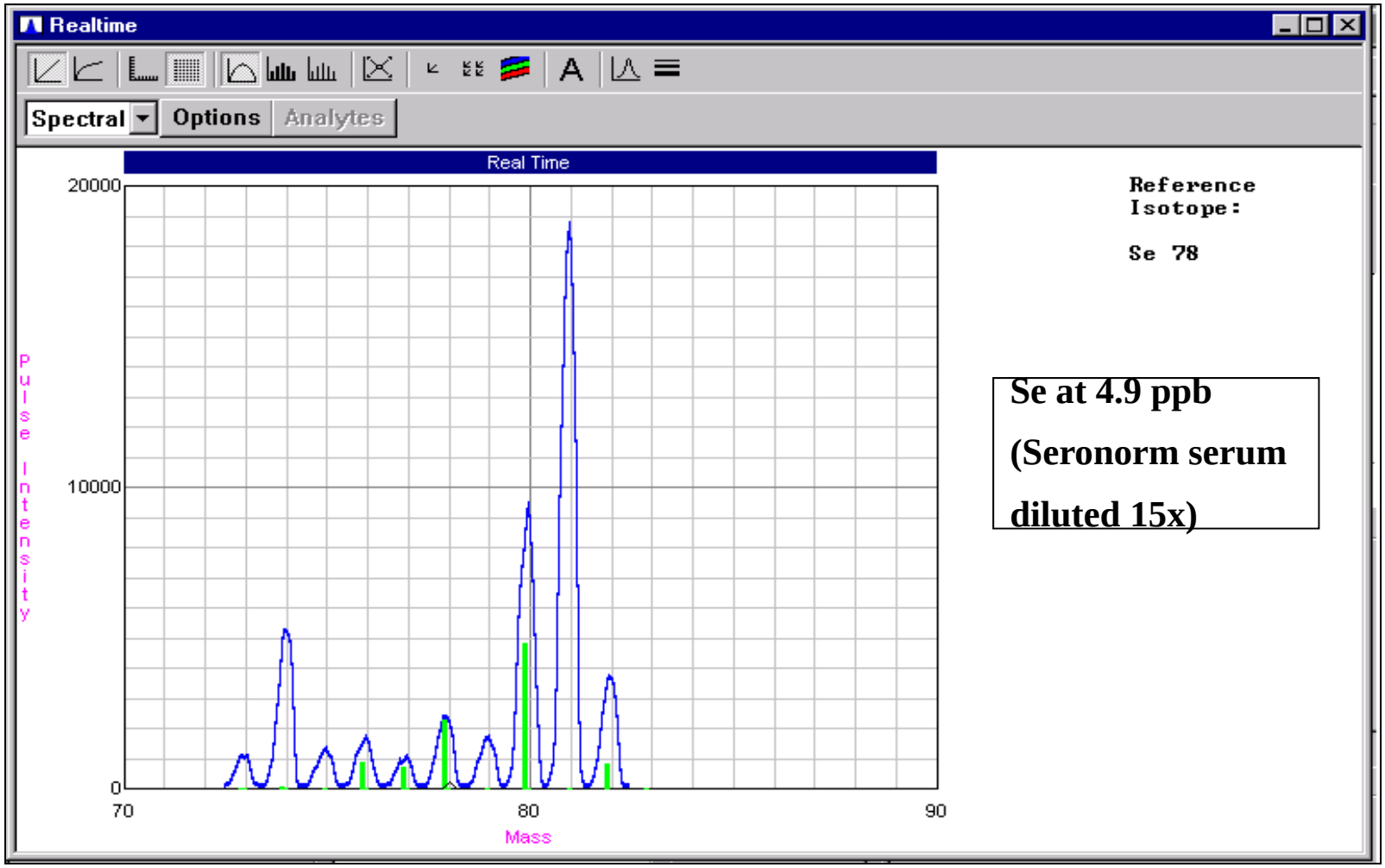


Se-80 with CH_4 reaction gas

- ArAr interference on ^{80}Se with CH_4 reaction gas



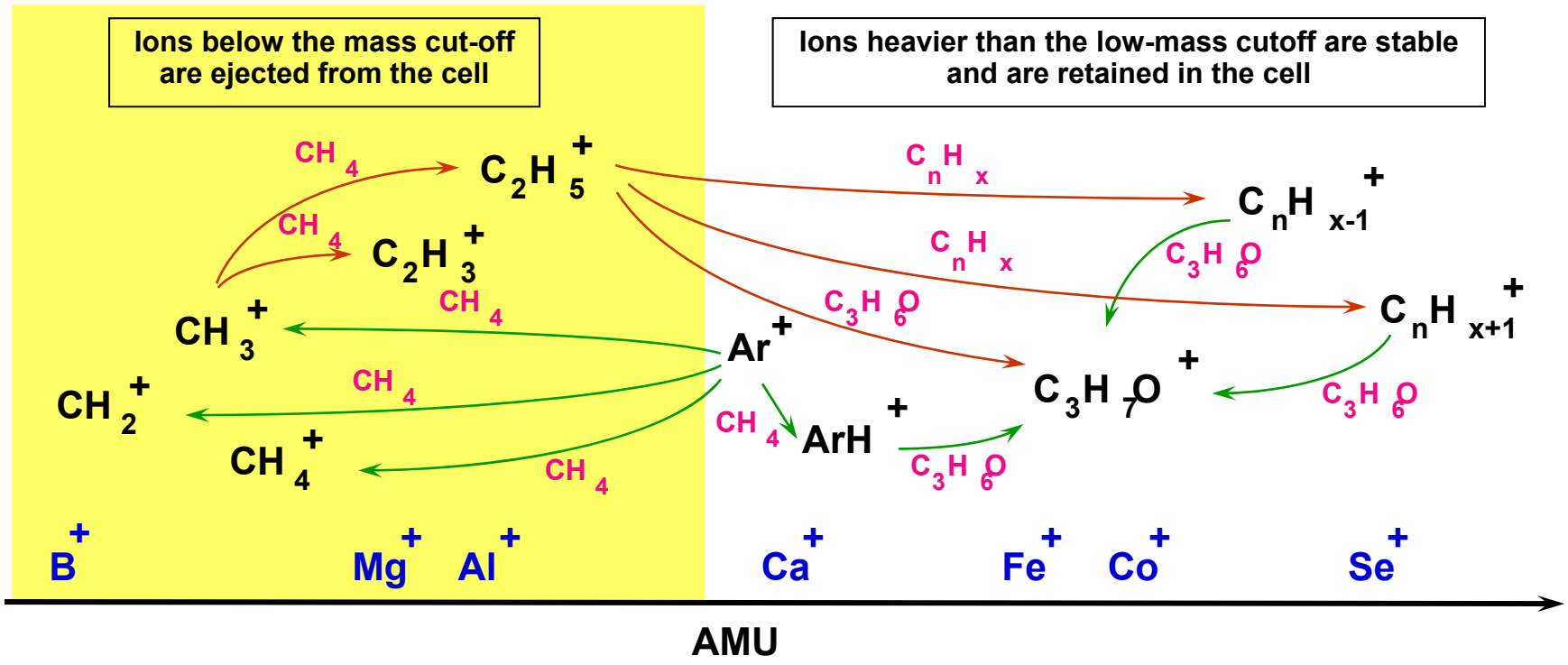
Se-80 with CH_4 reaction gas (CH_4 0.6 mL/min; q=0.4)



By using Se-78 as reference, mass 80 doesn't fit the Se isotopic pattern

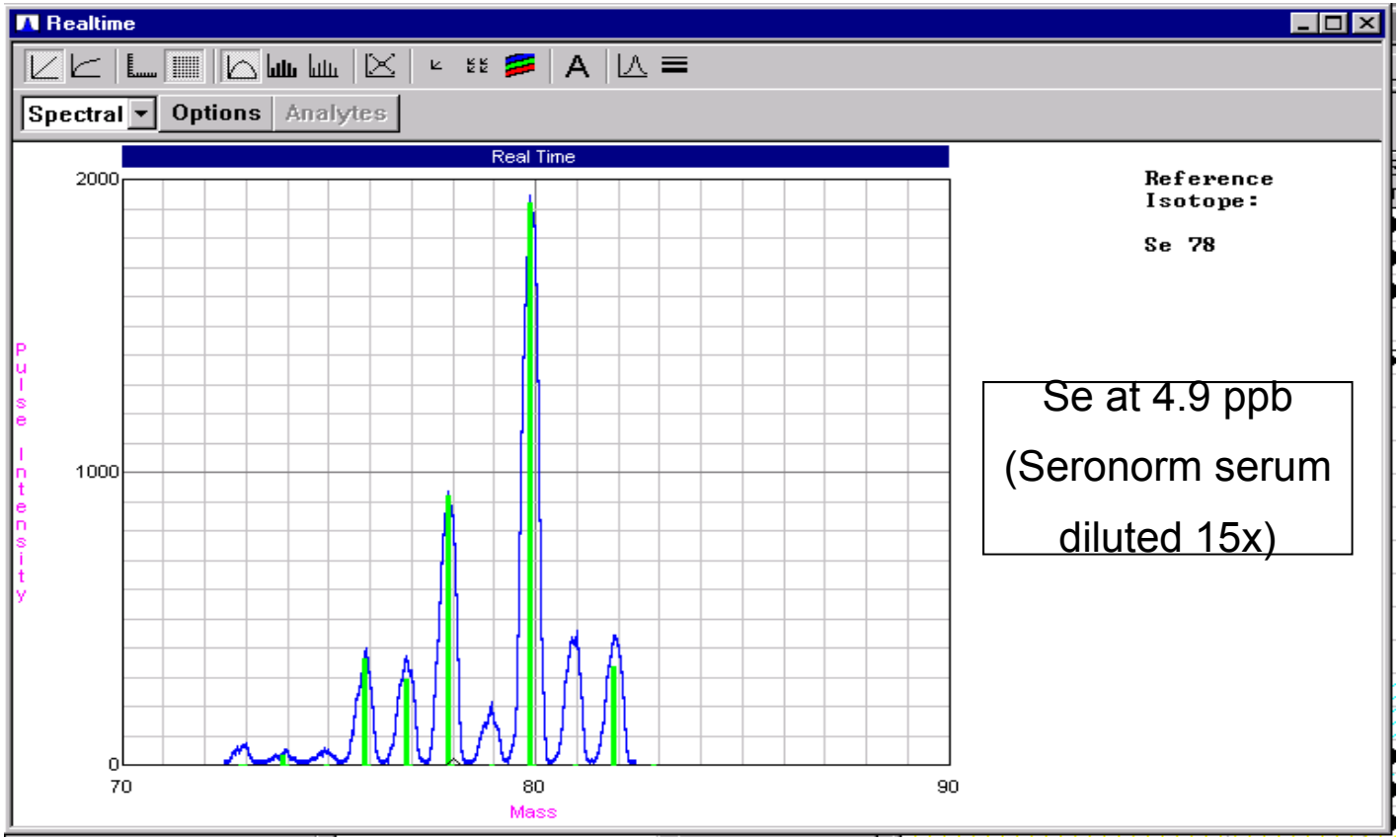
The need for low mass cut-off

- "q" parameter sets low mass cut-off to prevent unwanted chemistry
- Highe values of "q" increase the low-mass cutoff

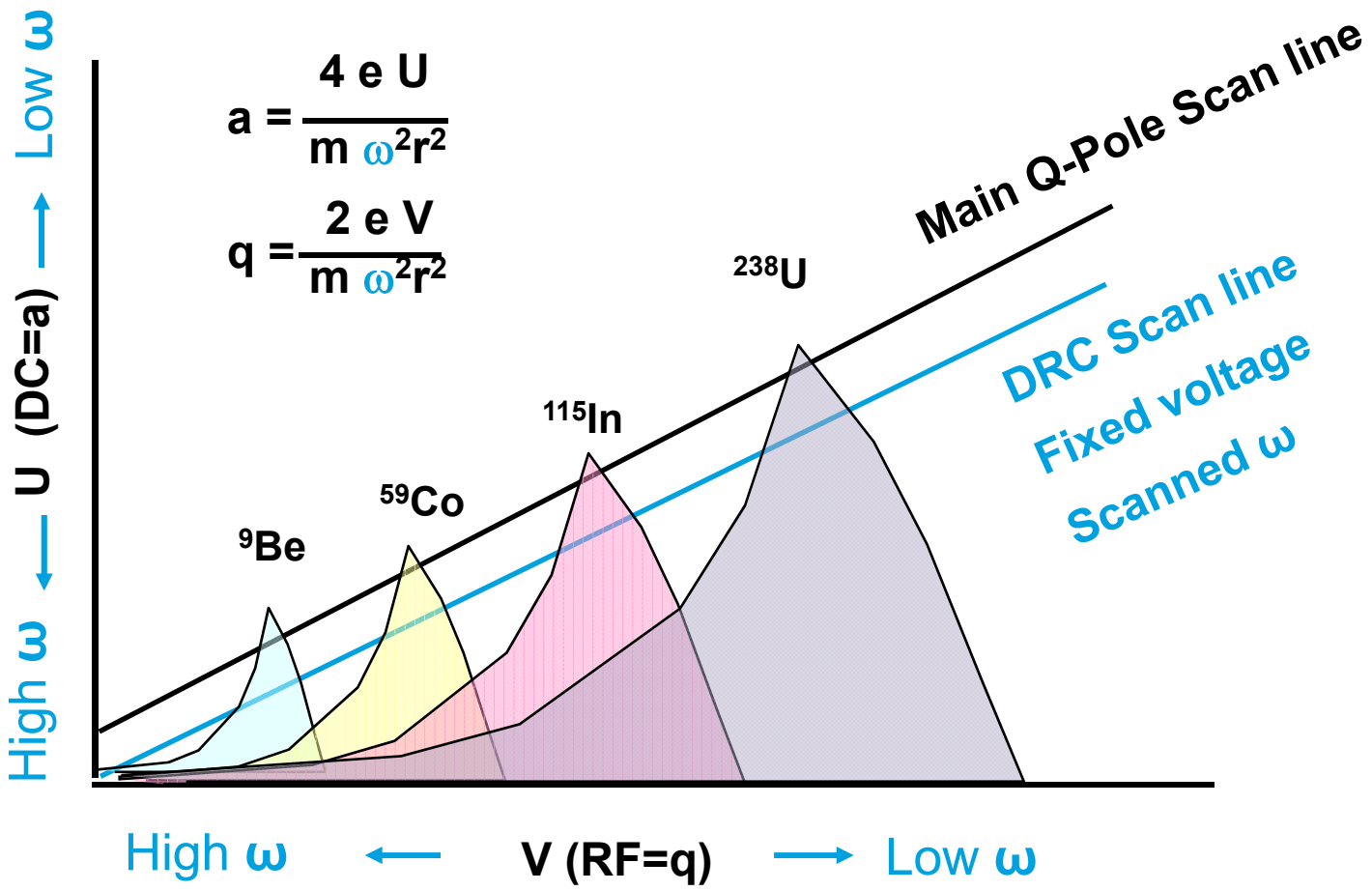


Se-80 with CH_4 reaction gas (CH_4 0.6 mL/min; q=0.7)

- Interferences are removed and isotope pattern is correct
  - Br and BrH cannot be removed, masses are too close



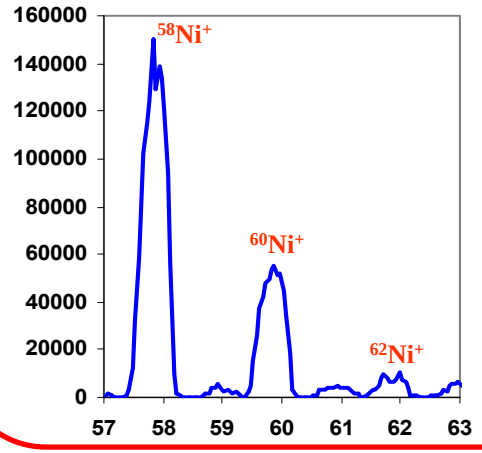
Q-pole Mass Scan Line and Stable Region (2)

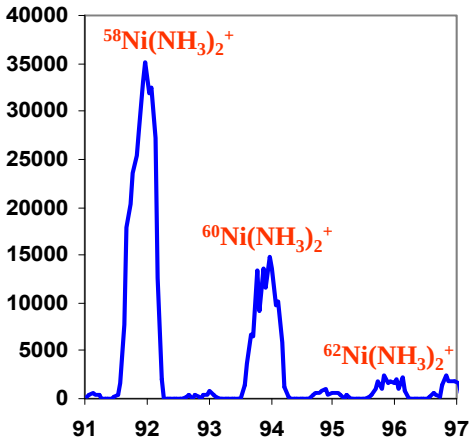


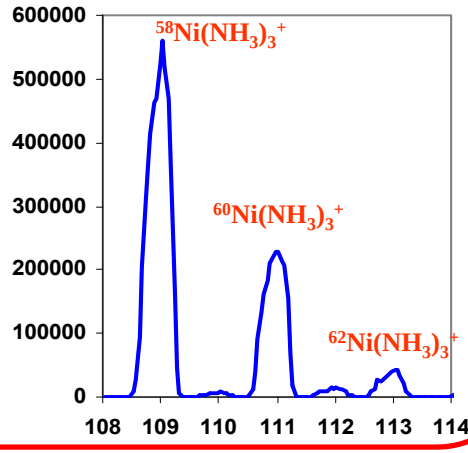
Easy to obtain on a Quad

Reaction Cells and Clusters Elimination

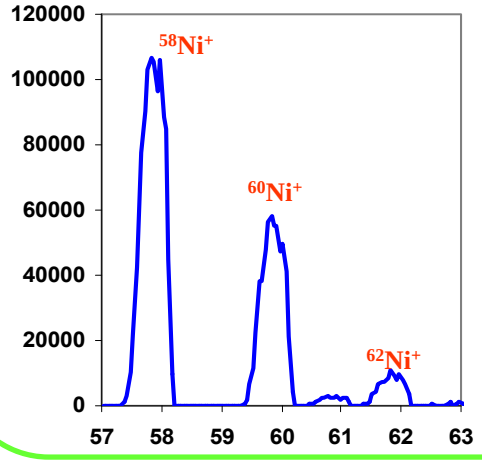
No Bandpass Filter Applied

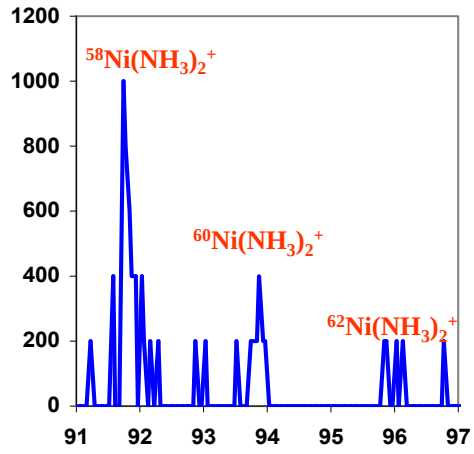


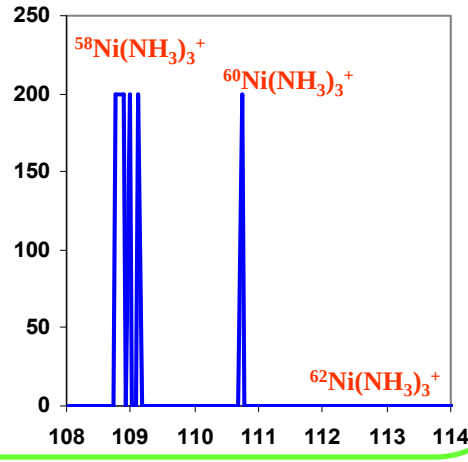




Bandpass Filter Applied





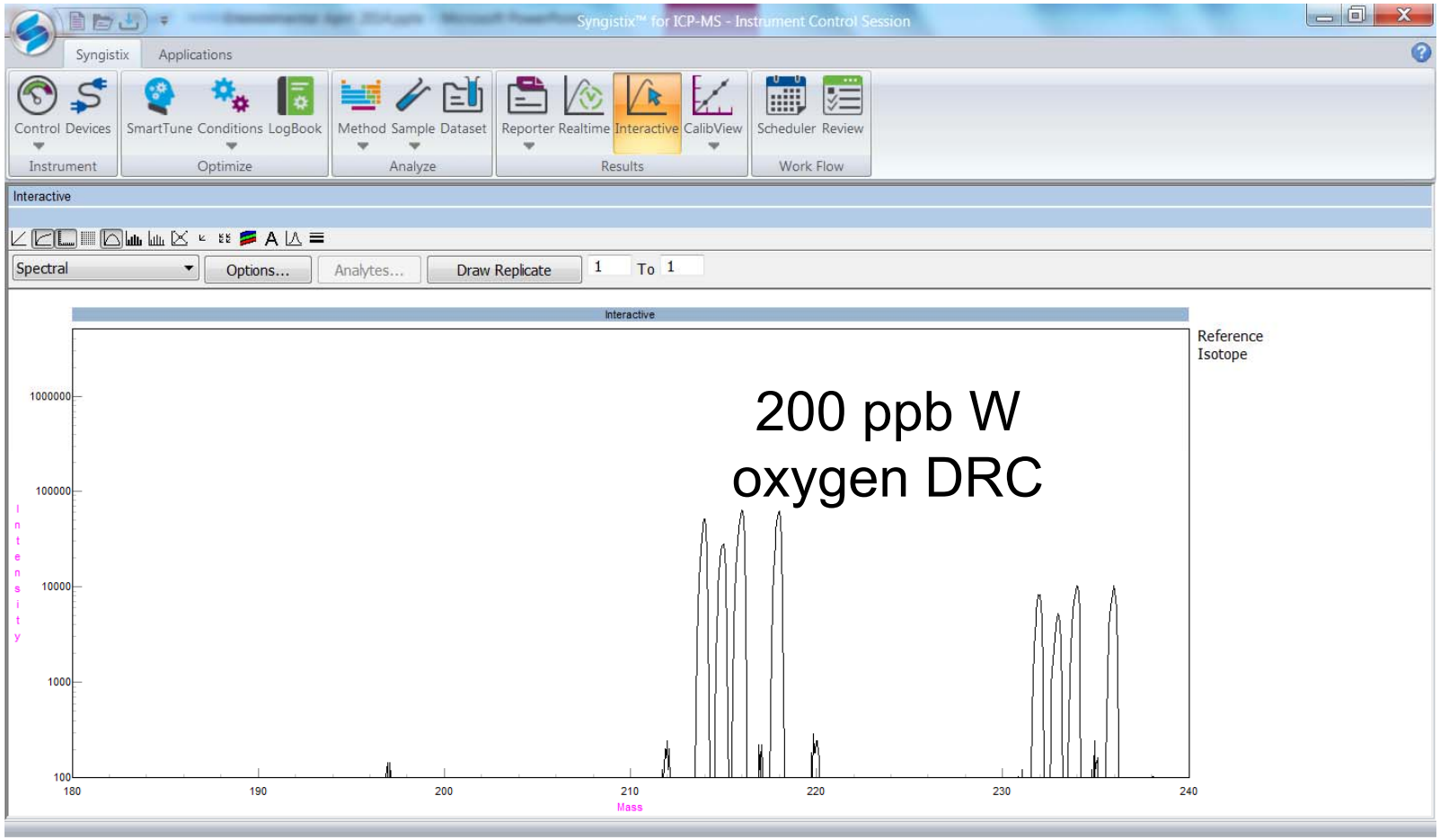


Arsenic in Chinese Medicines, Confirmation of Results

- Agreement between the different mechanisms of interferences reduction increases confidence in method's performances.

Mode	Analyte / Mass	Correction Mechanism	CM-1	CM-2	CM-3
Standard	As 75	Correction Equation	0.359	4.46	0.072
KED	As 75	Helium Collisions	0.475	1.97	0.054
DRC	AsO 91	Chemical Reaction	0.440	1.62	0.054

Elegant use of reaction mode solves the problem



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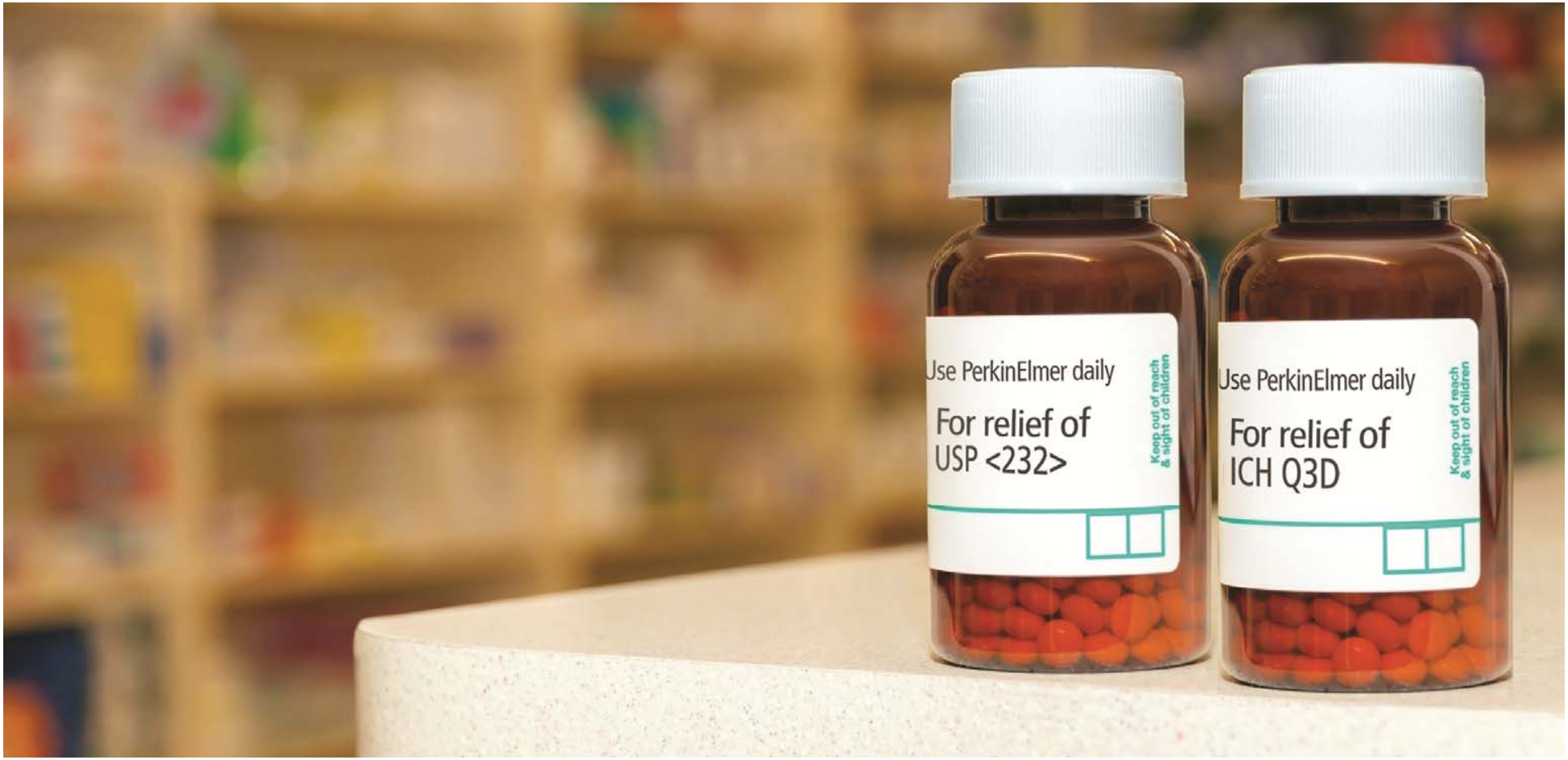
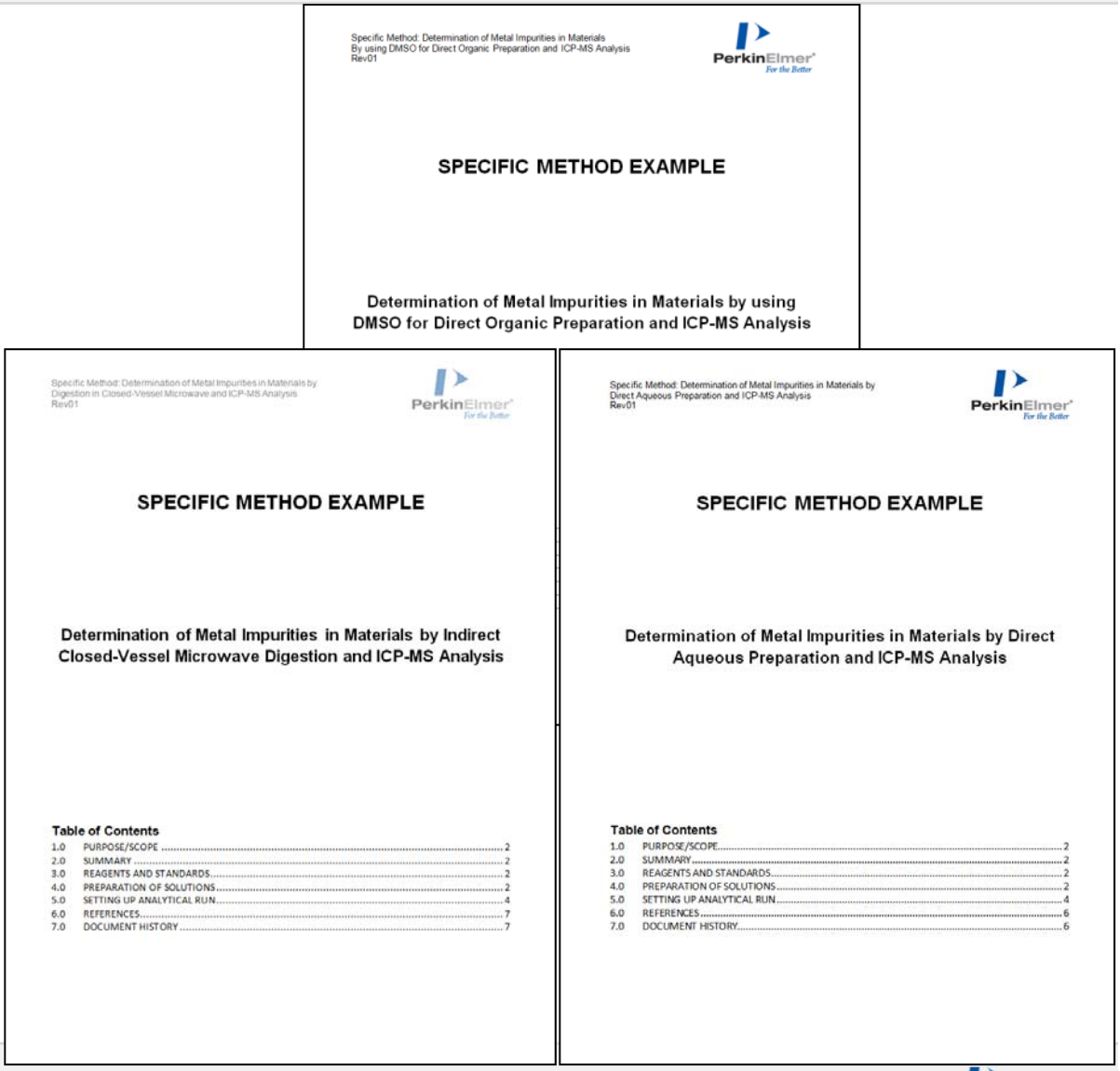


PerkinElmer ICH/USP <232>/<233> Toolkit

NexION ICP-MS Example Methods

- Contents:
  - Reagent and Standard Information
  - Reagent and Standard Preparation
  - Sample Preparation
  - Setting up the analytical run

- Gets you ready, faster.



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NexION Validation and Analytical Method Templates

- USP Specific Instrumental Methods

Sweeps / Reading	Est. Reading Time	MassCal File	
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Readings / Replicate	**Est. Replicate Time**	**Conditions File**	
1	0:00:13.380	default.dac	Browse...
Replicates	**Est. Sample Time**		
3	0:00:60.140	☑ Enable QC Checking	

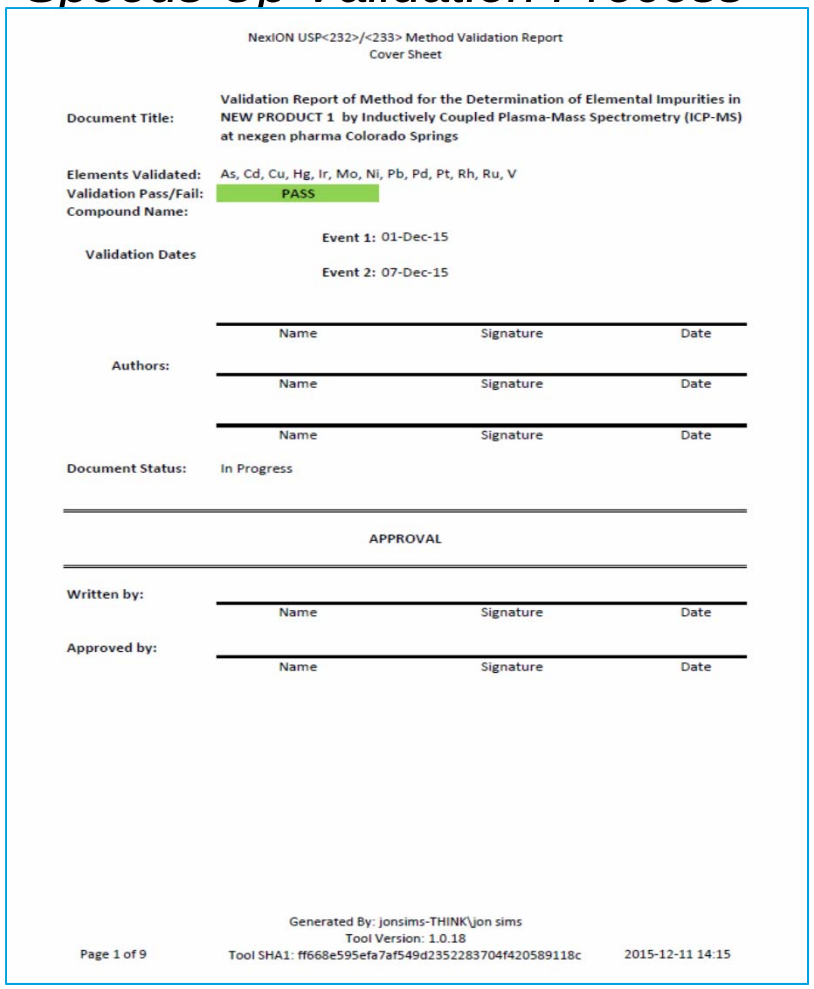
	Int Std	Analyte	Mass (amu)	Scan Mode (*)	MCA Channels	Dwell Time per AMU (ms)	Integration Time (ms)	Correction	Mode (*)	Cell
1		V	50.944	Peak Hopping	1	50	500		KED	0
2		Cr	51.9405	Peak Hopping	1	50	500		KED	0
3	↳	Ga	70.9249	Peak Hopping	1	50	500		KED	0
4		Ni	59.9332	Peak Hopping	1	50	500		KED	0
5		Cu	62.9298	Peak Hopping	1	50	500		KED	0
6		As	74.9216	Peak Hopping	1	100	1000		KED	0
7	↳	Ge	71.9217	Peak Hopping	1	50	500		KED	0
8		Mo	97.9055	Peak Hopping	1	50	500	Ru	KED	0
9		Ru	100.906	Peak Hopping	1	50	500		KED	0
10		Rh	102.905	Peak Hopping	1	50	500		KED	0
11		Pd	104.905	Peak Hopping	1	50	500		KED	0
12		Cd	110.904	Peak Hopping	1	100	1000		KED	0
13	↳	In	114.904	Peak Hopping	1	50	500	Sn	KED	0
14		Os	188.959	Peak Hopping	1	50	500		KED	0
15		Ir	192.963	Peak Hopping	1	50	500		KED	0
16		Pt	194.965	Peak Hopping	1	50	500		KED	0
17		Hg	201.971	Peak Hopping	1	100	1000		KED	0
18		Pb	207.977	Peak Hopping	1	50	500	Pb, Pb	KED	0
19	↳	Tb	158.925	Peak Hopping	1	50	500		KED	0

Sweeps / Reading	Est. Reading Time	MassCal File	
10	0:00:21.360	default.tun	Browse...
Readings / Replicate	**Est. Replicate Time**	**Conditions File**	
1	0:00:21.360	default.dac	Browse...
Replicates	**Est. Sample Time**		
3	0:01:24.080	☐ Enable QC Checking	

	Int Std	Analyte	Mass (amu)	Scan Mode (*)	MCA Channels	Dwell Time per AMU (ms)	Integration Time (ms)	Correction	Mode (*)	Cell Gas A	Cell Gas B	RP a	RP q
1		V	50.944	Peak Hopping	1	50	500		KED	0	5	0	0.25
2		Cr	51.9405	Peak Hopping	1	50	500		KED	0	5	0	0.25
3		Cr	52.9407	Peak Hopping	1	50	500		KED	0	5	0	0.25
4	↳	Ga	70.9249	Peak Hopping	1	50	500		KED	0	5	0	0.25
5		Ni	57.9353	Peak Hopping	1	50	500	Fe	KED	0	5	0	0.25
6		Ni	59.9332	Peak Hopping	1	50	500		KED	0	5	0	0.25
7		Cu	62.9298	Peak Hopping	1	50	500		KED	0	5	0	0.25
8		Cu	64.9278	Peak Hopping	1	50	500		KED	0	5	0	0.25
9		As	74.9216	Peak Hopping	1	100	1000		KED	0	5	0	0.25
10	↳	Ge	71.9217	Peak Hopping	1	50	500		KED	0	5	0	0.25
11		Mo	94.9058	Peak Hopping	1	50	500		KED	0	5	0	0.25
12		Mo	97.9055	Peak Hopping	1	50	500	Ru	KED	0	5	0	0.25
13		Ru	100.906	Peak Hopping	1	50	500		KED	0	5	0	0.25
14		Ru	101.904	Peak Hopping	1	50	500	Pd	KED	0	5	0	0.25
15		Rh	102.905	Peak Hopping	1	50	500		KED	0	5	0	0.25
16		Pd	104.905	Peak Hopping	1	50	500		KED	0	5	0	0.25
17		Pd	107.904	Peak Hopping	1	50	500	Cd	KED	0	5	0	0.25
18		Cd	110.904	Peak Hopping	1	100	1000		KED	0	5	0	0.25
19		Cd	113.904	Peak Hopping	1	100	1000	Sn	KED	0	5	0	0.25
20	↳	In	114.904	Peak Hopping	1	50	500	Sn	KED	0	5	0	0.25
21		Os	187.956	Peak Hopping	1	50	500		KED	0	5	0	0.25
22		Os	188.959	Peak Hopping	1	50	500		KED	0	5	0	0.25
23		Ir	190.961	Peak Hopping	1	50	500		KED	0	5	0	0.25
24		Ir	192.963	Peak Hopping	1	50	500		KED	0	5	0	0.25
25		Pt	193.963	Peak Hopping	1	50	500		KED	0	5	0	0.25
26		Pt	194.965	Peak Hopping	1	50	500		KED	0	5	0	0.25
27		Hg	201.971	Peak Hopping	1	100	1000		KED	0	5	0	0.25
28		Hg	203.974	Peak Hopping	1	100	1000	Pb	KED	0	5	0	0.25
29		Pb	205.975	Peak Hopping	1	50	500		KED	0	5	0	0.25
30		Pb	206.976	Peak Hopping	1	50	500		KED	0	5	0	0.25
31		Pb	207.977	Peak Hopping	1	50	500		KED	0	5	0	0.25
32	↳	Tb	158.925	Peak Hopping	1	50	500		KED	0	5	0	0.25

PerkinElmer USP <233> Method Validation Tool

- Automatically imports NexION USP <233> Method Validation data
- Calculates and Summarizes:
  - Batch Drift Checks
  - Accuracy (Standards)
  - Accuracy (Sample Spikes)
  - Repeatability
  - Ruggedness
- Gets you ready, faster.
- *Speeds Up Validation Process*



NexION USP<232>/<233> Method Validation Report
Cover Sheet

Document Title: Validation Report of Method for the Determination of Elemental Impurities in NEW PRODUCT 1 by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) at nexgen pharma Colorado Springs

Elements Validated: As, Cd, Cu, Hg, Ir, Mo, Ni, Pb, Pd, Pt, Rh, Ru, V
Validation Pass/Fail: PASS
Compound Name:

Validation Dates
Event 1: 01-Dec-15
Event 2: 07-Dec-15

	Name	Signature	Date
Authors:			
	Name	Signature	Date
	Name	Signature	Date

Document Status: In Progress

APPROVAL

	Name	Signature	Date
Written by:			
Approved by:	Name	Signature	Date

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Tool Version: 1.0.18
Page 1 of 9 Tool SHA1: ff668e595efa7af549d2352283704f420589118c 2015-12-11 14:15

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Validation Report – Sample Accuracy Summary

NexION USP<232>/<233> Method Validation Report
Standards Accuracy Summary

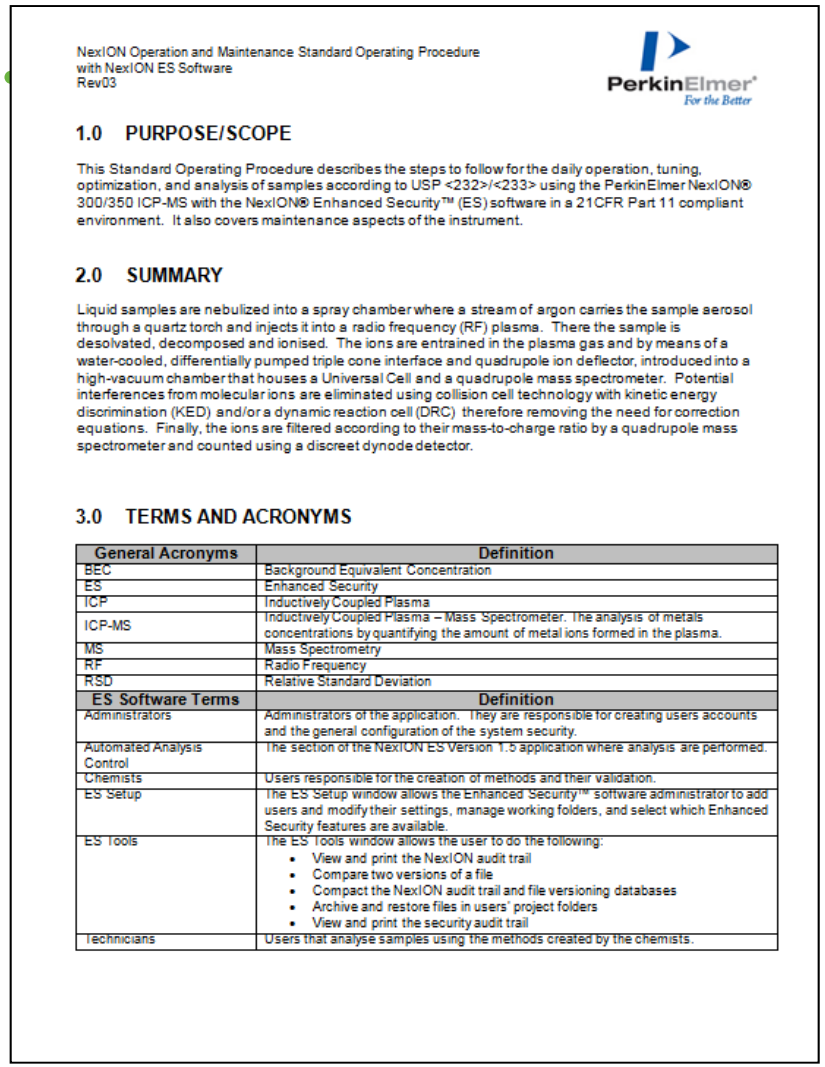
Element / Mass	Average Amount Present			Recovery (%)			Pass/Fail
	0.5 J	1 J	1.5 J	0.5 J	1 J	1.5 J	
As 75	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Cd 114	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Cr 52	0.48	1.67	1.48	95.3 %	167.5 %	98.7 %	Fail
Cu 63	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Hg 202	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Ir 193	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Mo 98	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Ni 60	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Pb 208	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Pd 105	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Pt 195	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
Rh 103	0.48	1.01	1.48	95.3 %	100.8 %	98.7 %	Pass
V 51	0.63	1.43	1.62	125.5 %	143.4 %	108.3 %	Pass

Procedure:
Prepare and run triplicate standard solutions containing Target Elements at concentrations that are 50%, 100% and 150% of the target limits.
Prepare and run triplicate spiked samples containing Target Elements at concentrations that are 50%, 100% and 150% of the target limits.

Acceptance Criteria:
Mean spike recoveries for each Target Element must be within 70%-150% of the theoretical concentrations.

NexION ICP-MS Operating and Maintenance Procedure

- SOPs
- Validation Experience
- Enhanced Security Software
- 21 CFR Part 11 Compliant



NexION Operation and Maintenance Standard Operating Procedure
with NexION ES Software
Rev03

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1.0 PURPOSE/SCOPE

This Standard Operating Procedure describes the steps to follow for the daily operation, tuning, optimization, and analysis of samples according to USP <232>/<233> using the PerkinElmer NexION® 300/350 ICP-MS with the NexION® Enhanced Security™ (ES) software in a 21CFR Part 11 compliant environment. It also covers maintenance aspects of the instrument.

2.0 SUMMARY

Liquid samples are nebulized into a spray chamber where a stream of argon carries the sample aerosol through a quartz torch and injects it into a radio frequency (RF) plasma. There the sample is desolvated, decomposed and ionised. The ions are entrained in the plasma gas and by means of a water-cooled, differentially pumped triple cone interface and quadrupole ion deflector, introduced into a high-vacuum chamber that houses a Universal Cell and a quadrupole mass spectrometer. Potential interferences from molecular ions are eliminated using collision cell technology with kinetic energy discrimination (KED) and/or a dynamic reaction cell (DRC) therefore removing the need for correction equations. Finally, the ions are filtered according to their mass-to-charge ratio by a quadrupole mass spectrometer and counted using a discreet dynode detector.

3.0 TERMS AND ACRONYMS

General Acronyms	Definition
BEC	Background Equivalent Concentration
ES	Enhanced Security
ICP	Inductively Coupled Plasma
ICP-MS	Inductively Coupled Plasma – Mass Spectrometer. The analysis of metals concentrations by quantifying the amount of metal ions formed in the plasma.
MS	Mass Spectrometry
RF	Radio Frequency
RSD	Relative Standard Deviation
ES Software Terms	**Definition**
Administrators	Administrators of the application. They are responsible for creating users accounts and the general configuration of the system security.
Automated Analysis Control	The section of the NexION ES Version 1.5 application where analysis are performed.
Chemists	Users responsible for the creation of methods and their validation.
ES Setup	The ES Setup window allows the Enhanced Security™ software administrator to add users and modify their settings, manage working folders, and select which Enhanced Security features are available.
ES Tools	The ES Tools window allows the user to do the following: • View and print the NexION audit trail • Compare two versions of a file • Compact the NexION audit trail and file versioning databases • Archive and restore files in users' project folders • View and print the security audit trail
Technicians	Users that analyse samples using the methods created by the chemists.

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PerkinElmer USP J Value Calculator

- User inputs:
  - Compound name
  - Dosing information
  - Preparation information
- Calculator outputs:
  - J Value
  - NexION Calibration Standard 1 (1.5 J)
  - NexION Calibration Standard 2 (0.5 J)

- J value is calculated by:

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

- For example: As has an Oral Daily Dose PDE of 15 µg/day. If we digest 0.1g of a material that has a daily dosage of 1 g and dilute the resulting solution to 50 mL, the J value with therefore be:

$$J = \frac{15\ \mu g/day}{\frac{1g}{day} \times \frac{0.1g}{50mL}} = 30\ \mu g/L$$

- *Let PerkinElmer help you get ready*

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ICH Q3D and USP <232>/<233> J Value Calculator

Compound Name:	Test Material
Doses Per Day:	1
Weight Per Dose:	10 g
Amount Digested:	0.1 g
Final Volume:	50 mL
Dilution:	1

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	Oral Daily Dose PDE[a] (µg/day)	J value (µg/L in solution)	Standard 1 (1.5 J [µg/L])	Standard 2 (0.5 J [µg/L])
Cd	5	1.0	1.5	0.5
Pb	5	1.0	1.5	0.5
Inorganic arsenic[b]	15	3.0	4.5	1.5
Inorganic mercury[b]	30	6.00	9	3
Co	50	10	15	5
V	100	20	30	10
Ni	200	40	60	20
Tl	8	1.6	2.4	0.8
Au	100	20	30	10
Pd	100	20	30	10
Ir	100	20	30	10
Os	100	20	30	10
Rh	100	20	30	10
Ru	100	20	30	10
Se	150	30	45	15
Ag	150	30	45	15
Pt	100	20	30	10
Li	550	110	165	55
Sb	1200	240	360	120
Ba	1400	280	420	140
Mo	3000	600	900	300
Cu	3000	600	900	300
Sn	6000	1200	1800	600
Cr	11000	2200	3300	1100

As long as the total daily dosage is not greater than what was inputted Standard 1 and Standard 2 are valid. However if a sample is greater than 1.5J in concentration than it must be diluted accordingly.

[a] PDE = Permissible daily exposure based on a 50-kg person.

[b] See Speciation section of USP <232>

PerkinElmer USP/ICH Standard Solutions

- ICH/USP Ready Custom Standard Solutions

Oral Elemental Impurites Standards Kit

PE Part No.	Description/Name	Volume
N9304361	ICH Elemental Impurities Standards Kit - Oral PDEs (Includes solutions below)	
N9304362	ICH Class 1 Elements + Tl - Oral PDE: 5mg/L:Cd, 5mg/L:Pb, 15mg/L:As 30mg/L:Hg, 8mg/L:Tl	125 mL
N9304363	ICH Class 2A Elements - Oral & Parenteral PDEs: 50mg/L:Co, 100mg/L:V, 200mg/L:Ni	125 mL
N9303728	100 mg/L Au	125 mL
N9304364	ICH Class 2B Precious Metal Elements (no Os) - All PDEs 100mg/L:Pd, Ir, Rh, Ru, Pt	125 mL
N9304365	ICH Class 2B Se & Ag - Oral PDE: 150mg/L: Se, Ag	125 mL
N9304366	ICH Class 3 Elements - Oral PDEs: 55mg/L:Li, 120mg/L:Sb, 140mg/L:Ba, 300mg/L:Mo, 300mg/L:Cu, 600mg/L:Sn, 1100mg/L:Cr	125 mL
N9304367	Internal Standards - All PDEs: 20mg/L: Ga, 50mg/L: Ge, 1mg/L:In,Tb	125 mL

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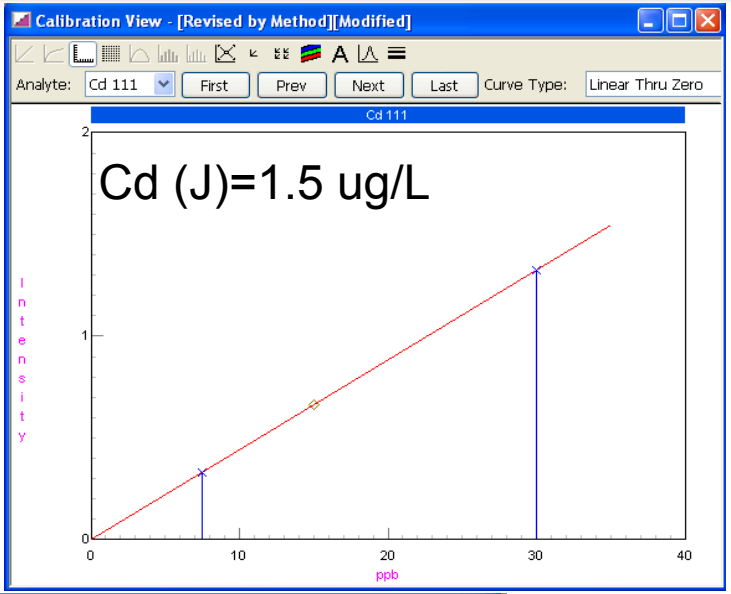
Analysis by NexION ICPMS as per USP <233>

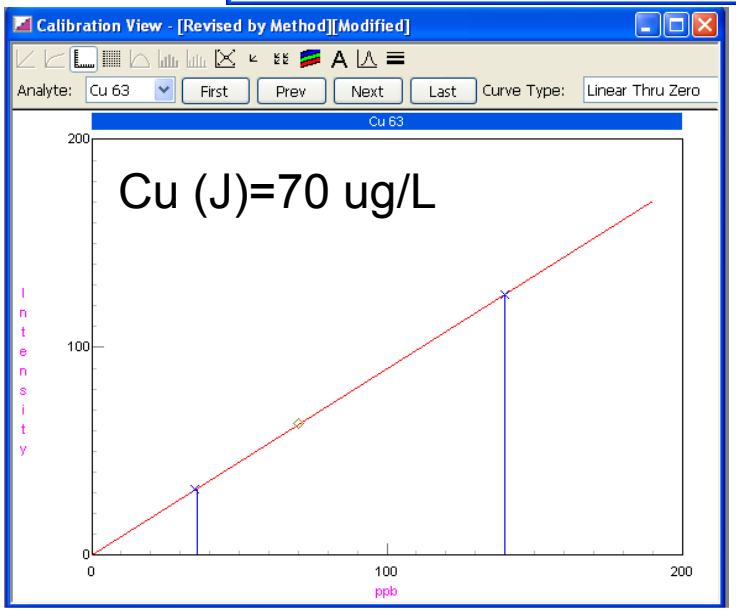
(J) values for Oral Drug Products in USP<232>

Element /Mass	Oral PDE (ug/day)	(J) Value (ug/L)	0.5 (J) Value (ug/L)	2 (J) Value (ug/L)	Linear Correlation Coefficient
Cd-114	25	5	2.5	10	0.99989
Pb (206+207+208)	5	1	0.5	2	0.99923
As-75	1.5	0.3	0.15	0.6	0.99985
Hg-202	15	3	1.5	6	0.99997
Ir-193	100	20	10	40	0.99998
Os-189	100	20	10	40	0.99997
Pd-105	100	20	10	40	0.99971
Pt-195	100	20	10	40	0.99995
Rh-103	100	20	10	40	0.99991
Ru-101	100	20	10	40	0.99992
Mo-95	100	20	10	40	1.00000
Ni-60	500	100	50	200	0.99993
V-51	100	20	10	40	0.99991
Cu-63	1000	200	100	400	1.00000

USP's Calibration Requirements

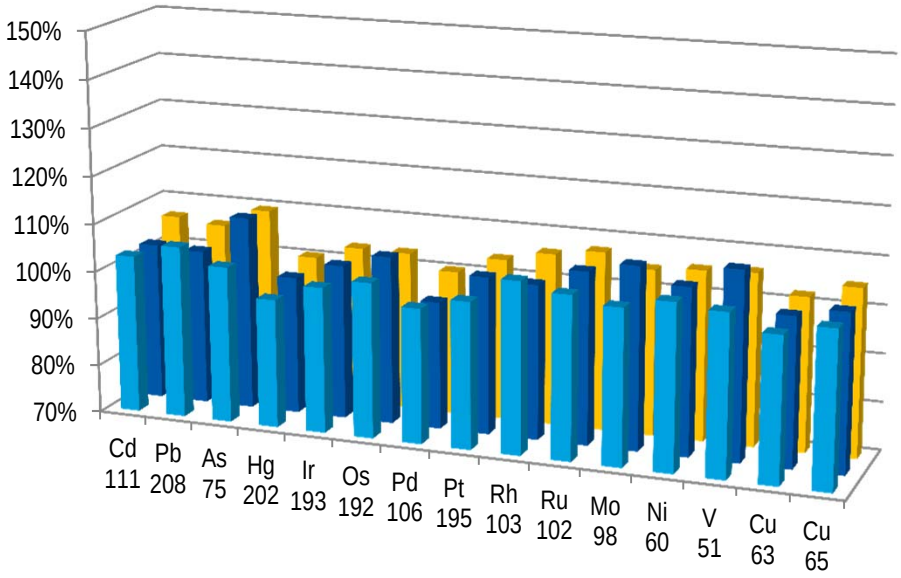
- (J) is the target value for the analyte in solution based
  - the particular analyte
  - the drug type
  - the dilution incurred for sample preparation (ug/L)
- 2-points calibration at half (0.5J) and twice (2J) the target value.
- Oral and inhalation (J) values are calculated on a daily dose of 10 g/day.
- Final dilution presented to the instrument is 500x
  - Matrix 2% HNO_3 / HCl 0.5%





USP QA/QC Validation Protocols

- Accuracy
  - % recovery of 0.8 (J) spike.
  - Requested recovery is 70 to 150 %
- Repeatability
  - Six samples spiked at target (J) levels
  - Requested RSD < 20 %
- Ruggedness
  - Repeatability testing with either different analyst, different days, different instruments, measuring % recovery and precision
- Stability
  - Measure 2(J) QC before and end of each sample batch



Accuracy Example: % recovery of 0.8(J) spike of 3 Oral medications

Measured Elemental Contaminants in Oral Drug Product

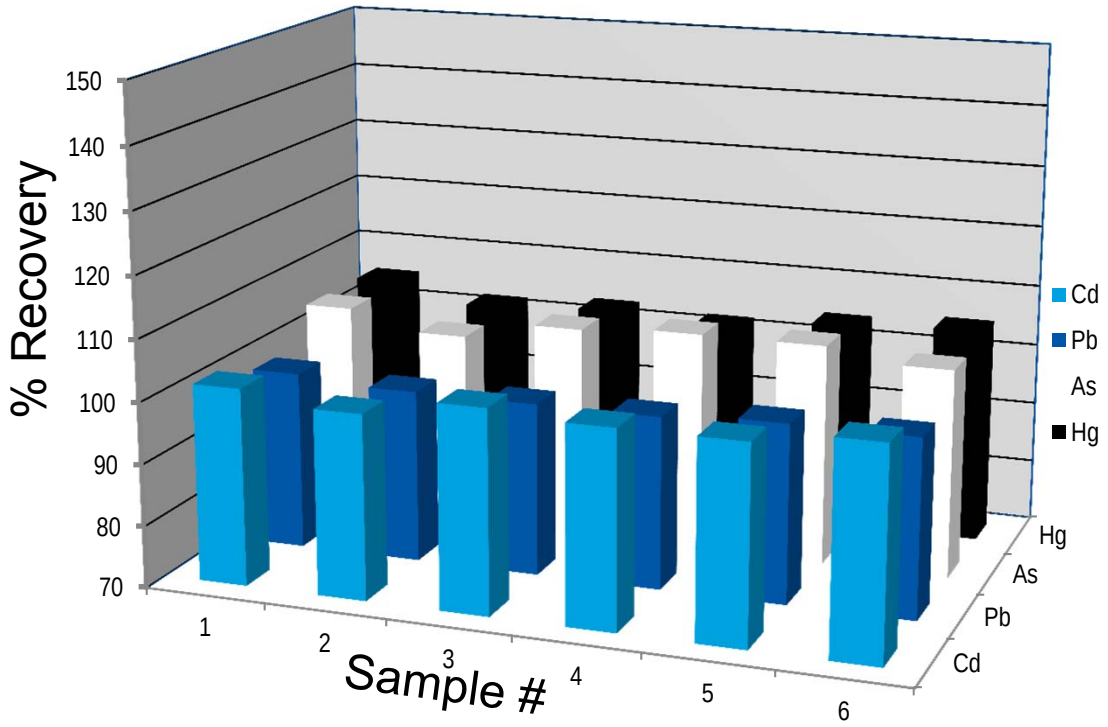
Element /Mass	Oral PDE (ug/g)	Cold /Flu Remedy (ug/g)	% Recovery 0.8 (J) Spike	MDL's 500x Dilution (ug/g)
Cd-114	2.5	<MDL	105	0.0004
Pb (206+207+208)	0.5	5	106	0.0007
As-75	0.15	1.5	110	0.0045
Hg-202	1.5	<MDL	105	0.0080
Ir-193	10	<MDL	105	0.0005
Os-189	10	<MDL	105	0.0010
Pd-105	10	<MDL	98	0.0025
Pt-195	10	<MDL	104	0.0019
Rh-103	10	<MDL	105	0.0002
Ru-101	10	0.002	106	0.0005
Mo-95	10	<MDL	105	0.003
Ni-60	50	<MDL	106	0.0026
V-51	100	0.054	105	0.0053
Cu-63	100	< MDL	103	0.002

Measured Elemental Contaminants in Inhalation Spray

Element	Inhalation Limits (ug/g) for 1 g/day Max Dose	Inhalation Allergy Med. Measured (ug/g)	% Recovery 0.8 (J) Spike	MDL's 50x Dilution (ug/g)
Cadmium	1.5	<MDL	101	0.0001
Lead	5	<MDL	106	0.0003
Arsenic (inorganic)	1.5	<MDL	101	0.0001
Mercury (inorganic)	1.5	0.0028	104	0.0002
Iridium	1.5	<MDL	104	0.0005
Osmium	1.5	<MDL	107	0.001
Palladium	1.5	<MDL	102	0.0006
Platinum	1.5	<MDL	103	0.0005
Rhodium	1.5	<MDL	102	0.0002
Ruthenium	1.5	<MDL	100	0.0003
Chromium	25	0.0013	104	0.0002
Molybdenum	250	<MDL	103	0.0001
Nickel	1.5	<MDL	102	0.0005
Vanadium	300	<MDL	103	0.0001
Copper	70	0.0054	102	0.0001

1(J) Spike recovery /precision of 6 samples of Flu Medication

- The cold /flu remedy is used to demonstrate repeatability, reproducibility and % spike recovery
  - USP acceptance criteria for spikes recovery is 70 to 150 %

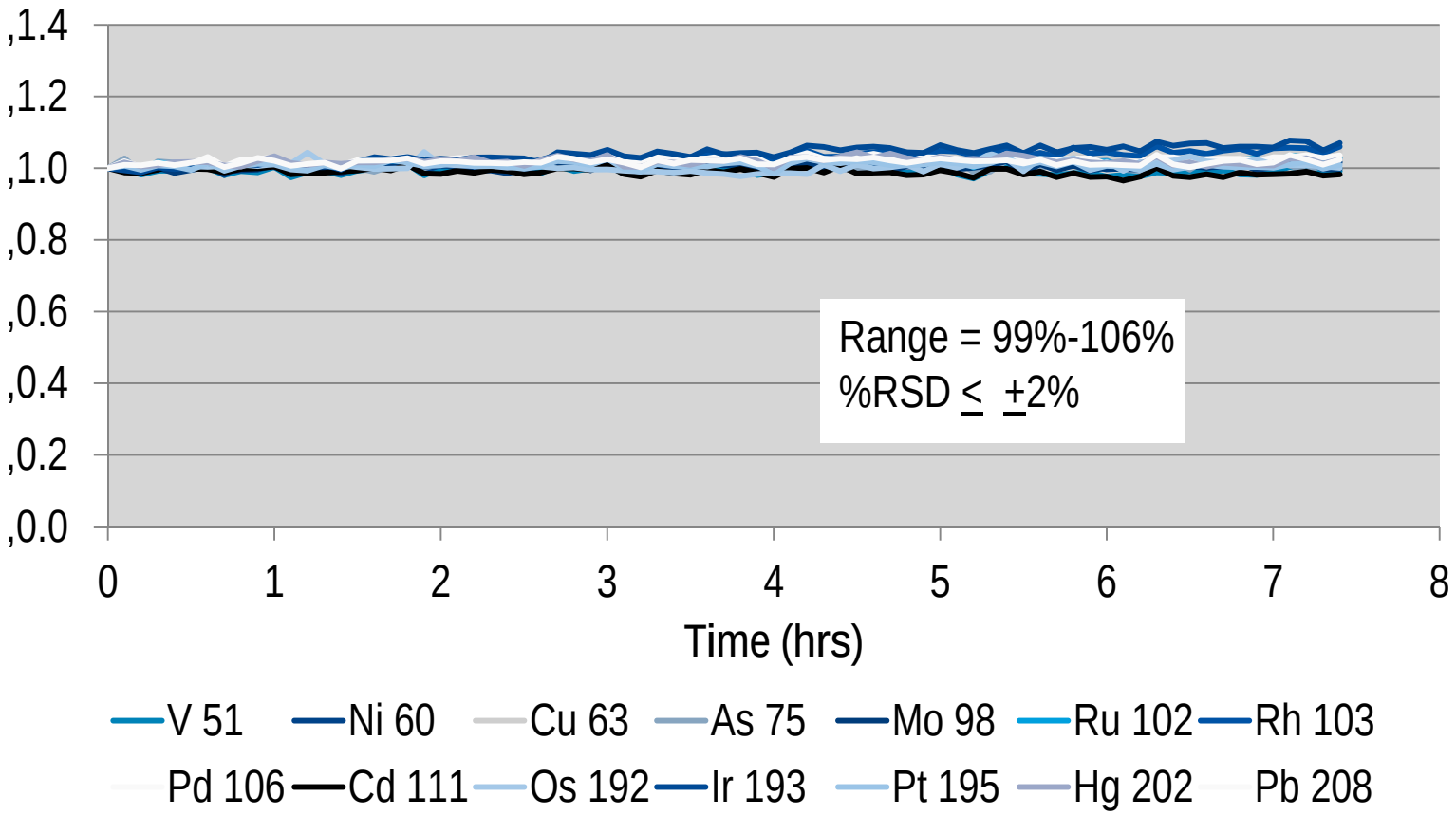


- Spike recovery graph showing just 4 of the elements (the most difficult ones).

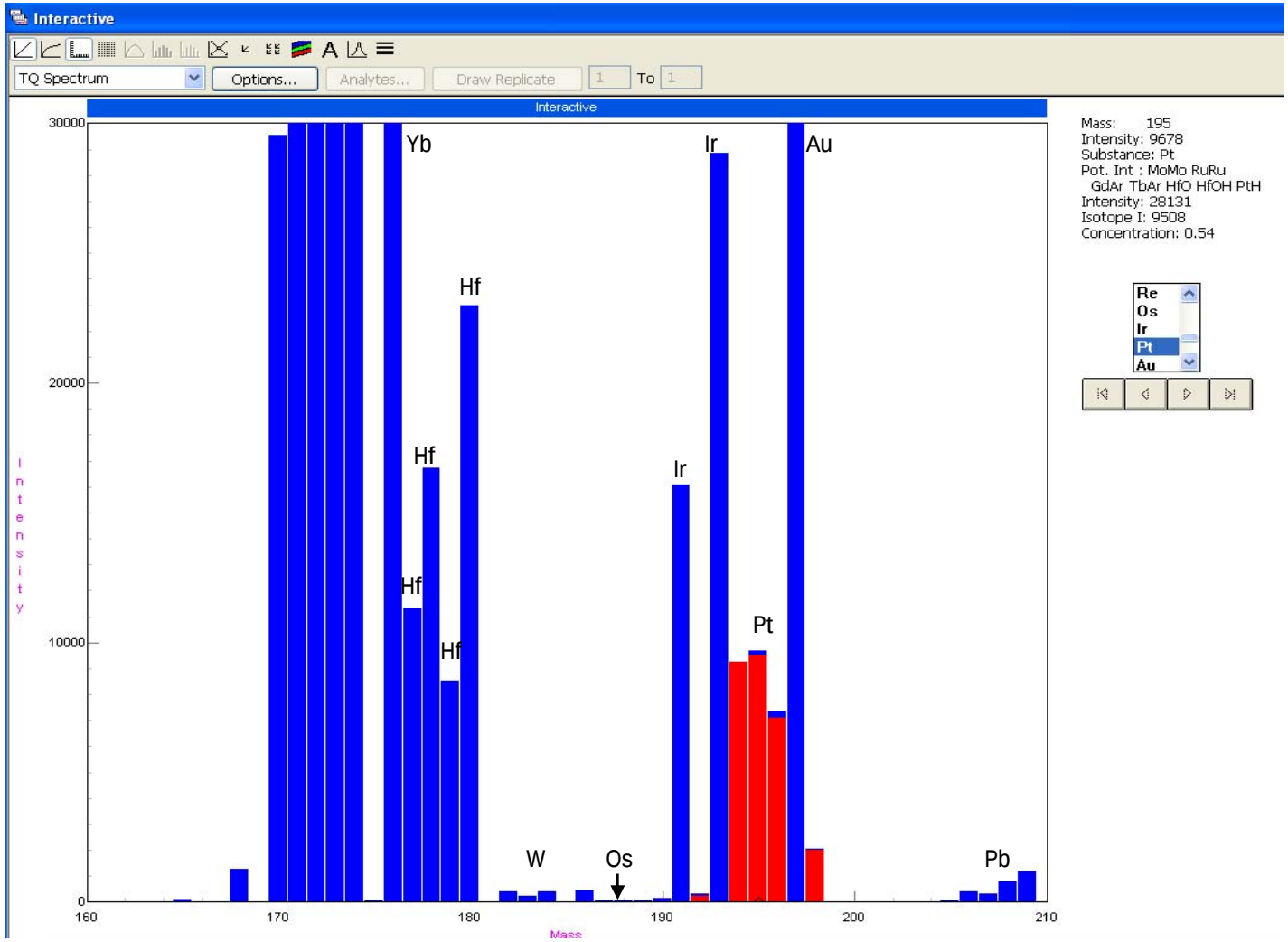
Element	% RSD (6 samples)
Cadmium	1.4
Lead	0.6
Arsenic	1.8
Mercury	1.2
Iridium	0.9
Osmium	0.9
Palladium	1.4
Platinum	0.9
Rhodium	1.2
Ruthenium	1.2
Molybdenum	1.2
Nickel	1.5
Vanadium	0.8
Copper	1.5

Stability with FAST system

- Spike Recoveries at 1(J) (Tb Internal Standard)



TotalQuant analysis of Acetaminophen, Osmium isotopes region



0.125 ug/g nominal spike of Hf, Ir, Pt in Acetaminophen. Pt isotopes shown in RED. Yb and Au present in the Internal Std Addition. Showing absence of osmium.

Portion of the TotalQuant Analysis of Acetaminophen Spike

Element	ug/L
Cs	0.00096
Ba	2.72985
La	0.00854
Ce	0.00674
Pr	0.00067
Nd	0.00223
Eu	0.0003
Gd	0.00016
Tb	0.00075
Dy	0.00016
Ho	0.00111
Er	0
Tm	0.00002
Yb (I.S.)	10.2536

Element	ug/L
Lu	0.00082
Hf*	0.54506
Ta	0.00033
W	0.02145
Re	0.00071
Os	0.00053
Ir*	0.52058
Pt*	0.51107
Au	62.5232
Hg	0
Tl	0.00113
Pb	0.02086
Bi	0.01986
Th	0.00395
U	0.00257

TotalQuant Analysis of a Acetaminophen solution.

* Spike of 0.5 µg/L Hf, Ir, Pt.

- Absence of Osmium
- Au is a stabilizer for Hg.
- Yb is an Internal Standard

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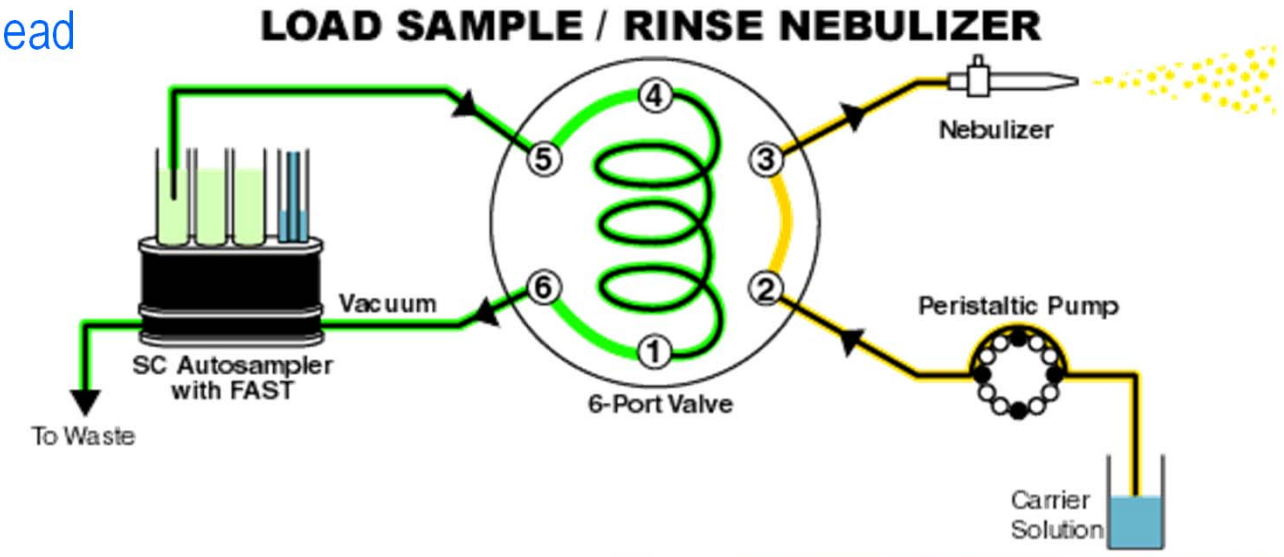
FAST and PrepFAST

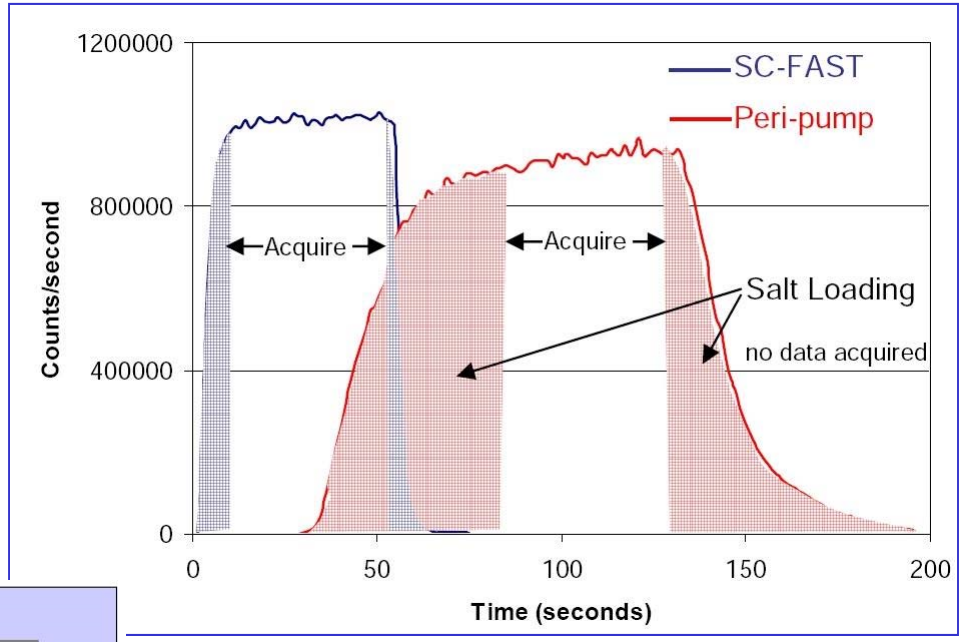
SC- FAST, a complete sample introduction system

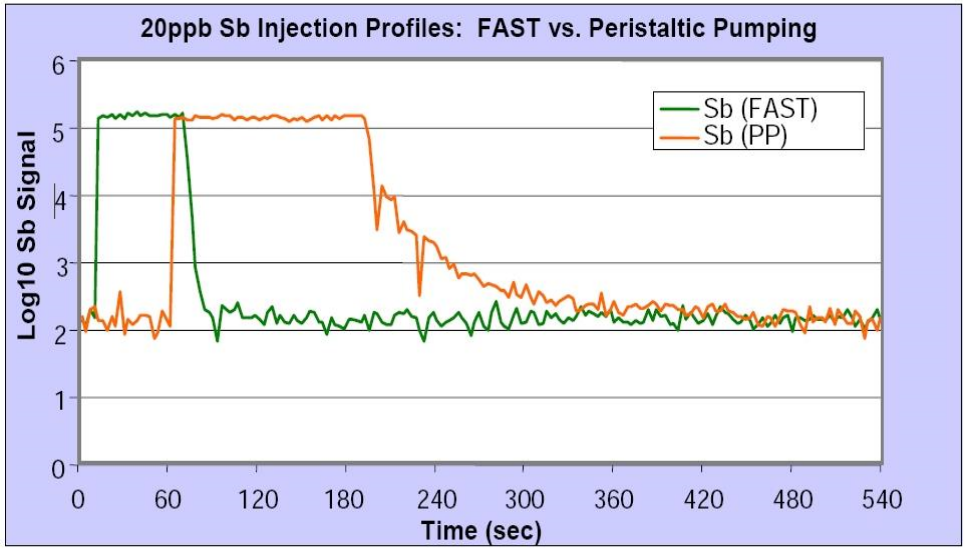
- FAST optimizes the 5 non-productive steps in the analytical process
  - 1) Autosampler movement
  - 2) Sample uptake time
  - 3) Stabilization time
  - 4) Measurement time
  - 5) Rinse time
  - 6) Instrument overhead



Two Real Examples

- Reduces exposure of the ICPMS to high salts from samples
- Reduces the need for cleaning





- Significantly cuts down washout time for ‘sticky’ elements
- Reduces analysis time per sample

PrepFAST, Automated Sample Introduction System

- Auto-calibrate from a single multi-element stock standard
  - Reduce errors in standard preparation
  - Reduce blank and improve linearity at low concentrations
- Capabilities
  - Inline sample dilution pre-defined or QC triggered for out of calibration range (up to 200x)
  - On-line internal standard addition
  - Discrete sampling through FAST
  - Solutions never touch peristaltic pump tubings
- Well-suited to the demands of a high throughput laboratories

Questions?