USP <232> and <233>

Understanding Your Path to Compliance with the New Elemental Impurity Chapters

Steve Wall
Agilent Technologies

Outline, USP <232> <233>

- USP Chapter <231>
- Chapter <232> Limits
- Chapter <233> Procedures
  - ICP-OES and ICP-MS
  - Digestion
  - Validation
  - J Value Calculator

- Electronic Records Compliance and 21CFR
- Revised Implementation Timeframe

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Trace Metal Analysis in Pharmaceuticals, Why?

The presence of elemental impurities in drug products can potentially have adverse health effects.

Limits have been established for permissible amounts of elemental impurities in drug products.

Elemental impurities may include

- Catalysts
- Environmental contaminants

Elemental impurities may arise from

- natural occurrence in raw materials
- introduced inadvertently (for example from manufacturing equipment)

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

- In use since 1905
- Not element specific
- Visual (subjective) comparison test
- Standard solution color can change over time resulting in poor reproducibility
- Issues with poor recovery when ash sample prep procedure used

Recognition of the Problems with USP <231>

Wang, T. et al, J. Pharm. & Biomed 2000

"Although still widely accepted and used in the pharmaceutical industry, these methods based on the intensity of the color of sulfide precipitation are non-specific, insensitive, time-consuming, labor intensive, and more often than hoped, yield low recoveries or no recoveries at all."

(Wang, T. et al, J. Pharm. & Biomed. Anal., Vol. 23 (2000) 867-890)

Recognition of the Problems with USP <231>

Traditional (wet chemical) method for heavy metals testing in pharma materials involves an ashing step and so gives low recoveries for volatile elements

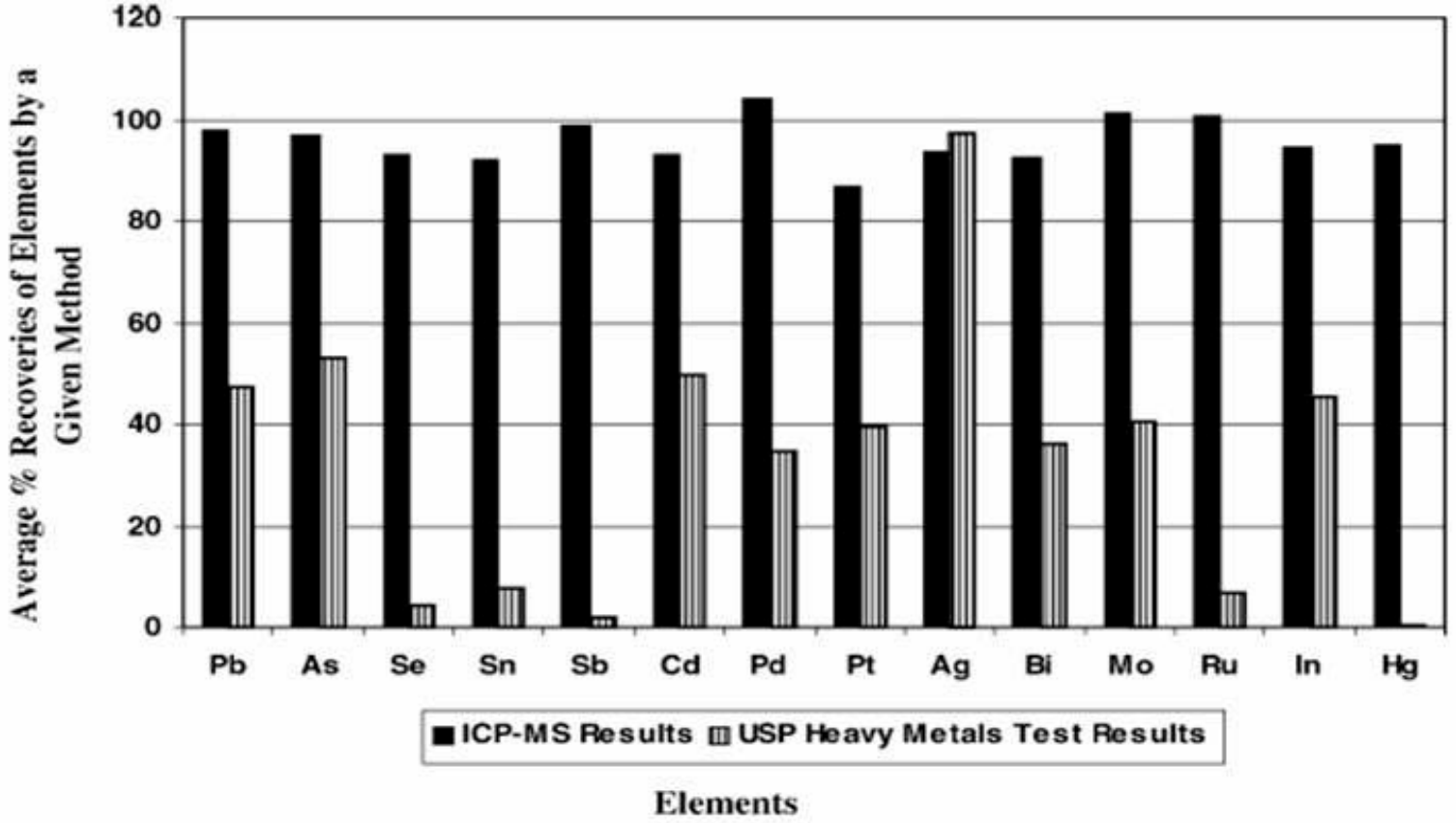


Fig. 2. Comparison of average (%) recoveries of elements: USP Heavy Metals test vs. ICP-MS Heavy Metals test.

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

Recognition of the Problems with USP <231>

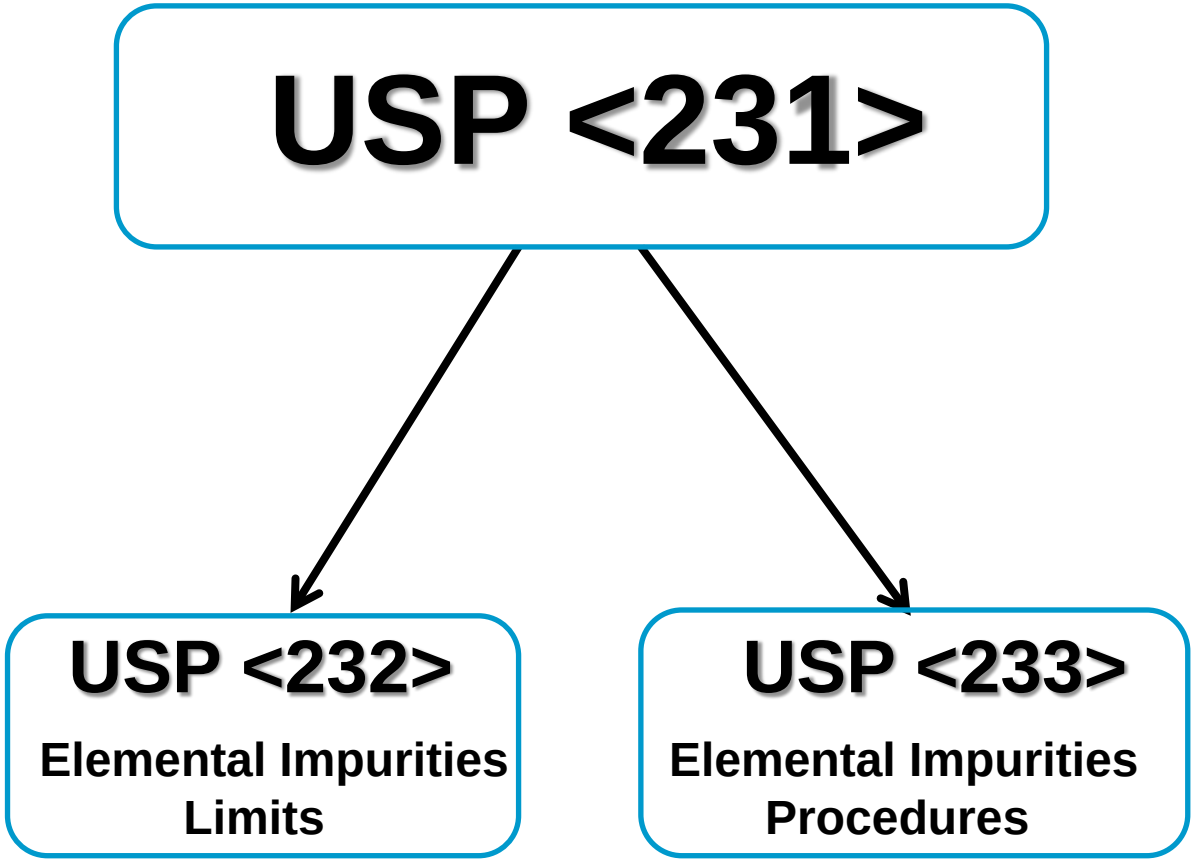
USP Meeting dated April 2009

- Problem Statement:

"We are committed to advancing the current standards (<231>) so that widely agreed upon safe limits for key metal impurities are properly measured, thereby protecting the public health"

Clear indication of acceptance that the current method (USP<231>) does not adequately protect the public health

USP <231> Replacement Chapters



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Elemental Impurities – Limits USP <232>

- This chapter specifies limits for the amounts of elemental impurities in drug products (Table 1).
- The presence of elemental impurities in drug substances and excipients must be controlled and, where present, reported (Table 2).
- Options for demonstrating compliance
  - Drug Product Analysis Option
  - Summation Option

Elemental Impurities – Limits USP <232>

Table 1. Elemental Impurities for Drug Products

Element	Oral Daily Dose PDE[a] (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalational Daily Dose PDE (µg/day)	LVP Component Limit (µg/g)
Cadmium	25	2.5	1.5	0.25
Lead	5	5	5	0.5
Inorganic arsenic[b]	1.5	1.5	1.5	0.15
Inorganic mercury[b]	15	1.5	1.5	0.15
Iridium	100	10	1.5	1.0
Osmium	100	10	1.5	1.0
Palladium	100	10	1.5	1.0
Platinum	100	10	1.5	1.0
Rhodium	100	10	1.5	1.0
Ruthenium	100	10	1.5	1.0
Chromium	—[c]	—[c]	25	—[c]
Molybdenum	100	10	•10• (ERR 1-Oct-2012)	1.0
Nickel	500	50	1.5	5.0
Vanadium	100	10	30	1.0
Copper	1000	100	•100• (ERR 1-Feb-2013)	•10• (ERR 1-Feb-2013)

[a] PDE = Permissible daily exposure based on a 50-kg person.
[b] See *Speciation* section.
[c] Not a safety concern.

- PDE is based on exposure route and scaled to maximum daily dose
- Options for demonstrating compliance:
- 1) Drug Product Analysis Option : Daily Dose PDE ≥ measured value x (maximum daily dose).
- 2) Summation Option : sum components and scale to maximum daily dose

Elemental Impurities – Limits USP <232> TO BE PROPOSED

Table 1. Elemental Impurities for Drug Products

Element	Oral Daily Dose PDE[a] (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalational Daily Dose PDE (µg/day)	LVP Component Limit (µg/g)
Cadmium	~~25~~ 5.0 1S (*USP38*)	2.5	~~4.5~~ 3.4 1S (*USP38*)	0.25
Lead	~~5~~ 5.0 1S (*USP38*)	~~5~~ 5.0 1S (*USP38*)	~~5~~ 5.0 1S (*USP38*)	0.5
Inorganic arsenic[b]	~~1.5~~ 15 1S (*USP38*)	~~1.5~~ 15 1S (*USP38*)	~~1.5~~ 1.9 1S (*USP38*)	~~0.15~~ 1.5 1S (*USP38*)
Inorganic mercury[b]	15	1.5	~~1.5~~ 1.2 1S (*USP38*)	0.15
Iridium	100	10	1.5	1.0
Osmium	100	10	1.5	1.0
Palladium	100	10	~~1.5~~ 1.0 1S (*USP38*)	1.0
Platinum	100	10	1.5	1.0
Rhodium	100	10	1.5	1.0
Ruthenium	100	10	1.5	1.0
Chromium	—[c]	—[c]	~~25~~ 2.9 1S (*USP38*)	—[c]
Molybdenum	~~100~~ 180 1S (*USP38*)	~~10~~ 90 1S (*USP38*)	~~10~~ 7.6 1S (*USP38*)	~~1.0~~ 9.0 1S (*USP38*)
Nickel	~~500~~ 600 1S (*USP38*)	~~50~~ 60 1S (*USP38*)	~~1.5~~ 6.0 1S (*USP38*)	~~5.0~~ 6.0 1S (*USP38*)
Vanadium	~~100~~ 120 1S (*USP38*)	~~10~~ 12 1S (*USP38*)	~~30~~ 1.2 1S (*USP38*)	~~1.0~~ 1.2 1S (*USP38*)
Copper	~~1000~~ 1300 1S (*USP38*)	~~100~~ 130 1S (*USP38*)	~~100~~ 13 1S (*USP38*)	~~10~~ 13 1S (*USP38*)

Elemental Impurities – Limits USP <232>

Table 2. Default Concentration Limits for Drug Substances and Excipients

Element	Concentration Limits (µg/g) for Oral Drug Products with a Maximum Daily Dose of ≤10 g/day	Concentration Limits (µg/g) for Parenteral Drug Products with a Maximum Daily Dose of ≤10 g/day	Concentration Limits (µg/g) for Inhalational Drug Products with a Maximum Daily Dose of ≤10 g/day
Cadmium	2.5	0.25	0.15
Lead	0.5	0.5	0.5
Inorganic arsenic	0.15	0.15	0.15
Inorganic mercury	1.5	0.15	0.15
Iridium	10	1.0	0.15
Osmium	10	1.0	0.15
Palladium	10	1.0	0.15
Platinum	10	1.0	0.15
Rhodium	10	1.0	0.15
Ruthenium	•10• (ERR 1-Oct-2012)	•1.0• (ERR 1-Oct-2012)	•0.15• (ERR 1-Oct-2012)
Chromium	—[a]	—[a]	2.5
Molybdenum	10	1.0	•1.0• (ERR 1-Oct-2012)
Nickel	50	5.0	0.15
Vanadium	•10• (ERR 1-Oct-2012)	•1.0• (ERR 1-Oct-2012)	•3.0• (ERR 1-Oct-2012)
Copper	100	10	•10• (ERR 1-Feb-2013)

- The acceptable levels for these impurities depends on the material's ultimate use.
- Therefore, drug product manufacturers must determine the acceptable levels used to produce their products.

Elemental Impurities – Limits USP <232>
TO BE PROPOSED

Table 2. Default Concentration Limits for Drug Substances and Excipients

Element	Concentration Limits (µg/g) for Oral Drug Products with a Maximum Daily Dose of ≤10 g/day	Concentration Limits (µg/g) for Parenteral Drug Products with a Maximum Daily Dose of ≤10 g/day	Concentration Limits (µg/g) for Inhalational Drug Products with a Maximum Daily Dose of ≤10 g/day
Cadmium	~~2.5~~ 0.5 1S (USP38)	0.25	~~0.15~~ 0.34 1S (USP38)
Lead	0.5	0.5	0.5
Inorganic arsenic	~~0.15~~ 1.5 1S (USP38)	~~0.15~~ 1.5 1S (USP38)	~~0.15~~ 0.19 1S (USP38)
Inorganic mercury	1.5	0.15	~~0.15~~ 0.12 1S (USP38)
Iridium	10	1.0	0.15
Osmium	10	1.0	0.15
Palladium	10	1.0	~~0.15~~ 0.1 1S (USP38)
Platinum	10	1.0	0.15
Rhodium	10	1.0	0.15
Ruthenium	10	1.0	0.15
Chromium	—[a]	—[a]	~~2.5~~ 0.29 1S (USP38)
Molybdenum	~~10~~ 18 1S (USP38)	~~1.0~~ 9.0 1S (USP38)	~~1.0~~ 0.76 1S (USP38)
Nickel	~~50~~ 60 1S (USP38)	~~5.0~~ 6.0 1S (USP38)	~~0.15~~ 0.60 1S (USP38)
Vanadium	~~10~~ 12 1S (USP38)	~~1.0~~ 1.2 1S (USP38)	~~0.3~~ 0.12 1S (USP38)
Copper	~~100~~ 130 1S (USP38)	~~10~~ 13 1S (USP38)	~~10~~ 1.3 1S (USP38)

[a] Not a safety concern. Will be included in a future informational chapter. 1S (USP38)

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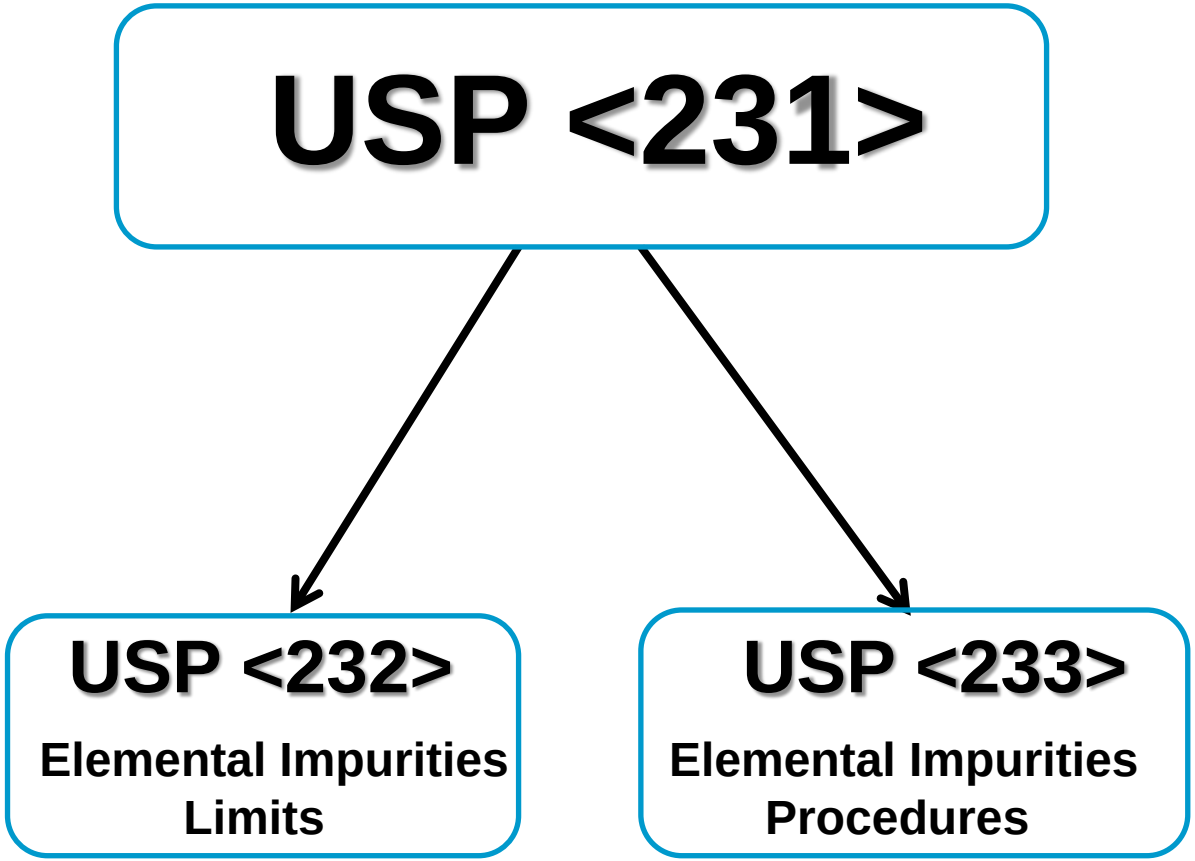

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Elemental Impurities – Procedures USP <233> Detection Techniques

- Two compendial procedures are listed

  Procedure 1 : ICP-OES

  Procedure 2 : ICP-MS

- Alternate procedures may be used. Must be validated and proven equivalent for the purposes of the test.

Agilent's Atomic Spectroscopy 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

Agilent's Atomic Spectroscopy Portfolio

Which Atomic Spectroscopy technique should you choose?

Use the table below to select the right Agilent instrument for your needs.

Criteria	Flame AA	GFAA	MP-AES	ICP-OES	ICP-MS	ICP-QQQ
Measurement range						
> 10%				●		
1-10%	●			●		
1-10000 ppm	●		●	●	●	●
100-1000 ppb	●	●	●	●	●	●
1-100 ppb		●	●	●	●	●
Number of samples						
Few	●	●	●	●	●	●
Several	●		●	●	●	●
Many				●	●	●
Number of Elements per Sample						
Single	●	●	●	●	●	●
Small (2-5)	●	●	●	●	●	●
Medium (5-10)	●		●	●	●	●
Large (> 10)				●	●	●
Sample Matrix						
< 3% solids	●	●	●	●	●	●
3-10%	●	●		●		
> 10%		●		●		

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Elemental Impurities – Procedures USP <233> Sample Preparation

- Neat
  - Direct analysis of unsolvated samples (liquid or solid with alt technique)
- Direct Aqueous Solution
  - Used when sample is soluble in an aqueous solvent
- Direct Organic Solution
  - Used where the sample is soluble in an organic solvent
- Indirect Solution
  - Used when material is not directly soluble in aqueous or organic solvents, for example closed vessel microwave digestion

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Elemental Impurities – Procedures USP <233> Validation: Accuracy, Precision, Specificity

Limit Procedure:

- System suitability must be evaluated prior to any sample analysis (at “J”, accounting for dilution)

- “Limit of Detection”
  - Standard Solution - SRM at the target concentration
  - Spike 1 - Actual sample spiked with SRM at the target concentration (“J”)
  - Spike 2 - Actual sample spiked with SRM at 80% of J
  - Acceptance: Spike 1 solution ≥ standard solution > Spike 2 solution

- Precision
  - Six samples of material under test spiked with SRM for the target analytes
  - Acceptance: Standard deviation NMT 20%

- Specificity
  - “Unequivocal” demonstration that target analytes may be determined in the presence of spectral (ICP-OES), isobaric (ICP-MS), and matrix interferences

Elemental Impurities – Procedures USP <233> Validation: Accuracy, Precision, Specificity

Quantitative Procedure:

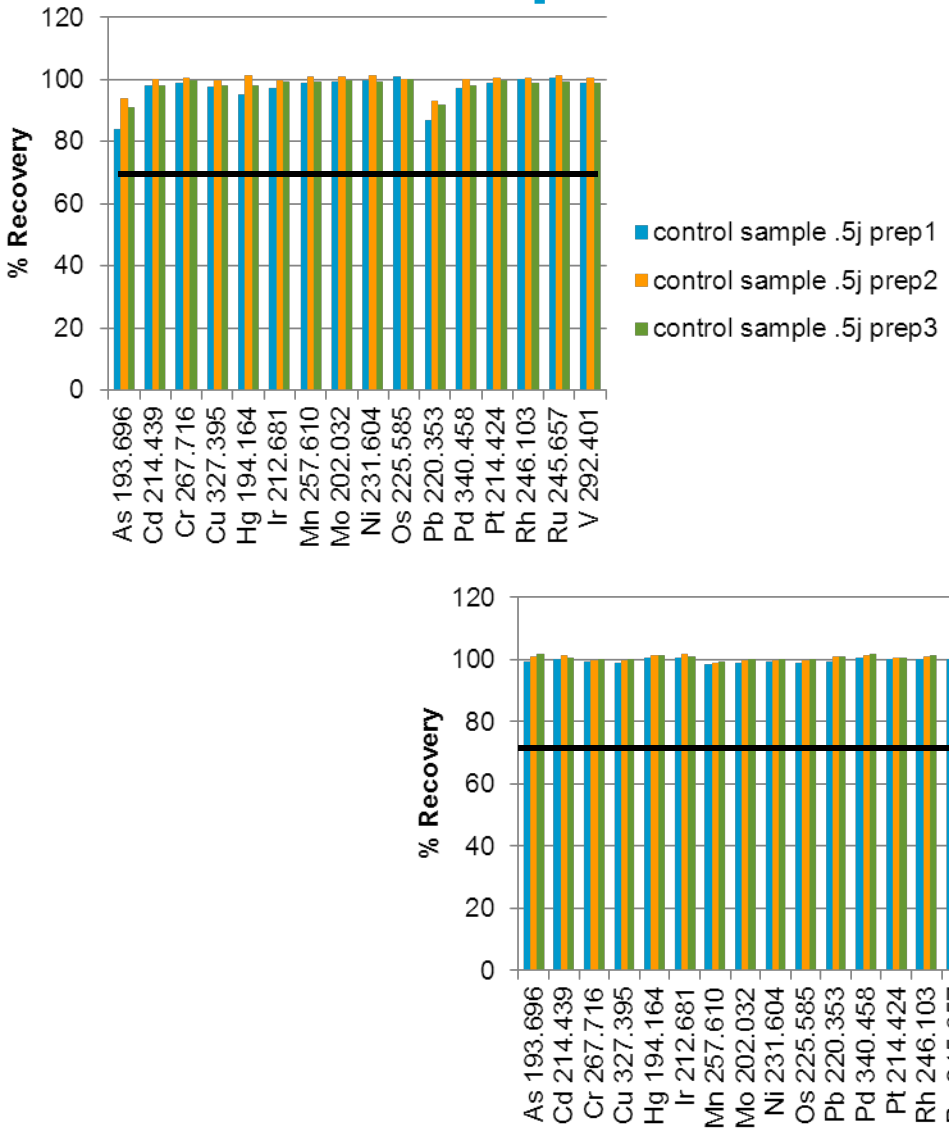
- Accuracy
  - Standard Solution - 3 replicate SRM solutions containing 50%-150% J of the target analytes
  - Test Samples - 3 replicate samples under test spiked with SRM at 50%-150% J
  - Acceptance - 70%-150% spike recovery at each concentration

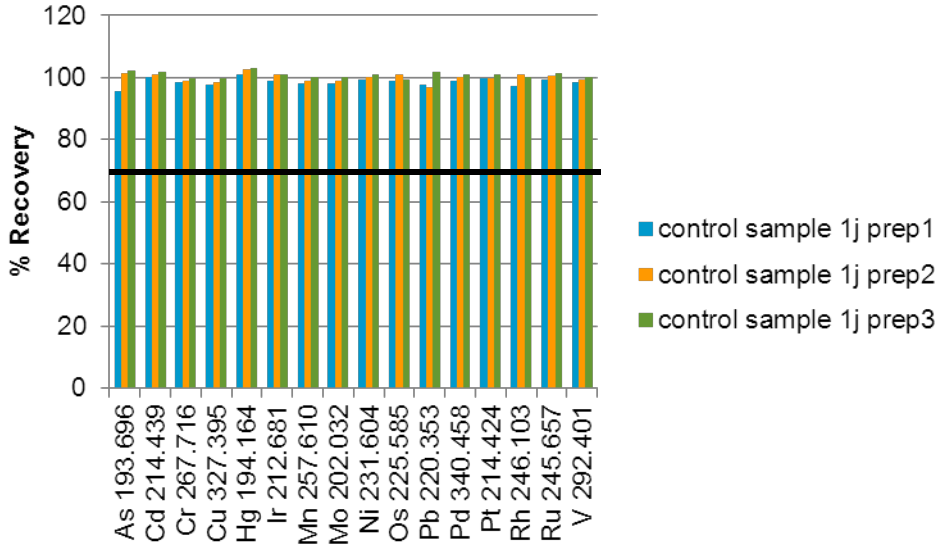
- Precision
  - Test Samples - Six samples spiked with target analytes at J
  - Acceptance - Standard deviation, NMT 20%

- Intermediate precision
  - Repeatability Test - Repeat analysis (choose one of the following)
    - On a different day
    - With a different instrument
    - With a different analyst
  - Acceptance - %RSD, NMT 25% for each target analyte

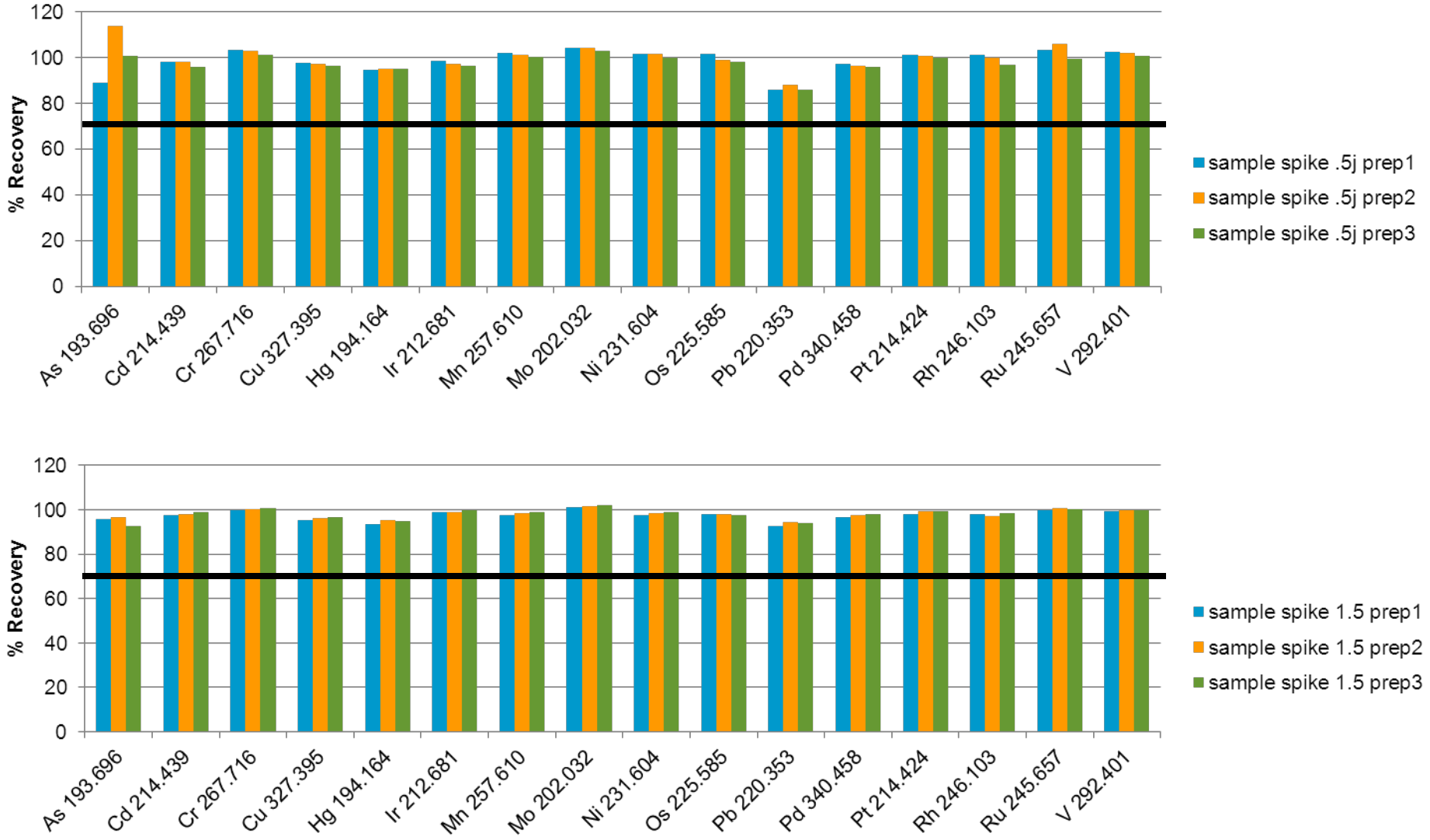
- Specificity
  - False-positive and false-negative check (interference check)

Control Sample Data ICP-OES

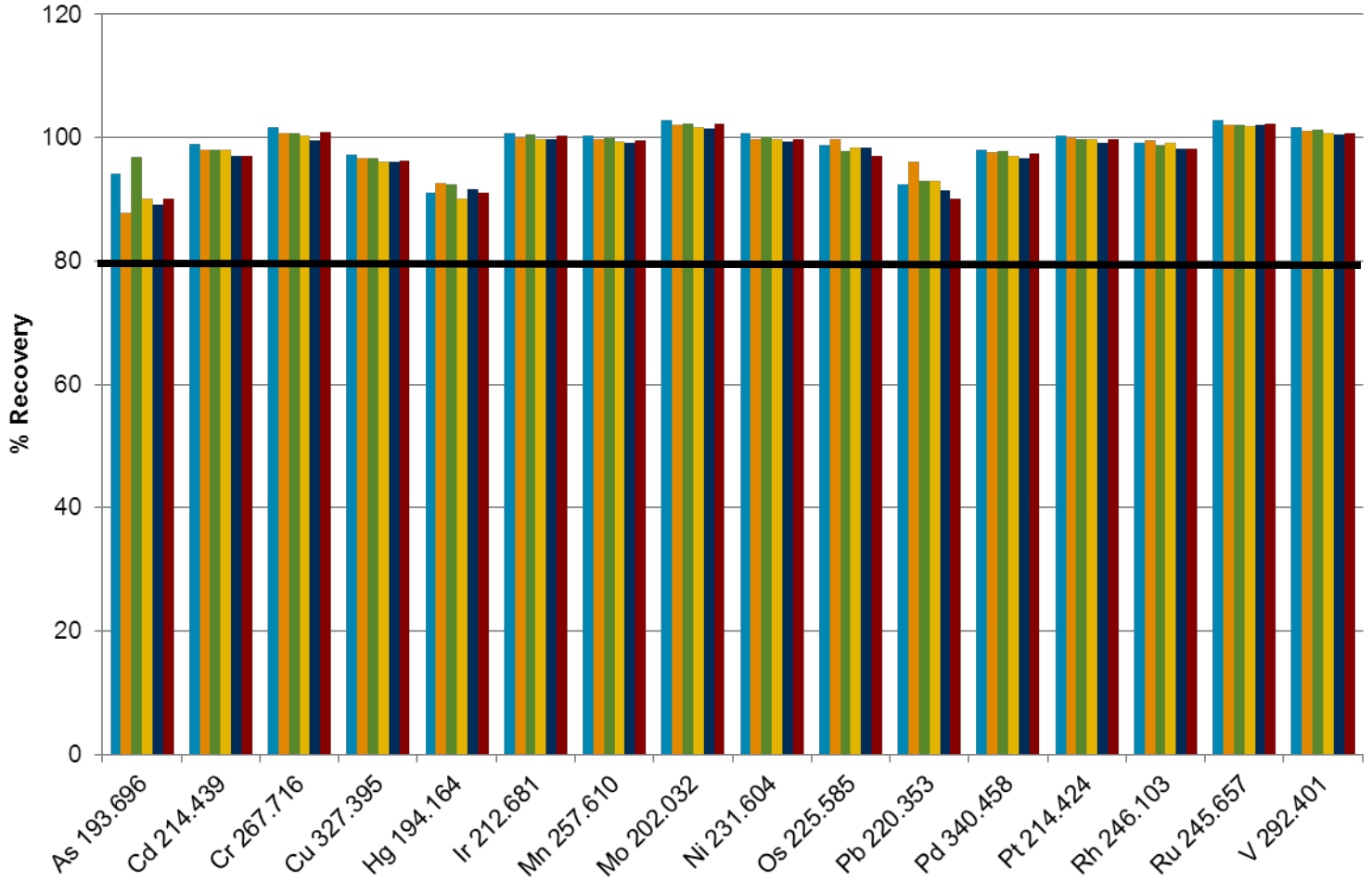




Amoxicillin Sample Spikes ICP-OES

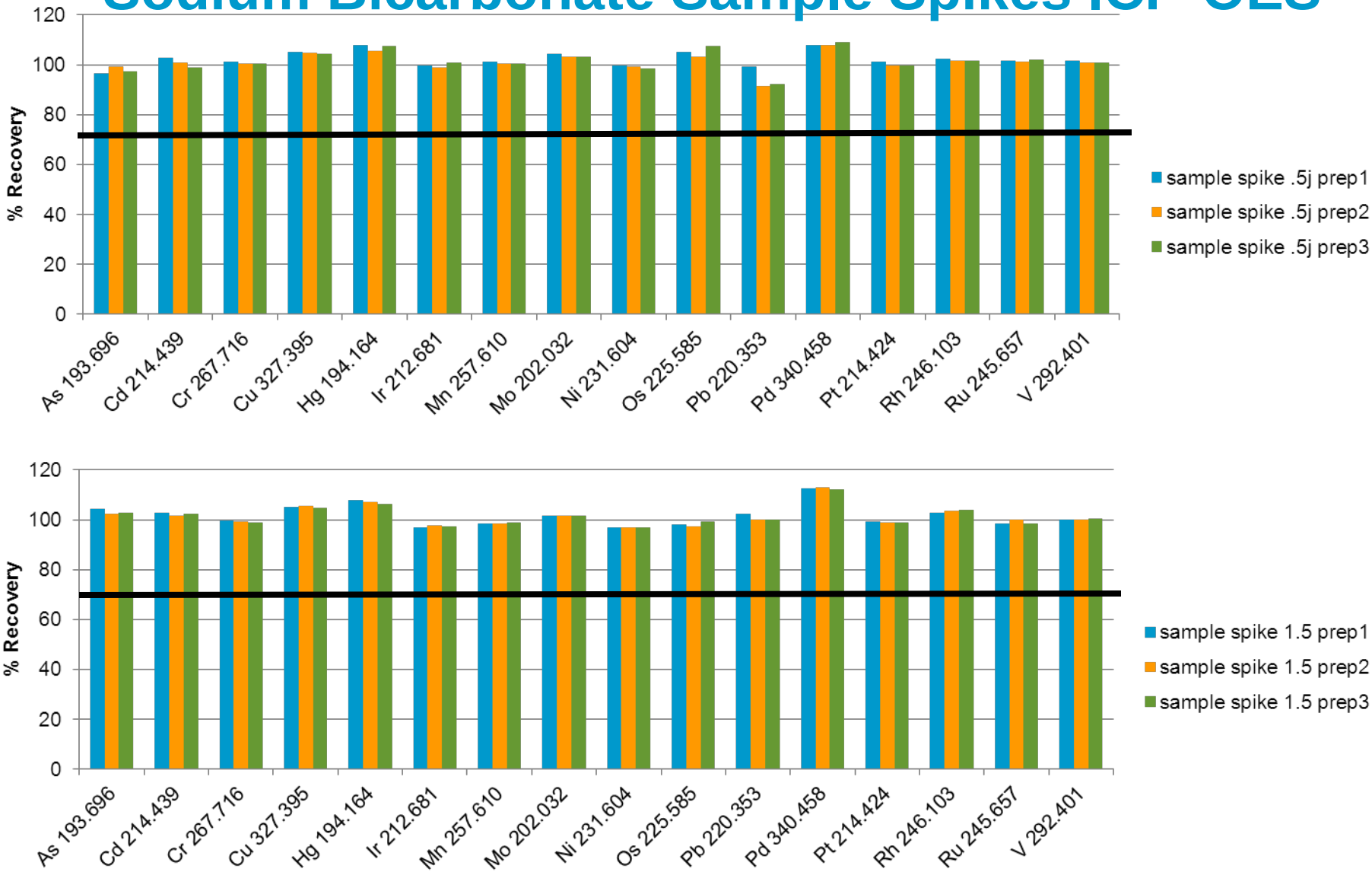


Amoxicillin Repeatability ICP-OES

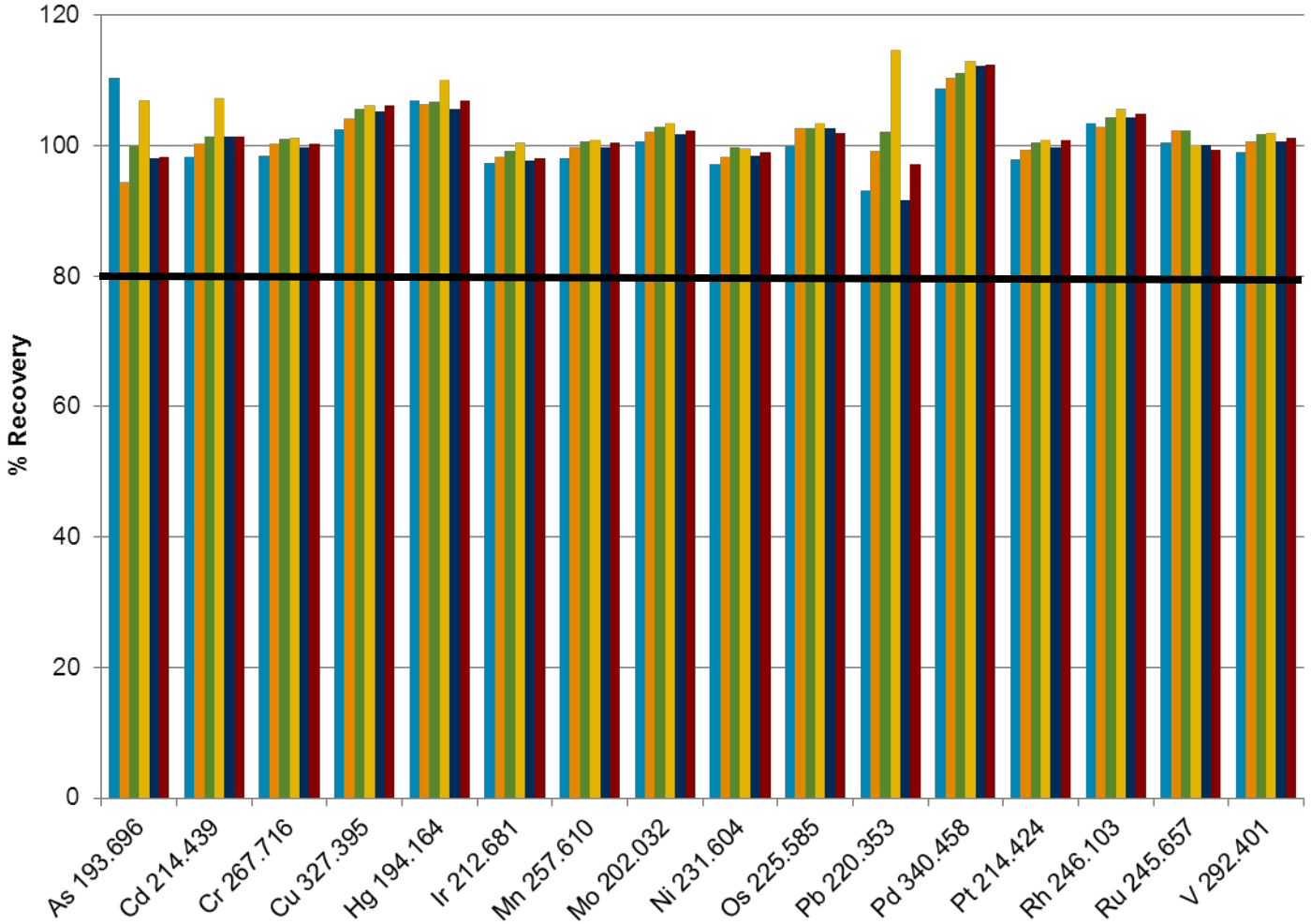


Element	% RSD
As	3.73
Cd	0.77
Cr	0.69
Cu	0.48
Hg	1.07
Ir	0.43
Mn	0.44
Mo	0.47
Ni	0.43
Os	0.96
Pb	2.15
Pd	0.50
Pt	0.40
Rh	0.58
Ru	0.34
V	0.43

Sodium Bicarbonate Sample Spikes ICP-OES

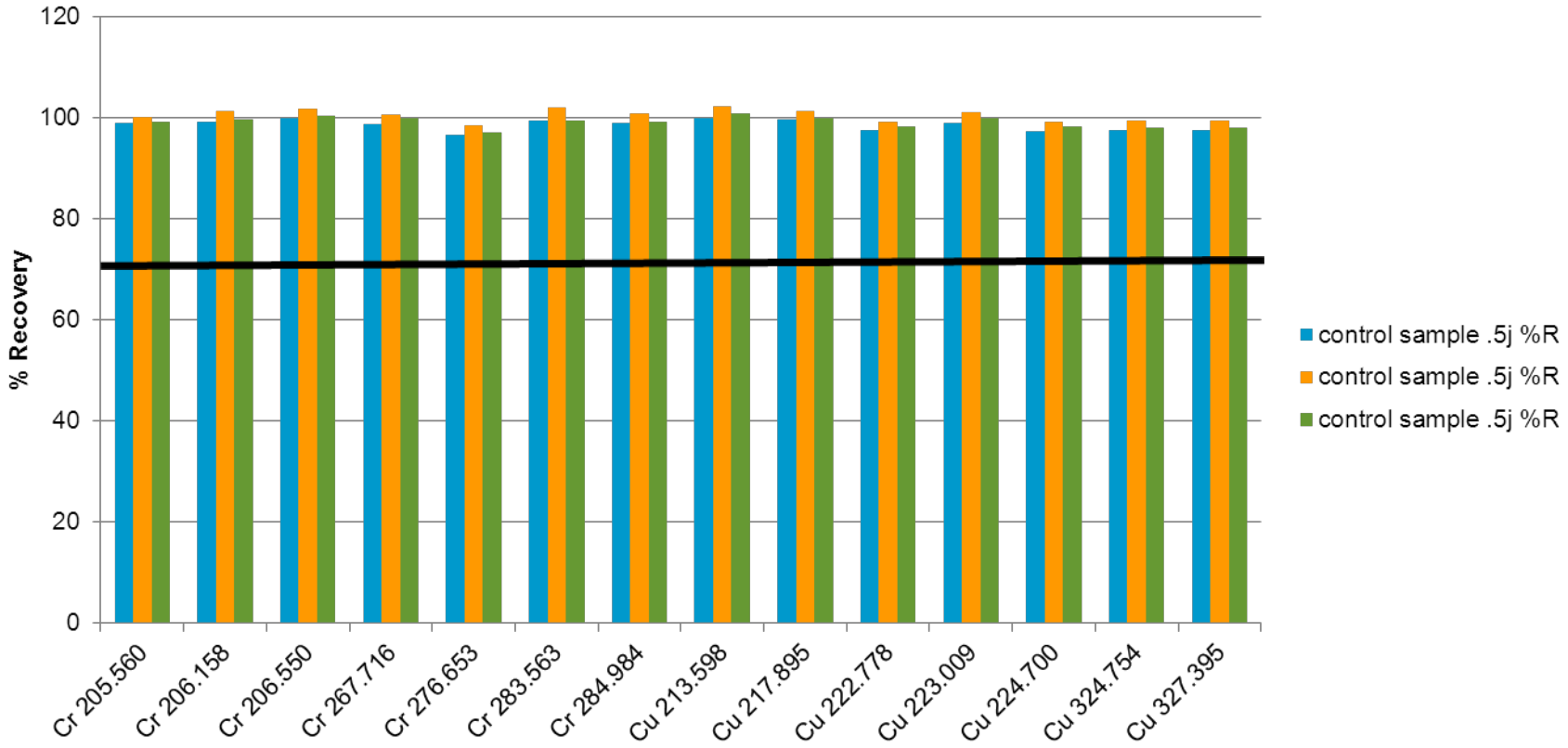


Sodium Bicarbonate Repeatability ICP-OES

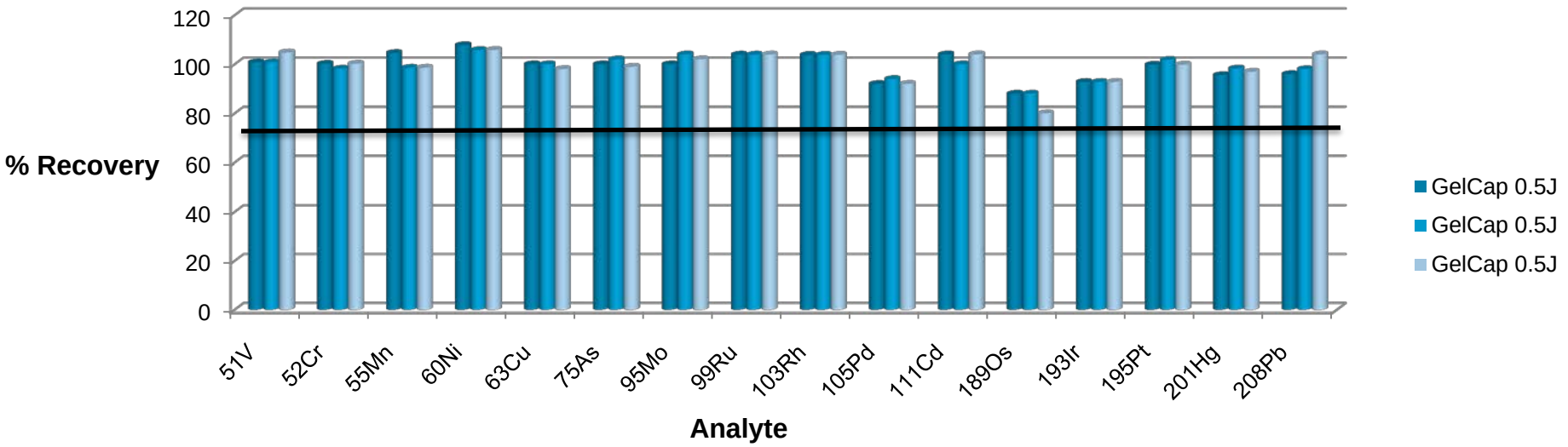


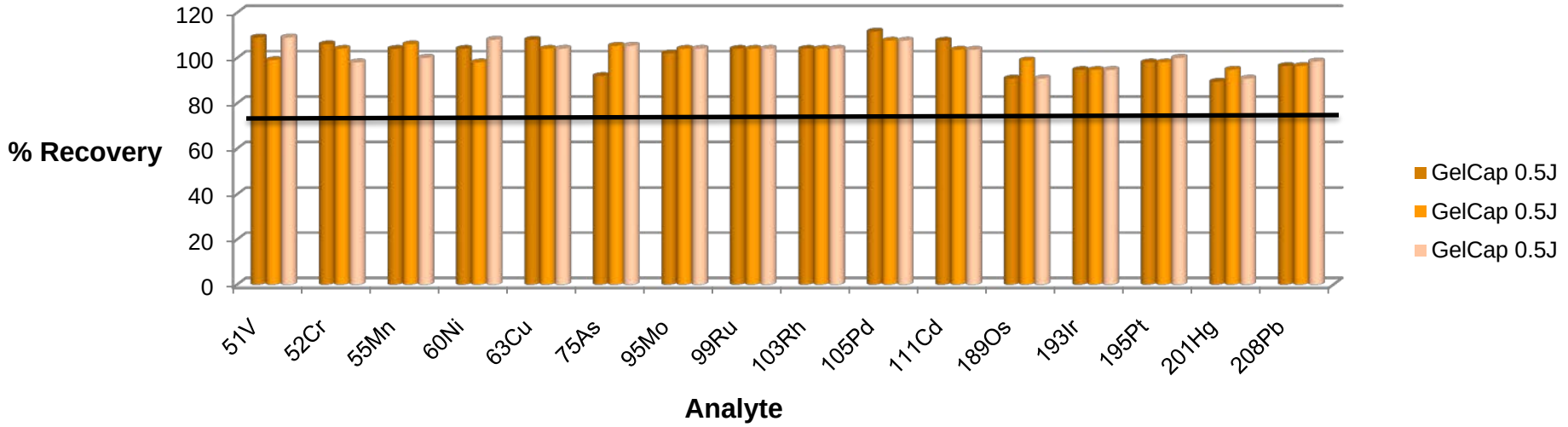
Element	% RSD
As	5.99
Cd	2.96
Cr	0.97
Cu	1.34
Hg	1.40
Ir	1.17
Mn	1.00
Mo	0.95
Ni	0.99
Os	1.19
Pb	8.32
Pd	1.39
Pt	1.18
Rh	0.95
Ru	1.24
V	1.01

Results Confirmation Capability

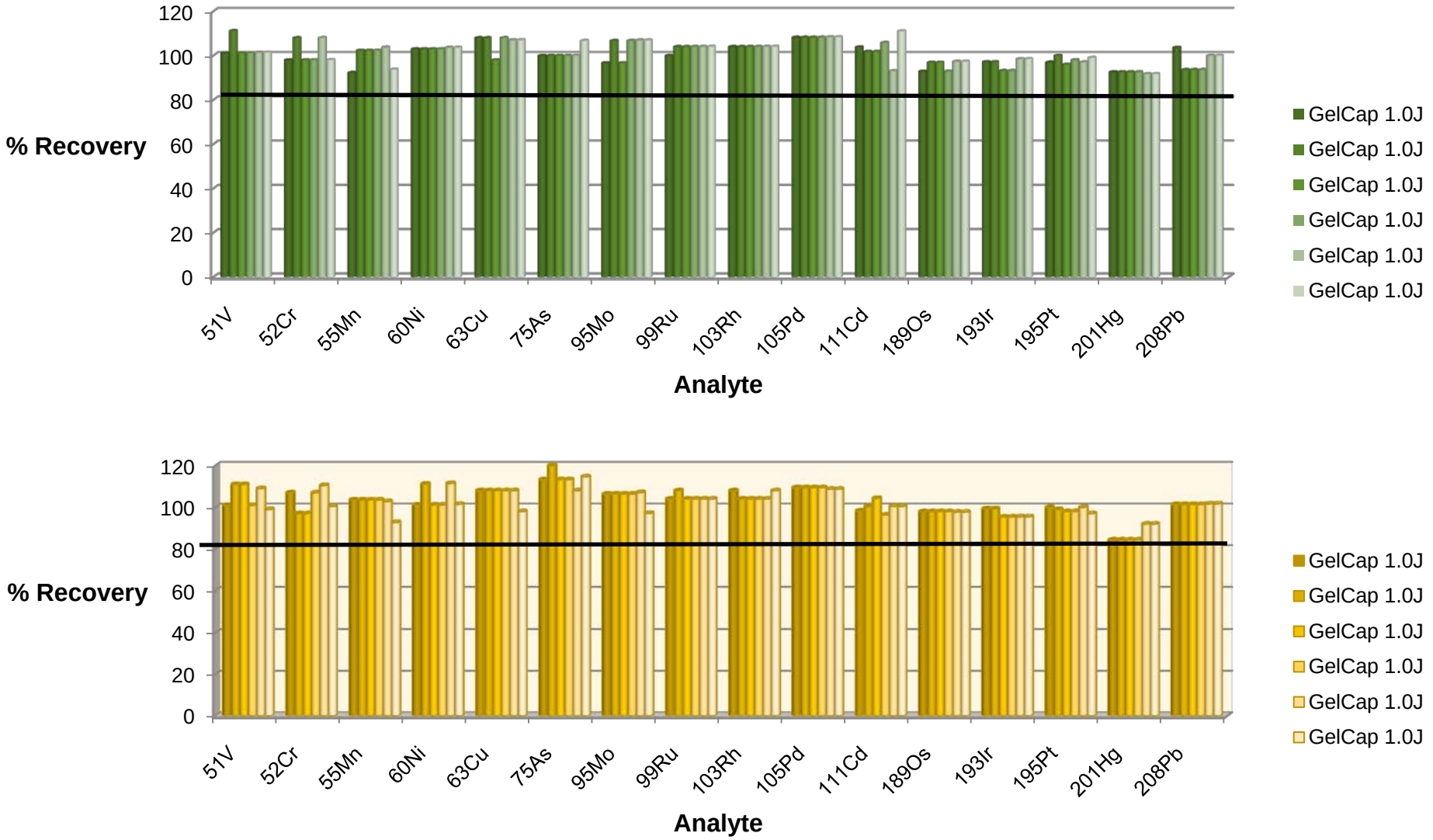


Gelatin Capsules 0.5 J Spike Recovery ICP-MS

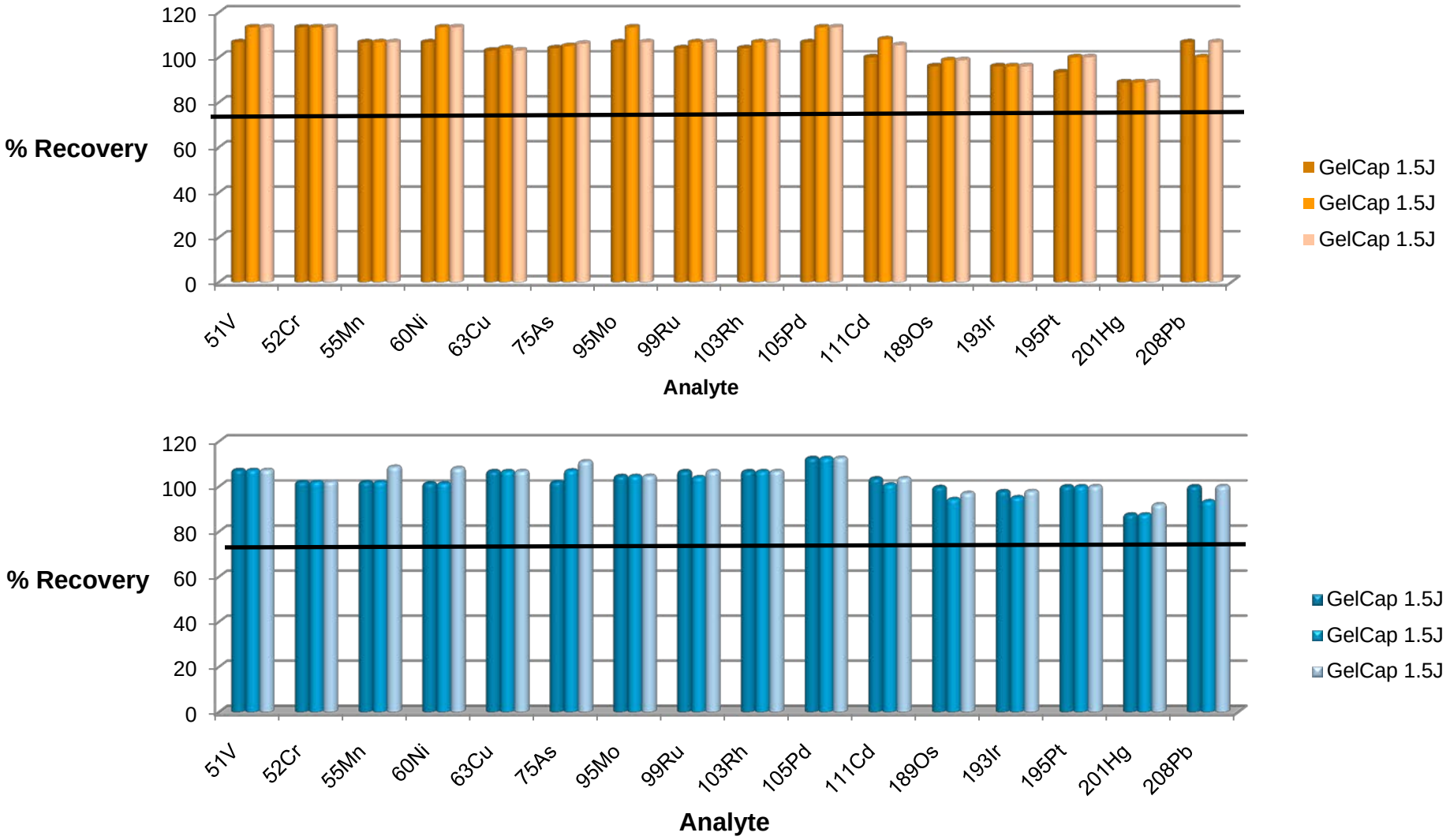




Gelatin Capsules 1.0 J Spike Recovery ICP-MS



Gelatin Capsules 1.5 J Spike Recovery ICP-MS



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Decoding Required Detection Limits and “J” value

Interactive calculator for the drug product analysis option

USP Elemental Impurities Instrument Selector Tool/ J Value Calculator

	FROM <232> Oral Daily Dose PDE ug/day	Dilution Factor as result of digestion procedure	ADJUSTED FOR PREP Required DL ug/day	Maximum Daily Dose grams	ADJUSTED FOR MAX DAILY DOSE Required DL ug/g AKA "J" level	ADJUSTED TO .5 "J" LEVEL Required DL ug/g
Cd	25	50	0.5	1	0.5	0.250
Pb	5	50	0.10	1	0.1	0.050
As	1.5	50	0.03	1	0.03	0.015
Hg	15	50	0.30	1	0.3	0.150

- Example uses route of administration = oral
- 50x dilution factor from digestion (.5g diluted to 25mL)
- Max daily dose = 1 grams

Decoding Required Detection Limits and “J” value

Interactive calculator for the drug product analysis option

USP Elemental Impurities Instrument Selector Tool/ J Value Calculator

	FROM <232> Oral Daily Dose PDE ug/day	Dilution Factor as result of digestion procedure	ADJUSTED FOR PREP Required DL ug/day	Maximum Daily Dose grams	ADJUSTED FOR MAX DAILY DOSE Required DL ug/g AKA "J" level	ADJUSTED TO .5 "J" LEVEL Required DL ug/g
Cd	25	10	2.5	1	2.5	1.250
Pb	5	10	0.50	1	0.5	0.250
As	1.5	10	0.15	1	0.15	0.075
Hg	15	10	1.50	1	1.5	0.750

- Example uses route of administration = oral
- 10x dilution factor from digestion (1g diluted to 10mL)
- Max daily dose = 1 grams

Decoding Required Detection Limits and “J” value

Interactive calculator for the drug product analysis option

USP Elemental Impurities Instrument Selector Tool/ J Value Calculator

	FROM <232> Oral Daily Dose PDE ug/day	Dilution Factor as result of digestion procedure	ADJUSTED FOR PREP Required DL ug/day	Maximum Daily Dose grams	ADJUSTED FOR MAX DAILY DOSE Required DL ug/g AKA "J" level	ADJUSTED TO .5 "J" LEVEL Required DL ug/g
Cd	25	10	2.5	2.5	1	0.500
Pb	5	10	0.50	2.5	0.2	0.100
As	1.5	10	0.15	2.5	0.06	0.03
Hg	15	10	1.50	2.5	0.6	0.300

- Example uses route of administration = oral
- 10x dilution factor from digestion (1g diluted to 10mL)
- Max daily dose = 2.5 grams

ICP-OES or ICP-MS?

-Detection limit suitability

  -Exposure Factor and Daily Dose

  -Dilution from Digestion

-Speciation capability desired?

  -ICP-MS

-Overall organizational needs

  -Excipient, API, or drug product manufacturer

  -Static production facility or dynamic QA or R&D lab

-Budget

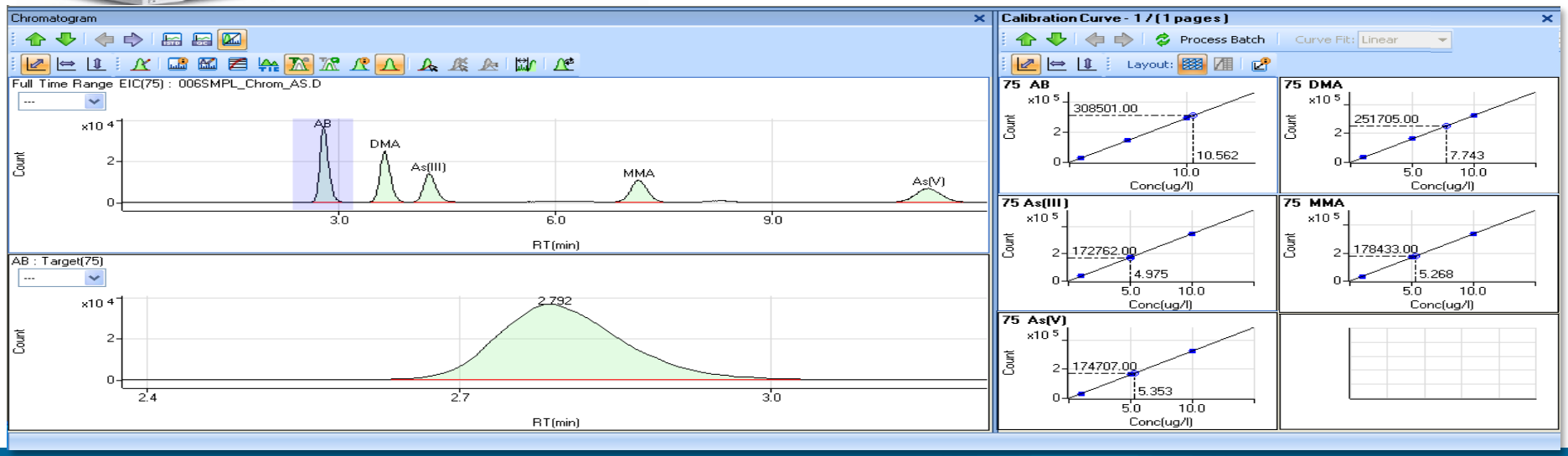
Speciation Analysis

Application as related to <232>

- The elemental impurity daily dose PDE limit for arsenic in drug products as listed in <232> is for inorganic arsenic
- Without speciation capability the result obtained for arsenic is total arsenic
- If the total arsenic result for the drug product being analyzed exceeds the inorganic arsenic limit a speciation analysis may be performed
- If speciation analysis concludes the inorganic arsenic component is less than the required limit the drug product is in compliance

Elemental Speciation Analysis

Agilent 7700x offers easy coupling to (and direct control of) Agilent LC systems, providing turn-key speciation to support the requirement to determine “inorganic As” if total As level exceed limit.



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ICP-OES and ICP-MS Compliance with 21 CFR Part 11

Agilent's complete solution for Compliance ensures:

- Data security
  - Secure central storage of data
  - User access limited to authorized individuals
- Data integrity
  - Automatic data storage and versioning
  - Full version control for ALL relevant data including original result reports
  - Integrated archival and long-term storage in a content management system
- Data traceability
  - Automatic user-independent audit trail
  - Electronic signatures

Full support of all requirements mandated by 21 CFR Part 11 in closed system

- Validation (IQ/OQ) is also available for both ICP-OES and ICP-MS

Outline, USP <232> <233>

- USP Chapter <231>
- Chapter <232> Limits
- Chapter <233> Procedures
  - ICP-OES and ICP-MS
  - Validation
  - Digestion
  - J Value Calculator

- Electronic Records Compliance and 21CFR
- **Revised Implementation Timeframe**

Updated Revision Timeline
Posted October 25, 2013

Background:

On September 23, 2013, the Elemental Impurities Expert Panel met to review the Step 2 limits of the ICH Q3D Elemental Impurities Working Group, which were released in June 2013. At its meeting the Expert Panel recommended revisions to General Chapter <232> *Elemental Impurities—Limits* to partially align with the ICH Q3D limits. In addition, the Expert Panel recommended other minor editorial changes to both General Chapter <232> and General Chapter <233> *Elemental Impurities—Procedures*. On October 16-17, 2013 the General Chapters—Chemical Analysis Expert Committee met and endorsed the recommendations of the Expert Panel.

These revisions will be proposed according to the timeline below.

Revision Timeline

- **January 1, 2014:** USP pre-publishes on the USP Elemental Impurities Key Issues web page the proposed revisions to <232> and <233>. Subject to further discussion with the Council of Experts Executive Committee (which is responsible for General Notices), with input from the Elemental Impurities Implementation Advisory Group, USP also anticipates posting at this time an announcement regarding the date of implementation of <232> and <233> as specified in General Notices section 5.60.30.

Revision Timeline

- **March 1, 2014:** USP publishes the proposed revisions to <232> and <233> in *PF* 40(2) [March-April 2014] for public comment. Comments will be accepted only on the proposed revisions to the general chapters.
- **May 31, 2014:** The 90-day comment period ends (comment period is from March 1, 2014 through May 31, 2014).
- **June 2014:** The Expert Panel considers comments received on the proposed revisions and also reviews ICH Q3D Step 4 limits, which are expected in June 2014.

Revision Timeline

- **July-August 2014:** Expert Panel meets to make recommendations regarding any final revisions to the general chapters.
- **September 2014:** General Chapters—Chemical Analysis Expert Committee meets to review Elemental Impurities Expert Panel recommendations and consider final revisions to the general chapters.

Revision Timeline

- **October 2014:** USP pre-posts the approved revised General Chapters <232> and <233>, the Commentary, and a notice about the removal of General Chapter <231> on the USP Elemental Impurities Key Issues web page.
- **February 2015:** The approved revised General Chapters are published in the *USP 38-NF 33 First Supplement*, which publishes in February 2015 and becomes official August 1, 2015.

Note: USP anticipates that the implementation date for the General Chapters as elaborated in section 5.60.30 of General Notices is expected to be on or after the official date of the revised General Chapters.

Latest update from Dec 27, 2013

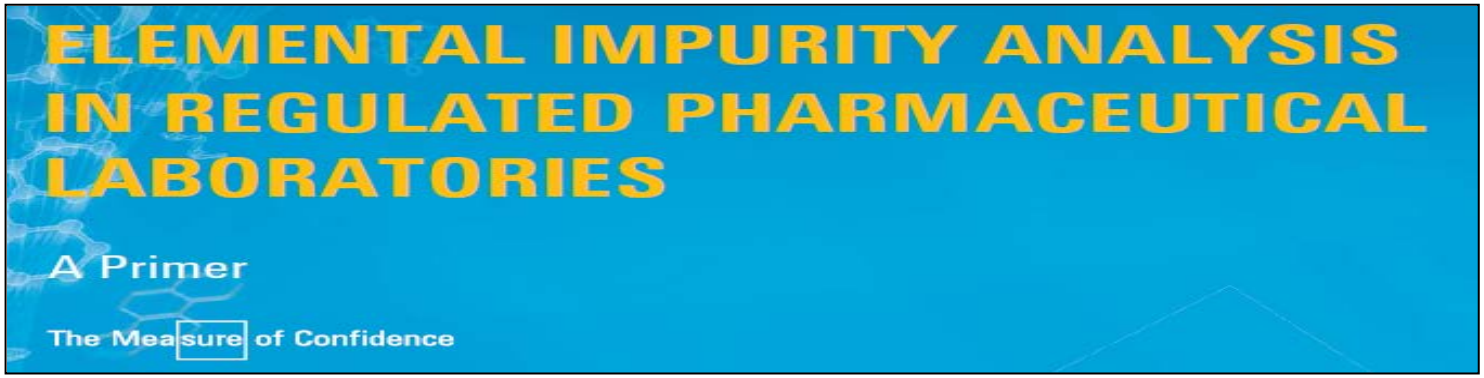
Revision Timeline

- **December 27, 2013:** USP posts the final version of General Notices section 5.60.30, which includes the date of applicability of <232> and <2232>. USP also pre-publishes on the USP Elemental Impurities Key Issues web page the proposed revisions to <232> and <233>.
- **March 1, 2014:** USP publishes the proposed revisions to <232> and <233> in *PF* 40(2) [March-April 2014] for public comment. Comments will be accepted only on the proposed revisions to the general chapters.
- **May 31, 2014:** The 90-day comment period ends (comment period is from March 1, 2014 through May 31, 2014).
- **May 2014:** The General Chapters—Chemical Analysis Expert Committee ballots on the removal of General Chapter <231> *Heavy Metals*. Note that the removal of <231> was previously proposed in *PF* 39(1) [January-February 2013] and will specify an

official date that aligns with the applicability of General Chapters <232> and <2232>, which is specified in General Notices section 5.60.30 as December 1, 2015.

- **June 2014:** The Expert Panel considers comments received on the proposed revisions and also reviews ICH Q3D Step 4 limits, which are expected in June 2014. The revised General Notices appears in the *Second Supplement to USP 37-NF 32* with an official date of December 1, 2015.
- **July-August 2014:** The Expert Panel meets to make recommendations regarding any final revisions to revised General Chapters <232> and <233>.
- **September 2014:** General Chapters—Chemical Analysis Expert Committee meets to review Elemental Impurities Expert Panel recommendations and consider final revisions to revised General Chapters <232> and <233>.
- **October 2014:** The General Chapters—Chemical Analysis Expert Committee ballots on the revised General Chapters <232> and <233>.
- **October 2014:** USP pre-posts the approved revised General Chapters <232> and <233>, the Commentary, and a notice about the removal of General Chapter <231> on the USP Elemental Impurities Key Issues web page.
- **November 2014:** All references to <231> in individual *USP 38-NF 33* monographs are removed in with official dates of December 1, 2015, which align with the applicability of <232> and <233> via General Notices 5.60.30.
- **February 2015:** The approved revised General Chapters <232> and <233> are published in the *First Supplement to USP 38-NF 33*, which publishes in February 2015 and becomes official August 1, 2015.
- **August 1, 2015:** The *First Supplement to USP 38-NF 33* becomes official, including revised General Chapters <232> and <233>
- **December 1, 2015:** General Notices section 5.60.30 becomes official, making <232> and <2232> applicable to drug product monographs. The *Second Supplement* becomes official, including the omission of General Chapter <231>.

Additional Support Literature Available from Agilent



Validating the Agilent 7700x ICP-MS for the determination of elemental impurities in pharmaceutical ingredients according to draft USP general chapters <232> / <233>

Application note

Pharmaceutical

Proposed new USP general chapters <232> and <233> for elemental impurities: The application of ICP-MS for pharmaceutical analysis

White paper

THANK YOU

QUESTIONS?