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ANALYTICAL METHOD FOR THE DETERMINATION OF ICH Q3D ELEMENTAL IMPURITIES (CLASS 1, 2A, 2B, 3 & 4) BY INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY (ICP-MS) IN CYTIDINE, URIDINE, L-ARGININE HCl, AND L-GLUTAMINE

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1. PURPOSE:

- 1.1. To provide a procedure for the assessment of Elemental Impurities via the NexION 350X S/N 85VN5093001 ICP-MS. This procedure was assessed as a full quantitative option-1 procedure as per validation reports, BSI-RPT-0800 v1.0 and BSI-RPT-0801 v1.0, and follows the validation parameters for quantitation procedures as outlined in USP <233>.
- 1.2. Elements under validated for this test method are as follows:
 - 1.2.1. Class 1: Hg, As, Cd, and Pb
 - 1.2.2. Class 2A: Co, V, and Ni
 - 1.2.3. Class 2B: Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, and Pt
 - 1.2.4. Class 3: Li, Sb, Ba, Mo, Cu, Cr, and Sn
 - 1.2.5. Class 4: Fe, Mn, Zn, Ca, K, Mg, and Na

2. SCOPE:

- 2.1. Applies to Cytidine, Uridine, L-Arginine HCl, and L-Glutamine products manufactured at BioSpectra.
- 2.2. Applies to the NexION 350X S/N 85VN5093001 ICP-MS located in the Quality Control (QC) Laboratory at the BioSpectra Bangor, PA facility.

3. RESPONSIBILITIES:

- 3.1. The Laboratory Technology Manager, or other qualified designated individual, is responsible for the control, implementation, training, and maintenance of this method.
- 3.2. The QC Staff is responsible for complying with the requirements of this procedure
- 3.3. If any abnormalities are determined during routine use of the ICP-MS or during calibration, the QC Managers shall be promptly notified. If necessary, the ICP-MS will be serviced and recalibrated by Perkin Elmer before being approved for use.

4. REFERENCES:

- 4.1. BSI-PRL-0419, Determination of ICH Q3D Elemental Impurities by ICP-MS in L-Arginine HCl and L-Glutamine
- 4.2. BSI-PRL-0474, Analytical Method Validation Protocol: Determination of ICH Q3D Elemental Impurities (Class 1, 2A, 2B, 3, & 4) by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) in Cytidine and Uridine
- 4.3. BSI-RPT-0800, Analytical Validation Report: Elemental Impurities by ICP-MS in Cytidine and Uridine
- 4.4. BSI-RPT-0801, Analytical Method Validation Report: L-Arginine HCl and L-Glutamine
- 4.5. BSI-SOP-0303, NexION 350X ICP-MS SOP
- 4.6. BSI-SOP-0304, NexION 350X ICP-MS Care and Maintenance SOP
- 4.7. ICH Guideline for Elemental Impurities Q3D Current
- 4.8. NexION Operation with Syngistix Software Guide
- 4.9. USP <232>, Elemental Impurities- Limits
- 4.10. USP <233> Elemental Impurities- Procedures
- 4.11. USP <730> Plasma Spectrochemistry
- 4.12. USP <1730> Plasma Spectrochemistry—Theory and Practice

TABLE 1: LIMITS FOR APPLICABLE PRODUCTS (10 GRAM/DAY PATIENT EXPOSURE)

Elements	ICH Class	Parenteral PDE Limits (µg/day)	0.3J LOQ (µg/g) in sample	0.5J Target (µg/g) in sample	1.0J Target (µg/g) in sample	1.5J Target (µg/g) in sample
As	1	15	0.45	0.75	1.5	2.25
Cd	1	2.0	0.06	0.10	0.20	0.30
Hg	1	3.0	0.09	0.15	0.30	0.45
Pb	1	5.0	0.15	0.25	0.50	0.75
Co	2A	5.0	0.15	0.25	0.50	0.75
Ni	2A	20	0.60	1.0	2.0	3.0
V	2A	10	0.30	0.50	1.0	1.5
Tl	2B	8.0	0.24	0.40	0.80	1.2
Se	2B	80	2.4	4.0	8.0	12
Ag	2B	10	0.30	0.50	1.0	1.5
Au	2B	100	3.0	5.0	10	15
Pd	2B	10	0.30	0.50	1.0	1.5
Ir	2B	10	0.30	0.50	1.0	1.5
Os	2B	10	0.30	0.50	1.0	1.5
Pt ²	2B	10	0.30	0.50	1.0	1.5
Rh	2B	10	0.30	0.50	1.0	1.5
Ru	2B	10	0.30	0.50	1.0	1.5
Ba	3	700	21	35	70	105
Sb	3	90	2.7	4.5	9.0	13.5
Li	3	250	7.5	12.5	25	37.5
Mo	3	¹ 150	4.5	7.5	15	22.5
Cu	3	¹ 50	1.5	2.5	5.0	7.5
Sn	3	600	18	30	60	90
Cr	3	¹ 50	1.5	2.5	5.0	7.5
Fe	4	¹ 50	1.5	2.5	5.0	7.5
Mn	4	¹ 50	1.5	2.5	5.0	7.5
Zn	4	¹ 50	1.5	2.5	5.0	7.5
Ca	4	¹ 500	15	25	50	75
K	4	¹ 500	15	25	50	75
Mg	4	¹ 50	1.5	2.5	5.0	7.5
Na	4	¹ 500	15	25	50	75

¹PDE calculated based on manufacturer specification or derived from other internal product specifications.

²LOQ is 1.0J for cytidine products.

5. MATERIALS AND EQUIPMENT:

- 5.1. Equipment
 - 5.1.1. Analytical Balance
 - 5.1.2. NexION 350X ICP-MS S/N 85VN5093001, or other qualified ICP-MS
- 5.2. Reagents
 - 5.2.1. Nitric Acid, Trace metals grade or equivalent
 - 5.2.2. Hydrochloric Acid, Trace metals grade or equivalent
 - 5.2.3. Sulfuric acid, Trace metals grade or equivalent
 - 5.2.4. Deionized (DI) water (Type 1 Ultrapure)
 - 5.2.5. Thiourea, 99+ % grade
 - 5.2.6. NexION Setup Solution
 - 5.2.7. NexION KED Setup Solution, or equivalent preparation
- 5.3. Consumable Supplies
 - 5.3.1. SCP Digitubes® 15 mL, 50 mL, and 100 mL
 - 5.3.2. Pipette Tips of various sizes
 - 5.3.3. SiliaPrep MB SPE Cartridges, Silica-Based AMPA
- 5.4. Personnel
 - 5.4.1. All personnel that executed the protocol are trained on ICP-MS or are considered Subject Matter Experts. This test method will be assigned a mark as read training to QC analysts involved with the execution.

TABLE 2: REFERENCE STANDARDS

Identification ¹	Manufacturer	Concentrations / Elements
Pharma-CAL Standard Parenteral STD# 1 IA 140-131-201	SCP Science	Ag (10 µg/mL), As (15 µg/mL), Cd (2 µg/mL), Co (5 µg/mL), Hg (3 µg/mL), Ni (20 µg/mL), Pb (5 µg/mL), Se (80 µg/mL), Tl (8 µg/mL), V (10 µg/mL)
USP232/ICH Q3D Parenteral STD# 2 IA 140-131-211	SCP Science	Au (100 µg/mL); Ir, Os, Pd, Pt, Rh, & Ru (10 µg/mL)
Pharma-CAL Custom Standard Parenteral STD# 3 AQ0-150-191	SCP Science	Ba (700 µg/mL), Cr (50 µg/mL), Cu (50 µg/mL), Fe (50 µg/mL) Li (250 µg/mL), Mn (50 µg/mL), Mo (150 µg/mL), Sb (90 µg/mL), Sn (600 µg/mL), Zn (50 µg/mL), Ca (500 µg/mL), K (500 µg/mL)
Sodium Stock Standard	SCP Science	Na (1,000 µg/mL)
Magnesium Stock Standard	SCP Science	Mg (1,000 µg/mL)
Pharma-CAL Custom Standard AQ0-086-125 (Internal Standard)	SCP Science	Be, Sc, Y, Re (10 µg/mL); Te (25 µg/mL); Ge, Tb, Bi (5 µg/mL)

¹ Additional standards/custom standards can be used as long as the concentration remains the same in final preparations.

6. PROCEDURE:

- 6.1. All standards will be prepared volumetrically from stock solutions purchased from certified vendors. If the vendor supplied stock standard is within 2% of the nominal value as per the certificate of analysis, then the nominal value will be used to calculate the concentration of the standard. If the stock standard certificate of analysis value is greater than or less than 2% of the nominal value, then the certificate of analysis value will be used for the stock standard concentration.
- 6.2. Acid Digestion Mix
 - [2:1] Nitric Acid (HNO_3): Sulfuric Acid (H_2SO_4)
 - 6.2.1. Caution: Combining nitric acid and sulfuric acid generates excessive heat. Never seal cap tightly before solution has completely cooled.
 - 6.2.2. To prepare, add 50 mL of nitric acid to a 100 mL Digitube® and then slowly add 25 mL of sulfuric acid. Solution can be placed in a cold-water bath to aid cooling.
 - 6.2.2.1. Scale as necessary for use (Prepare same day).
- 6.3. Internal Standard/Complexing Solution
 - 6.3.1. Weigh approximately 1.0 gram of Thiourea into a 50 mL Digitube®
 - 6.3.2. Add approximately 20 mL of deionized water and mix to dissolve.
 - 6.3.3. Filter solution through a SiliaPrep Cation Solid Phase Extraction (SPE) cartridge into a separate 50 mL digitube.
 - 6.3.4. Add 2.5 mL of Internal Standard Intermediate followed by 25 mL of hydrochloric acid.
 - 6.3.5. Dilute to a final volume of 50 mL with deionized water and mix well.
 - 6.3.6. Scale proportionally as needed for use.
- 6.4. 2% Thiourea Solution
 - 6.4.1. Weigh approximately 1.0 gram of Thiourea into a 50 mL Digitube®.
 - 6.4.2. Add approximately 20 mL of deionized water and mix to dissolve.
 - 6.4.3. Filter solution through a SiliaPrep Cation Solid Phase Extraction (SPE) cartridge into a separate 50 mL digitube.
 - 6.4.4. Dilute to a final volume of 50 mL with deionized water and mix well.
 - 6.4.5. Scale proportionally as needed for use.

6.5. Intermediate Standard Preparation

6.5.1. Prepare a standard solution containing the elements listed in Table 3, using the standards STD#1 IA, STD#2 IA, STD#3 and additional single source stock standards.

6.5.2. Prepare by adding stock standards to a 15 mL Digitube®.

6.5.3. Add DI Water to approximately 8 mL and add hydrochloric acid (HCl).

6.5.4. Dilute to volume using DI Water.

6.5.5. Do not allow stock standards to contact concentrated acids while preparing solutions.

TABLE 3: INTERMEDIATE STANDARD

Identification	Element	Stock Identification	Amount Added (mL)	HCl (mL)	Final Volume (mL)	Final Concentration (µg/mL)
Intermediate Standard	As	STD# 1 IA 140-131-201	1.0	1.0	10.0	1.5
	Cd					0.20
	Hg					0.30
	Pb					0.50
	Co					0.50
	Ni					2.0
	V					1.0
	Tl					0.80
	Se					8.0
	Ag					1.0
	Au	STD# 2 IA 140-131-211	1.0			10
	Pd					1.0
	Ir					1.0
	Os					1.0
	Pt					1.0
	Rh					1.0
	Ru					1.0
	Ba	STD# 3 AQ0-150-191	1.0			70
	Sb					9.0
	Li					25
	Mo					15
	Cu					5.0
	Sn					60
	Cr					5.0
	Fe					5.0
	Mn					5.0
	Zn					5.0
	Ca					50
	K					50
	Mg	Mg 1,000 µg/mL	0.050			5.0
	Na	Na 1,000 µg/mL	0.500			50

6.6. 0.5J Calibration Standard Preparation

- 6.6.1. Prepare a solution containing the elements listed in Table 4 below in 5.0% HNO₃, 2.5% H₂SO₄, 2.0% HCl and 0.04% (400 µg/mL) Thiourea with Be, Sc, Y, Re, Te, Ge, Tb, and Bi internal standards.
- 6.6.2. Add 0.050 mL of intermediate standard to separate 50 mL Digitube[®] followed by addition of approximately 35 mL of deionized water.
- 6.6.3. Add 0.500 mL of Hydrochloric acid (HCl) and 3.75 mL of Acid Mixture then dilute to 45 mL using deionized water.
- 6.6.4. Add 1.0 mL of internal standard/complexing solution and dilute to volume using deionized water. (Prepare fresh each time before analysis)

TABLE 4: 0.5J CALIBRATION STANDARD

Identification	Element	Intermediate Standard (mL)	HCl (mL)	Acid Mix (mL)	Internal Standard/Complexing Solution (mL)	Final Volume (mL)	Final Concentration (µg/L)
0.5J Calibration Standard	As	0.050	0.500	3.75	1.0	50	1.5
	Cd						0.20
	Hg						0.30
	Pb						0.50
	Co						0.50
	Ni						2.0
	V						1.0
	Tl						0.80
	Se						8.0
	Ag						1.0
	Au						10
	Pd						1.0
	Ir						1.0
	Os						1.0
	Pt						1.0
	Rh						1.0
	Ru						1.0
	Ba						70
	Sb						9.0
	Li						25
	Mo						15
	Cu						5.0
	Sn						60
	Cr						5.0
	Fe						5.0
	Mn						5.0
	Zn						5.0
	Ca						50
	K						50
	Mg						5.0
	Na						50

6.7. 1.5J Calibration Standard Preparation

- 6.7.1. Prepare a solution containing the elements listed in Table 5 below in 5.0% HNO₃, 2.5% H₂SO₄, 2.0% HCl and 0.04% (400 µg/mL) Thiourea with Be, Sc, Y, Re, Te, Ge, Tb, and Bi internal standards.
- 6.7.2. Add 0.150 mL of intermediate standard to separate 50 mL Digitube® followed by addition of approximately 35 mL of deionized water.
- 6.7.3. Add 0.500 mL of Hydrochloric acid (HCl) and 3.75 mL of Acid Mixture then dilute to 45 mL using deionized water.
- 6.7.4. Add 1.0 mL of internal standard/complexing solution and dilute to volume using deionized water. (Prepare fresh each time before analysis)

TABLE 5: 1.5J CALIBRATION STANDARD

Identification	Element	Intermediate Standard (mL)	HCl (mL)	Acid Mix (mL)	Internal Standard/Complexing Solution (mL)	Final Volume(mL)	Final Concentration (µg/L)
1.5J Calibration Standard	As	0.150	0.500	3.75	1.0	50	4.5
	Cd						0.60
	Hg						0.90
	Pb						1.5
	Co						1.5
	Ni						6.0
	V						3.0
	Tl						2.4
	Se						24
	Ag						3.0
	Au						30
	Pd						3.0
	Ir						3.0
	Os						3.0
	Pt						3.0
	Rh						3.0
	Ru						3.0
	Ba						210
	Sb						27
	Li						75
	Mo						45
	Cu						15
	Sn						180
	Cr						15
	Fe						15
	Mn						15
	Zn						15
	Ca						150
	K						150
	Mg						15
	Na						150

6.8. 2.0J Calibration Standard Preparation

- 6.8.1. Prepare a solution containing the elements listed in Table 6 below in 5.0% HNO₃, 2.5% H₂SO₄, 2.0% HCl and 0.04% (400 µg/mL) Thiourea with Be, Sc, Y, Re, Te, Ge, Tb, and Bi internal standards.
- 6.8.2. Add 0.200 mL of intermediate standard to separate 50 mL Digitube® followed by addition of approximately 35 mL of deionized water.
- 6.8.3. Add 0.500 mL of Hydrochloric Acid (HCl) and 3.75 mL of Acid Mixture then dilute to 45 mL using deionized water.
- 6.8.4. Add 1.0 mL of internal standard/complexing solution and dilute to volume using deionized water. (Prepare fresh each time before analysis)

TABLE 6: 2.0J CALIBRATION STANDARD

Identification	Element	Intermediate Standard (mL)	HCl (mL)	Acid Mix (mL)	Internal Standard/Complexing Solution (mL)	Final Volume(mL)	Final Concentration (µg/L)
2.0J Calibration Standard	As	0.200	0.500	3.75	1.0	50	6.0
	Cd						0.80
	Hg						1.2
	Pb						2.0
	Co						2.0
	Ni						8.0
	V						4.0
	Tl						3.2
	Se						32
	Ag						4.0
	Au						40
	Pd						4.0
	Ir						4.0
	Os						4.0
	Pt						4.0
	Rh						4.0
	Ru						4.0
	Ba						280
	Sb						36
	Li						100
	Mo						60
	Cu						20
	Sn						240
	Cr						20
	Fe						20
	Mn						20
	Zn						20
	Ca						200
	K						200
	Mg						20
	Na						200

6.9. Calibration Blank

- 6.9.1. Prepare a solution containing 5.0% HNO₃, 2.5% H₂SO₄, 2.0% HCl and 0.04% (400 µg/mL) Thiourea as described in Table 7 below.
- 6.9.2. To a separate 50 mL Digitube®, add approximately 35 mL of DI Water.
- 6.9.3. Add 0.500 mL of Hydrochloric acid (HCl) and add 3.75 mL of Acid Mixture then dilute to 45 mL using DI Water.
- 6.9.4. Add 1.0 mL of internal standard/complexing solution and dilute to volume using DI Water.
- 6.9.5. Do not allow Internal Standard Solution to contact concentrated acids.

TABLE 7: CALIBRATION BLANK

Description	Internal Standard/ Complexing Solution (mL)	HCl (mL)	Acid Digestion Mix (mL)	Final Volume (mL)
Cal Blank	1.0	0.500	3.75	50

6.10. Method Blank Preparation

- 6.10.1. Refer to Calibration Blank

6.11. Sample Preparation

- 6.11.1. Prepare samples fresh before analysis.
- 6.11.2. Weigh approximately 100 mg of the sample into a 50 mL Digitube®.
- 6.11.3. Add 5.0 mL of deionized water and swirl solution to dissolve solid.
- 6.11.4. Add 0.500 mL of Hydrochloric Acid.
- 6.11.5. Add 3.75 mL of Acid Digestion Mixture and swirl solution periodically to evolve gasses that are produced during the reaction.
- 6.11.6. Add deionized water to approximately 45 mL and then transfer 1.0 mL of Internal Standard/ Complexing Solution.
- 6.11.7. Dilute to a final volume of 50 mL with deionized water and mix thoroughly.

6.12. Isobaric Overlap Corrections

- 6.12.1. An isobaric interference results from equal mass isotopes of different elements present in the sample solution. Analysis sequences that are processed utilizing multi-element standards will require the use of correction equations to compensate for known isobaric overlaps originating from the elemental standard and sample. The following correction equations should be used:

KED Mode:

$$M_c(58) = M_u(58) \times 1 - M_{(rm)}(57) \times 0.13208$$

$$M_c(98) = M_u(98) \times 1 - M_{(rm)}(99) \times 0.14655$$

$$M_c(106) = M_u(106) \times 1 - M_{(rm)}(111) \times 0.09766$$

$$M_c(108) = M_u(108) \times 1 - M_{(rm)}(111) \times 0.06953$$

$$M_c(120) = M_u(120) \times 1 - M_{(rm)}(125) \times 0.01273$$

$$M_c(123) = M_u(123) \times 1 - M_{(rm)}(125) \times 0.12588$$

$$M_c(190) = M_u(190) \times 1 - M_{(rm)}(195) \times 0.00036$$

$$M_c(192) = M_u(192) \times 1 - M_{(rm)}(195) \times 0.02315$$

$$M_c(196) = M_u(196) \times 1 - M_{(rm)}(202) \times 0.005023$$

The correction equations can be derived from the following equation:

$$M_c = M_u - [M_{(rm)} \times (A_{(i.e.)}/A_{(rm)})]$$

Where:

M_c = Corrected Count Rate for the analyte

M_u = Uncorrected count rate for the analyte

$M_{(rm)}$ = Count Rate of Reference Mass (rm) for the Interfering Element

$A_{(i.e.)}$ = Percent Abundance of Interfering Element (i.e.) at the analyte mass

$A_{(rm)}$ = Percent Abundance of Interfering Element at the Reference Mass (rm)

Example:

$$M_c(58) = M_u(58) \times 1 - M_{(rm)}(57) \times (0.28 / 2.12)$$

- 6.12.2. All correction coefficients were calculated based on the Agilent Technologies 2016 Relative Isotopic Abundance Table.
- 6.12.3. Multiplier used in the correction equation may differ slightly from the multiplier used in the Syngistix instrument method due to rounding.

7. INSTRUMENT PROCEDURE:

- 7.1. Perform the ICP-MS daily performance check prior to beginning the analytical sequence. Refer to NexION 350X ICP-MS SOP, BSI-SOP-0303, for Daily Check procedures.
- 7.2. A calibration curve of no less than two standards and a blank must be used. The calibration correlation coefficient (R) must be ≥ 0.99 .
- 7.3. Set up the sequence as per Table 8.
- 7.4. Confirm the calibration by analyzing the 1.5J standard after the calibration. The calibration check must recover $\pm 20\%$ of the calculated theoretical concentration for multi-element analysis and $\pm 10\%$ for single element determinations.
- 7.5. The check standard must be verified after the calibration. A re-analysis of the check standard will be performed a minimum of once every 10 samples and at the end of the analytical run.
- 7.6. The drift between the bracketing standard checks must be NMT 20% for each Target element.
- 7.7. The sample concentration is calculated as:

$$\text{Conc. } (\mu\text{g/g}) = \frac{\text{Solution Conc. } (\mu\text{g/L}) \times \text{Solution vol. (L)} \times \text{Dilution Factor}}{\text{Sample Mass (g)}}$$

TABLE 8: EXAMPLE SAMPLE ANALYSIS SEQUENCE

ID	Type	Level
Cal Blank	Cal Blank	Level 1
0.5J Cal Std	Cal Std	Level 2
1.5J Cal Std	Cal Std	Level 3
2.0J Cal Std	Cal Std	Level 4
Cal Blank Check	QC Check	Not Applicable
1.5J Check Std 1	QC Check	Not Applicable
Method Blank	Sample	Not Applicable
Sample(s) 10 or less	Sample	Not Applicable
1.5J Check Std 2	QC Check	Not Applicable

7.8. Instrument Setup and Parameters

- 7.8.1. Instrument settings are only listed as guidelines. Settings may be changed in order to accommodate changes in sample matrix or hardware configurations.
- 7.8.2. The AMS-II makeup gas must be engaged during analysis using a minimum dilution gas ratio of 20%.
- 7.8.3. The elements arsenic and selenium are analyzed using hydrogen reaction gas in order to remove poly atomic interferences. A hydrogen DRC flow rate of approximately 4 mL/min should be used.
- 7.8.4. The instrument method is stored under the Approved Test Method Folder labelled as “Cytidine_Uridine_L-Arg_L-Glut_EI_Profile.mth” for elemental impurities testing along with “Cytidine_Uridine_L-Arg_L-Glut_Trace_Metals.mth” for trace metal or finished good analyses.

TABLE 9: ICP-MS PARAMETERS

ICP-MS System	Perkin Elmer NexION350X Inductively Coupled PlasmaMass Spectrometry (ICP-MS) with Syngistix Software
Sweeps/Reading	20
Replicates	3
Nebulizer Gas	Argon
Collision Gas	Helium
Reaction Gas	Hydrogen
Dilution Gas	Argon
Sample and Skimmer Cone	Platinum
Sample Rinses	Rinse-1: 60 sec at 45 rpm 5% HNO ₃ , 2.5% HCl, with 0.04% Thiourea or as applicable to mitigate carry over

TABLE 10: LINEAR RANGE AND CORRESPONDING TUNE MODE

Isotope	Internal Standard	Mode	Linear Range (µg/L)	Isotope	Internal Standard	Mode	Linear Range (µg/L)
7Li	9Be	STD	15-100	108Pd	89Y	KED	0.60-4.0
23Na	45Sc	KED	30-200	109Ag	125Te	KED	0.60-4.0
24Mg	45Sc	KED	3.0-20	113Cd	125Te	KED	0.12-0.80
39K	45Sc	KED	30-200	118Sn	125Te	KED	36-240
44Ca	45Sc	KED	30-200	119Sn	125Te	KED	36-240
51V	45Sc	KED	0.60-4.0	120Sn	125Te	KED	36-240
52Cr	45Sc	KED	3.0-20	121Sb	125Te	KED	5.4-36
53Cr	45Sc	KED	3.0-20	123Sb	125Te	KED	5.4-36
55Mn	45Sc	KED	3.0-20	135Ba	159Tb	KED	42-280
57Fe	45Sc	KED	3.0-20	137Ba	159Tb	KED	42-280
58Ni	45Sc	KED	1.2-8.0	138Ba	159Tb	KED	42-280
59Co	45Sc	KED	0.30-2.0	188Os	209Bi	KED	0.60-4.0
60Ni	45Sc	KED	1.2-8.0	189Os	209Bi	KED	0.60-4.0
62Ni	45Sc	KED	1.2-8.0	190Os	209Bi	KED	0.60-4.0
63Cu	45Sc	KED	3.0-20	191Ir	209Bi	KED	0.60-4.0
65Cu	45Sc	KED	3.0-20	192Os	209Bi	KED	0.60-4.0
67Zn	72Ge	KED	3.0-20	193Ir	209Bi	KED	0.60-4.0
68Zn	72Ge	KED	3.0-20	194Pt	209Bi	KED	0.60-4.0
75As	89Y	H ₂ DRC	0.90-6.0	195Pt	209Bi	KED	0.60-4.0
77Se	89Y	H ₂ DRC	4.8-32	196Pt	209Bi	KED	0.60-4.0
78Se	89Y	H ₂ DRC	4.8-32	197Au	209Bi	KED	6.0-40
95Mo	89Y	KED	9.0-60	199Hg	209Bi	KED	0.18-1.2
97Mo	89Y	KED	9.0-60	200Hg	209Bi	KED	0.18-1.2
98Mo	89Y	KED	9.0-60	202Hg	209Bi	KED	0.18-1.2
99Ru	89Y	KED	0.60-4.0	203Tl	209Bi	KED	0.48-3.2
101Ru	89Y	KED	0.60-4.0	205Tl	209Bi	KED	0.48-3.2
103Rh	89Y	KED	0.60-4.0	206Pb	209Bi	KED	0.30-2.0
105Pd	89Y	KED	0.60-4.0	207Pb	209Bi	KED	0.30-2.0
106Pd	89Y	KED	0.60-4.0	208Pb	209Bi	KED	0.30-2.0
107Ag	125Te	KED	0.60-4.0				

8. REPORTING

- 8.1. Any result below the 0.3J target concentration will be reported as less than the corresponding LOQ value listed in Table 1, except for Pt where the LOQ is 1.0J for any cytidine related products. Results above the LOQ concentration will be reported in µg/g (ppm) according to Table 11 below. Report the average result for multiple isotopes of the same element that are above the LOQ concentration.

TABLE 11: RESULT REPORTING

Result	Reporting
If < LOQ	Report as < LOQ
If \geq LOQ and < 1.0 ppm	Report to two (2) decimal places
If \geq LOQ and \geq 1.0 ppm	Report to whole number