Written by/ Date	Reviewed by/ Date	Approved by/ Date
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Title: Analytical Development Scientist	**Title: Quality Laboratory Manager**	**Title: QA/QC Director**

1.0 Purpose

This procedure provides guidelines for the elemental analysis of raw materials and finished products using ICP-MS.

2.0 Scope

This procedure applies to the testing of label claim elements and elemental impurities in finished products and raw materials in the QC laboratory at Ion Labs. The ICP-MS method for the elemental analysis of raw materials and finished products has two functions:

2.1 The measurement of elemental impurities including, but not limited to, As, Ag, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl, V.

2.2 The measurement of macro-elements associated with label claims including, but not limited to B, Ca, Cr, Cu, Fe, K, Mg, Mn, Mo, Na, P, Se, Sr, V, and Zn.

3.0 Responsibility

3.1 It is the responsibility of QC Laboratory Management to ensure that elemental analyses are performed in accordance with the procedure described herein.

3.2 It is the responsibility of Analytical Development personnel and/or QC Laboratory Analysts to perform routine analyses and method validations.

3.3 It is the responsibility of Analytical Development personnel and/or QC Laboratory Management to determine if a product specific method validation is required for products being analyzed for the first time using this method.

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3.4 It is the responsibility of the Analytical Development personnel and/or QC Laboratory Management to keep this procedure current with the latest Ion Labs Practices.

4.0 Definitions

4.1 **PDE** – Permitted Daily Exposure for individual elemental impurities. For drug products and raw materials used in drug products, these values are typically taken from USP <232>. For dietary supplements, dietary ingredients, cosmetics, and raw materials used in cosmetics, USP <2232> and California Proposition 65 apply. The specifications listed in raw material or finished product profiles may differ from and always supersede USP or California Proposition 65 guidelines due to product specific or customer requirements.

4.2 ***Daily Dose PDE*** $\left(\frac{\mu g}{g}\right) = PDE\ \left(\frac{\mu g}{day}\right) \div Max\ Daily\ Dose\ \left(\frac{g}{day}\right)$

4.3 **J** – The Daily Dose PDE must be corrected for the dilution factor and sample amount to calculate the limit of each elemental impurity in the final prepared sample (J). For example, the oral PDE for lead is 5 µg/day. If the maximum daily dose is 10 g/day, the sample amount is 1 g, and the dilution factor is 100 mL/sample, then J is calculated by:

$$J = 5\frac{\mu g}{day} \div 10\frac{g}{day} \times 1\frac{g}{sample} \div 100\frac{mL}{sample} \times 1000\frac{ng}{\mu g} = 5\frac{ng}{mL}$$

4.4 **ICP-MS** – Inductively Coupled Plasma – Mass Spectrometry

4.5 **QC** – Quality Control

4.6 **AD** – Analytical Development

4.7 **EI** – Elemental Impurities

4.8 **LC** – Label Claim

4.9 **BEC** – Background Equivalent Concentration

4.10 **Use Class** – All finished products and raw materials manufactured at Ion Labs can be categorized into four basic classes based on their intended use:

4.10.1 **Drug –** The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations define the term drug as:

4.10.1.1 A substance recognized by an official pharmacopoeia or formulary.

4.10.1.2 A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

4.10.1.3 A substance (other than food) intended to affect the structure or any function of the body.

4.10.1.4 A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.

4.10.1.5 Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

4.10.2 **Dietary Supplement –** The Dietary Supplement Health and Education Act of 1994 (DHSEA) defines a dietary supplement as a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food or a sole item of a meal or diet.

4.10.2.1 **Dietary Ingredient** – DHSEA defines a dietary ingredient as a component of a dietary supplement. A dietary ingredient must be one or any combination of the following: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent or extract.

4.10.2.2 **New Dietary Ingredient** – A new dietary ingredient is a dietary ingredient that was not sold in the U.S. before October 15, 1994.

4.10.3 **Cosmetic** – The FD&C Act defines cosmetics as "articles intended to be rubbed, poured, sprinkled, sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance." Included in this definition are products such as skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, shampoos, permanent waves, hair colors, toothpastes, and deodorants, as well as any material intended for use as a component of a cosmetic product.

4.10.4 **Food** – Food is any substance that is usually composed of carbohydrates, fats, proteins and water. It can be eaten or drunk by any animal including humans for nutrition or pleasure. Most of the foods are of plant or animal origin.

5.0 References

5.1 USP <232> Elemental Impurities - Limits

5.2 USP <233> Elemental Imputities - Procedures

5.3 USP <2232> Elemental Contaminants in Dietary Supplements

5.4 California Proposition 65 – Safe Drinking Water and Toxic Enforcement Act of 1986

5.5 21 U.S. Code Sections 321-399i – Federal Food, Drug, and Cosmetic Act

5.6 U.S. Department of Health and Human Services, National Institutes of Health, Office of Dietary Supplements, Dietary Supplement Health and Education Act of 1994.

5.7 D-105, SOP, Out of Specification / Out of Trend Investigation

5.8 D-825, SOP, Calibration, Verification and Operation of a Multiwave Go Microwave System

5.9 D-777-F1, Form, ICP Intermediate Standard Prep Form

5.10 D-777-F2, Form, ICP Working Standard Prep Form

5.11 D-777-F3, Form, ICP Sample Prep Form

5.12 D-777-F4, Electronic Form, ICP Standard Concentration Calculator

5.13 D-777-F5, Electronic Form, ICP Validation/Sample Preparation Calculator

5.14 D-777-F6, Electronic Form, ICP LC Raw Material Sample Prep Calculator

5.15 D-777-F7, Electronic Form, ICP Dilution Calculator

5.16 D-777-F8, ICP Data Review Checklist

5.17 D-118, SOP, Laboratory Quality Assurance Activities Plan (Proficiency Testing)

5.18 A-106, SOP, Documentation Guidelines for cGMP Records

5.19 C-501, SOP, Document Control Procedure

5.20 C-502, SOP, Record Storage, Retention, and Destruction

6.0 Equipment and Materials

6.1 Agilent 7800 ICP-MS System with MassHunter software

6.2 Agilent SPS 4 Autosampler

6.3 Anton Paar Multiwave GO Digestion System

6.4 Nitric Acid – 67% - 70% Trace Metal Grade

6.5 Hydrochloric Acid – 32% - 35% Trace Metal Grade

6.6 Isopropanol – HPLC Grade

6.7 Single Element Standards Containing each of the following elements at 1000 ppm: B, Ca, Cr, Cu, Fe, K, Mg, Mn, Mo, Na, P, Se, Sr, V, and Zn. Other elements may be required to support product label claims.

6.8 10 ppm or 1000 ppm Hg Standard.

6.9 Class 1 Stock Solution (SCP Science Custom Standard Part #AQ0-113-205 or equivalent) Ag ≈ 150 ppm, As ≈ 15 ppm, Cd ≈ 5 ppm, Co ≈ 50 ppm, Ni ≈ 200 ppm, Pb ≈ 5 ppm, Se ≈ 150 ppm, Tl ≈ 8 ppm, V ≈ 100 ppm, 10% Nitric Acid Matrix

6.10 Class 2 Stock Solution (SCP Science Part #140-131-111 or equivalent) Au ≈ 100 ppm, Ir ≈ 100 ppm, Os ≈ 100 ppm, Pd ≈ 100 ppm, Pt ≈ 100 ppm, Rh ≈ 100 ppm, Ru ≈ 100 ppm, 10% Hydrochloric Acid Matrix

6.11 Class 3 Stock Solution (SCP Science Part #140-131-121 or equivalent) Ba ≈ 140 ppm, Cr ≈ 1100 ppm, Cu ≈ 300 ppm, Li ≈ 55 ppm, Mo ≈ 300 ppm, Sb ≈ 120 ppm, Sn ≈ 600 ppm, 5% Nitric Acid + 0.5% Hydrofluoric Acid Matrix

6.12 Internal Standard Stock Solution (SCP Science Part #140-111-081 or equivalent) Bi ≈ 10 ppm, Ge ≈ 10 ppm, In ≈ 10 ppm, Li(6) ≈ 10 ppm, Sc ≈ 10 ppm, Tb ≈ 10 ppm, Y ≈ 10 ppm, 5% Nitric Acid Matrix

6.13 Tuning Solution Stock (Agilent Part # 5188-6564 or equivalent) Ce ≈ 10 ppm, Co ≈ 10 ppm, Li ≈ 10 ppm, Tl ≈ 10 ppm, Y ≈ 10 ppm, 2% Nitric Acid Matrix

6.14 50-mL Plastic Tubes

6.15 15-mL Plastic Tubes

6.16 10-mL Adjustable Auto-Pipet

6.17 1-mL Adjustable Auto-Pipet

6.18 200-µL Adjustable Auto-Pipet

6.19 1000-mL Plastic Graduated Cylinder

6.20 Plastic Beakers and Bottles for Liquid Transfer and Storage

7.0 Preparation of Solutions

7.1 Autosampler Rinse Solution Preparation

Note: Rinse Solution has no expiration. Preparation may be scaled as needed.

7.1.1 Transfer 910 mL of Water to a suitable container.

7.1.2 Add 30 mL of Nitric Acid and 60 mL of Hydrochloric Acid.

7.1.3 Close the container and mix well.

7.2 5% Nitric Acid Solution Preparation

Note: Nitric Acid Solution has no expiration. Preparation may be scaled as needed.

7.2.1 Transfer 190 mL of Water to a suitable container.

7.2.2 Add 10 mL of Nitric Acid

7.2.3 Close the container and mix well.

7.3 Diluent Preparation

Note: Diluent has an expiration of six months. Preparation may be scaled as needed.

7.3.1 Transfer 880 mL of water to a suitable container.

7.3.2 Slowly add 100 mL of Nitric Acid.

7.3.3 Slowly add 20 mL of Hydrochloric Acid.

7.3.4 Close the container and mix well.

7.4 Tuning Solution Preparation

Note: The Tuning Solution has an expiration of one year.

7.4.1 Transfer 25 µL of Tuning Solution Stock into a 250-mL plastic container.

7.4.2 Add 240 mL of Water.

7.4.3 Add 10 mL of Nitric Acid.

7.4.4 Close the container and mix well.

7.5 Internal Standard Preparation

Note: The Internal Standard Solution has an expiration of six months.

7.5.1 Transfer 25 mL of Internal Standard Stock Solution to a suitable container.

7.5.2 Add 315 mL of Water.

7.5.3 Add 10 mL of Nitric Acid.

7.5.4 Add 150 mL of Isopropanol.

7.5.5 Close the container and mix well.

8.0 Standard Preparation

8.1 Preparation of EI and LC Intermediate Standard Solutions is documented on Form D-777-F1 ICP Stock Standard Preparation Form.

8.2 Preparation of EI and LC Working Standard Solutions is documented on Form D-777-F2 ICP Working Standard Preparation Form.

8.3 Electronic Form D-777-F4 is used to calculate the concentration of ICP working standards for both EI and LC.

8.4 For a new set of standards, the following tasks must be performed:

8.4.1 Forms D-777-F1, D-777-F2, and a printed copy of the electronic form D-777-F4 should be reviewed along with a printout of the first calibration generated with the standards.

8.4.1.1 This review ensures that stock standard concentrations and the volumes/weights for all dilutions were transcribed correctly into D-777-F4.

8.4.1.2 This review ensures that the working standard concentrations generated by D-777-F4 were transcribed correctly into the ICP software.

8.4.2 After review, the documents shall be scanned into electronic format and archived in the F:/Laboratory/ICPMS/ folder.

8.4.3 After scanning, the printed documents will be included with the test results packet of one of the finished products analyzed during the run.

8.4.4 Thereafter, when these standards are used for an analysis, the scanned copy will be printed for inclusion into the test results packet of finished products tested during the run.

8.5 EI Standards Preparation

Note: The 10 ppm Mercury Solution has an expiration of 3 months if prepared in-house. The EI Intermediate Standard has an expiration of 3 months. The EI Working Standards have an expiration of 1 week. Keep containers closed when not in use and be sure not to mix up lids for the different concentration solutions.

8.5.1 Mercury 10 ppm Solution (only required if the Stock Solution is 1000 ppm).

8.5.1.1 Document preparation of the Mercury 10 ppm Solution in a Laboratory Notebook.

8.5.1.2 Use a 100-mL glass volumetric flask that has been previously soaked for at least one hour in a 5% nitric acid solution and rinsed with water to remove residual contamination.

8.5.1.3 Transfer about 50 mL of water to a 100-mL glass volumetric flask.

8.5.1.4 Add 10 mL of Nitric Acid.

8.5.1.5 Add 1.0 mL of 1000 ppm Hg Stock Solution.

8.5.1.6 Dilute to volume with water.

8.5.1.7 Close the container and mix well.

8.5.1.8 Alternatively use commercially available 10 ppm Hg standard.

8.5.2 EI Intermediate Standard Preparation

8.5.2.1 Transfer 0.63 mL of Class 1 Stock, 0.63 mL of Class 2 Stock, and 6.3 mL of Class 3 Stock, and 0.6 mL of 10 ppm Hg Stock to a 50-mL container. If not performing analysis of all elements listed in USP <232>, addition of the Class 2 and 3 Stock solutions may be omitted.

8.5.2.2 Dilute to volume with Diluent.

8.5.2.3 Close the container and mix well.

8.5.3 EI Working Standard #5

8.5.3.1 Transfer 1.0 mL of EI Intermediate Standard to a 50-mL container.

8.5.3.2 Dilute to volume with Diluent.

8.5.3.3 Close the container and mix well.

8.5.4 EI Working Standard #4

8.5.4.1 Transfer 0.75 mL of EI Intermediate Standard to a 50-mL container.

8.5.4.2 Dilute to volume with Diluent.

8.5.4.3 Close the container and mix well.

8.5.5 EI Working Standard #3

8.5.5.1 Transfer 0.5 mL of EI Intermediate Standard to a 50-mL container.

8.5.5.2 Dilute to volume with Diluent.

8.5.5.3 Close the container and mix well.

8.5.6 EI Working Standard #2

8.5.6.1 Transfer 0.25 mL of EI Intermediate Standard to a 50-mL container.

8.5.6.2 Dilute to volume with Diluent.

8.5.6.3 Close the container and mix well.

8.5.7 EI Working Standard #1

8.5.7.1 Transfer 0.8 mL of EI Working Standard #3 to a 50-mL container.

8.5.7.2 Dilute to volume with Diluent.

8.5.7.3 Close the container and mix well.

8.6 LC Standards Preparation

Note: The LC Intermediate Standard has an expiration of one month. The LC Working Standards have an expiration of one week. Keep containers closed when not in use and be sure not to mix up the lids for the different concentration solutions. Track the weight of tubes during each step of standard preparation according to D-777-F4 (LC-weight section) if quantitation is to be performed on w/w basis.

Note: The presence of strontium (Sr) hinders the determination of ^{44}Ca due to interference from doubly charged ^{88}Sr. Prepare strontium standards separate from all other elements. Prepare the strontium Intermediate Standard by diluting 5.0 mL of a 1000 µg/mL strontium stock to a final volume of 50 mL. Prepare strontium Working Standards in the same manner as for other LC standards.

8.6.1 LC Intermediate Standard Solution

8.6.1.1 Transfer 0.125 mL of the following 1000 µg/mL single element standards to a single 50-mL container: Cr, Cu, Mn, Mo, Se, and V.

8.6.1.2 Transfer 5.0 mL of the following 1000 µg/mL single element standards to the same 50-mL container: B, Ca, Fe, K, Mg, Na, P, Zn

8.6.1.3 Dilute to volume with Diluent.

8.6.1.4 Close the container and mix well.

8.6.2 LC Working Standard #6

8.6.2.1 Transfer 4.0 mL of the LC Intermediate Standard Solution to a 50-mL container.

8.6.2.2 Dilute to volume with Diluent.

8.6.2.3 Close the container and mix well.

8.6.3 LC Working Standard #5

8.6.3.1 Transfer 3.0 mL of LC Intermediate Standard Solution to a 50-mL container.

8.6.3.2 Dilute to volume with Diluent.

8.6.3.3 Close the container and mix well.

8.6.4 LC Working Standard #4

8.6.4.1 Transfer 2.0 mL of LC Intermediate Standard Solution to a 50-mL container.

8.6.4.2 Dilute to volume with Diluent.

8.6.4.3 Close the container and mix well.

8.6.5 LC Working Standard #3

8.6.5.1 Transfer 1.0 mL of LC Intermediate Standard Solution to a 50-mL container.

8.6.5.2 Dilute to volume with Diluent.

8.6.5.3 Close the container and mix well.

8.6.6 LC Working Standard #2

8.6.6.1 Transfer 0.4 mL of LC Intermediate Standard Solution to a 50-mL container.

8.6.6.2 Dilute to volume with Diluent.

8.6.6.3 Close the container and mix well.

8.6.7 LC Working Standard #1

8.6.7.1 Transfer 0.1 mL of LC Intermediate Standard Solution to a 50-mL container.

8.6.7.2 Dilute to volume with Diluent.

8.6.7.3 Close the container and mix well.

9.0 Sample Preparation

9.1 Sample preparation is documented on Form D-777-F3 ICP Sample Preparation Form.

9.2 Sample preparation involves either dissolution and/or dilution in Diluent (for LC samples where the target element is soluble and/or EI samples where the entire sample is soluble) or closed-vessel microwave digestion with subsequent dilution in Diluent (for LC samples where the target analyte is not soluble and/or EI samples that do not completely dissolve in the diluent).

9.3 The dilution factor and sample amount are chosen so that the final concentrations for all elements, which may correspond to either a limit or a label claim, are within the linear range for the analytical procedure. Multiple dilutions may be required.

9.3.1 EI are always determined in units of µg/mL; therefore, the dilution factor should be calculated in units of mL.

9.3.2 LC can be determined in units of either µg/g or µg/mL.

9.3.2.1 Determination in units of µg/g is more precise and should generally be used for finished product release testing. This requires that the weight of the sample be tracked during the entire sample preparation process in order to calculate the dilution factor in units of g.

9.3.2.2 Determination in units of µg /mL is easier but less precise and may be used for complex determinations such as product specific LC validations. In this case, dilution factors should be calculated in units of mL.

9.4 Finished Products

9.4.1 Test details including sample weight, dilutions, digestion reagents, and digestion program are included as an attachment to the finished product test ticket.

9.4.1.1 The optimal sample weight and dilutions for inclusion into a Test Details page are generated using electronic form D-777-F5. In the case of product requiring testing of multiple label claim elements, the dilutions specified by the form may be adjusted so that fewer dilutions must be performed. However, the concentration of all target elements

in the working sample are within the linear range of the method (200 – 8000 ng/mL for B, Ca, K, Fe, Mg, Na, P, Sr, Zn and 5 – 200 ng/mL for Cr, Cu, Mo, Mn, Se, and V).

- For example, D-777-F5 specifies a 0.4/15 mL dilution for Na and a 0.5/15 mL dilution for K. In this case, the dilution for K may be changed to 0.4/15 mL to reduce the total number of dilutions required.

9.4.1.2 The digestion or dissolution parameters for inclusion into a Test Details page shall be determined using the guidelines presented in Section 10.

9.4.2 If Test Details for a finished product are not attached to the test ticket, use electronic form D-777-F5 to determine the optimal sample preparation parameters including sample weight and dilutions. Instructions for using D-777-F5 are included with the form. Refer to section 10 to determine digestion or dissolution conditions.

9.4.3 A product specific method validation is recommended in the following cases to demonstrate accuracy and precision:

9.4.3.1 A new target element is to be analyzed for which there is no previous instance of a product specific method validation.

9.4.3.2 An aspect of the product (e.g. dosage form, sample matrix, label claim, elemental impurities limits, etc.) is significantly different from those which have undergone previous validation and/or is expected to present difficulty during sample preparation and/or analysis.

9.4.3.3 If release testing has been conducted on a product that has not undergone validation and the results do not meet product release specifications, a product specific validation may be performed as part of an investigation conducted according to D-105.

9.4.4 For Raw Materials:

9.4.4.1 For EI, the sample weight is always 132 mg.

9.4.4.2 For EI, the total dilution is always 50 mL.

9.4.4.3 For LC, the default sample weight is 132 mg. Other weights may be used. A larger sample weight may be more appropriate for a raw material with very low content of the target element and/or heterogeneous appearance.

9.4.4.4 For LC, the sample must be diluted into the linear range of the method. Use electronic form D-777-F6 to determine the correct dilution(s). Print the completed form D-777-F6 and include it with the data packet.

10.0 Sample Digestion or Dissolution

10.1 If the sample is completely soluble or miscible in the diluent (clear or colored solution, but not cloudy), no digestion is required. For determination of label claim elements: if the target element is completely soluble in the diluent, no digestion is required.

10.1.1 Homogenize the sample thoroughly before removing a portion for testing.

10.1.1.1 Solid powders of uniform particle size: mix the sample by turning end-over-end for at least 30 seconds or mix the sample by coning and quartering.

10.1.1.2 Solid powders of irregular particle size: grind the sample in a mortar and pestle or blender to obtain a powder of uniform particle size.

10.1.1.3 Liquid solutions or suspensions: mix the sample by turning end-over-end for at least 30 seconds. Sample suspensions immediately after mixing before settling occurs.

10.1.1.4 Tablets: Record the weight of at least 10 dosage units, and calculate the average tablet weight. Grind in a mortar and pestle or blender to

obtain a powder of uniform particle size. The sample weight for digestion should be determined as outlined above.

10.1.1.5 Capsules containing solid powder: Pool at least 10 dosage units and completely remove all fill material from the capsules. A small spatula may be useful in removing fill material that sticks in the capsules. Record the weight of the pooled fill material and calculate the average fill weight per capsule. Typically, the sample for digestion will be one capsule shell combined with an amount of powder equivalent to the average fill weight. When transferring the sample to a digestion vessel, record the weight of fill material and capsule shell separately.

10.1.1.6 Capsules containing liquid fill: Typically, a single capsule will be digested without homogenization.

10.1.2 Place a 50-mL container directly on the balance and tare.

10.1.2.1 Other volumes may be used.

10.1.2.2 If containers are to be re-used, clean them in the following manner:

- Soak containers for at least one hour in a 1% citranox solution.
- Rinse containers with hot tap water.
- Rinse containers with DI water.
- Allow containers to air dry before use.

10.1.3 Transfer the required sample weight to the container.

10.1.4 Dilute the sample to the final volume using Diluent.

10.1.5 Close the container and mix well. This is the Stock Sample.

10.1.6 Perform any further dilutions required for EI and/or LC analysis using the dilution volumes determined in Section 9.

10.1.7 Proceed to Section 11.

10.2 If the sample and/or target element is not soluble in the diluent:

10.2.1 Homogenize the sample before removing a portion for testing as outlined in Section 10.1.

10.2.2 Place a digestion vessel directly on the balance and tare.

10.2.3 Transfer the sample weight calculated in Section 9 to the digestion vessel, and record the weight.

10.2.4 Transfer the digestion vessel to an exhaust hood.

10.2.5 Slowly add the required digestion reagents washing any sample that may have stuck to the sides of the vessel to the bottom during the addition. For most samples, 5.0 mL of Nitric Acid and 1.0 mL of Hydrochloric Acid is suitable for sample digestion. If a product specific validation is applicable, use the digestion reagents listed in the validation report.

10.2.6 Install the safety vent and screw cap on the vessel, but do not tighten the cap.

10.2.7 Wait at least 5 minutes for pre-digestion reactions to subside. For sample sizes greater than 0.5 g, it is advisable to wait for at least 15 minutes with occasional swirling before proceeding. For samples containing > 10% oil, wait at least one hour with occasional swirling before proceeding. If a validation has been performed, use the pre-digestion time listed in the validation report. For raw materials, 5 minutes is sufficient.

10.2.8 Tighten the vessel screw cap until the center piece on the top is just flush with the outer portion of the cap.

10.2.9 **Immediately place the closed vessel into the rotor body. Pressurization inside the vessel could cause irreversible bulging if the closed vessel is not placed into the rotor body immediately.**

10.2.10 Repeat steps 10.2.1 to 10.2.9 until all samples have been prepared for digestion. If fewer than 12 samples are being digested, samples should be evenly distributed (balanced) in the rotor body. When digesting multiple sample types in a single digestion run, it is advisable to match sample types and sample sizes as closely as possible.

10.2.11 Place the rotor lid onto the rotor body.

10.2.12 Ensure that the drip cup and drive ring are properly installed in the microwave cavity.

10.2.13 Install the rotor into the microwave cavity and close the door.

10.2.14 On the main screen, click Create Run.

10.2.15 Enter the Run Name. Ideally, the run name should uniquely identify the sample(s) being digested. For raw materials, the date followed by "raw mat" is sufficient.

10.2.16 Select the Method to be used for the run:

10.2.16.1 Most samples (including raw materials)

- Ramp 5 min to 75°C and hold 5 min.
- Ramp 5 min to 120°C and hold 5 min.
- Ramp 5 min to 180°C and hold 10 min.

10.2.16.2 Large sample size or reactive sample such as oil

- Ramp 10 min to 50°C and hold 5 min.
- Ramp 10 min to 70°C and hold 5 min.
- Ramp 20 min to 180°C and hold 10 min.

10.2.17 If desired, enter a Run Note.

10.2.18 If digesting only a single vessel, it is necessary to prepare a second "dummy" sample that is identical to the first. Only the first sample is analyzed. It is not required to record the sample weight of the "dummy" sample.

10.2.19 Click Start.

10.2.20 After digestion is complete, remove and open each of the vessels from the rotor body. **After a vessel has been removed from the rotor body, it must be opened without delay or the pressure inside of the vessel could cause irreversible bulging.**

10.2.21 **Carefully and very slowly** open the digestion vessels inside of a hood. Cover the top of the screw cap with a paper towel, and point the vessel away from your body while opening.

10.2.22 Transfer the digested sample, using small portions of water to ensure complete transfer, into a 50-mL container.

10.2.23 Slowly dilute the sample to volume (usually 50 mL) using water, close the container, and mix well. This is the Stock Sample.

10.2.24 If it was determined above that dilutions are required for EI and/or LC analysis, perform dilutions using Diluent.

11.0 Starting the Software and Instrument

11.1 Turn on the Argon gas and adjust the pressure to 80 – 90 psi.

11.2 Ensure that the Helium gas is on and adjust the pressure to 14 – 17 psi.

11.3 Ensure that there is sufficient rinse solution to complete the analysis.

11.4 Ensure that there is sufficient Internal Standard Solution to complete the analysis.

11.5 Place the internal standard line into a container of Water.

11.6 Ensure that the waste container is not full.

11.7 Ensure that the 5% Nitric Acid rinse is in position 1 and the bottle is open.

11.8 Ensure that a container of DI water is in position 2 and the bottle is open.

11.9 Ensure that the Tuning Solution containing 1 ppb each of Ce, Co, Li, Tl, and Y is in position 3 and the bottle is open.

11.10 Ensure that the Diluent solution is in position 4 and the bottle is open.

11.11 Stretch the peristaltic pump tubing across the guides on the sampler and autosampler pumps.

11.12 Turn on the recirculating chiller.

11.13 Click Start→ICP-MS MassHunter Workstation→ICP-MS Instrument Control.

11.14 Enter User ID and Password.

11.15 In the dialog box, select Instrument Control.

11.16 Double click the Plasma gadget on the Dashboard.

11.17 In the dialog box, ensure that "execute configured ignition sequence" is selected and click OK.

11.18 After several minutes, the plasma is ignited.

11.19 If necessary, adjust the peristaltic pump tubing tension by reducing the tension until no flow is observed, slowly increasing tension until flow just starts, and then increasing tension 1 ¼ additional turns.

11.20 On the Menu bar, select View→Instrument Status. If no Menu bar is shown, press the F10 key.

11.21 Ensure that the Analyzer Pressure is $1x10^{-5} - 5x10^{-4}$. If the Analyzer Pressure is not within the required range, maintenance of the cones or vacuum system may be required.

11.22 After instrument warmup, the instrument will perform startup tuning.

11.23 Creating a Batch

11.23.1 Select Open Batch From Template from the Batch gadget pull-down menu.

11.23.2 Select the appropriate template depending on the current analysis type (EI or LC), and click OK.

11.23.3 In the Save Batch As dialog box, enter either EI or LC without any spaces for the type of analysis being performed. The software will append the date and time to create a unique batch name.

11.23.4 The software will create the new Batch.

11.23.5 In the Batch pane, click on the Sample List tab.

11.23.6 Under Acquisition Order, select Unknown Samples.

11.23.7 Enter Sample for Sample Type, Sample Name, and Vial # for the samples. Do not enter File Name since the instrument will automatically generate the File Name.

11.23.8 Under Comment, enter the units for the samples. The units should match the specification listed on the test ticket.

11.23.9 Enter the Sample Weight in g for each sample. For capsules: use the weight of fill material only for LC, and use the weight of fill material plus capsule shell for EI.

11.23.10 Enter the Final Volume or Final Weight for each sample (FV). This is calculated by taking into account the volume or weight of the initial stock solution in addition to all subsequent dilutions.

11.23.10.1 If the determination is to be made in units of µg/mL, calculate all dilutions in units of mL. For example, if the stock solution volume is 50 mL and a 0.4 mL aliquot of the stock solution was diluted to 15 mL, the Final Volume (FV) is:

$$FV = 50mL \times \frac{15mL}{0.4mL} = 1875mL$$

11.23.10.2 If the determination is to be made in units of µg/g, track the weight of the sample at each step in the sample preparation process and calculate all dilutions in units of g. Electronic form D-777-F7 should be used to calculate the dilution factors. For example, if the stock solution weight is 50 g and a 0.4 g aliquot of the stock solution was diluted to 15 g, the Final Weight (FV) is:

$$FV = 50g \times \frac{15g}{0.4g} = 1875g$$

11.23.11 Enter the Dilution Multiplier (DM) for each sample. Calculation of the DM will depend on sample type and specification:

11.23.11.1 Elemental Impurities

- If the specification is in µg/g (ppm), enter 0.001 for DM. This includes most raw material samples.
- If the specification is in µg/day, then DM is the maximum daily dose (MDD) in units of kg/day. This typically only applies to finished products. The MDD is calculated by multiplying the maximum recommended number of servings per day (from the product label) by the weight of a single serving (from the product profile or the weight variation test). For example, if the product directions instruct to take two capsules per day and each capsule weighs 0.5 g, then the MDD is 2 caps/day × 500 mg × 0.000001 kg/mg = 0.001 kg/day.

11.23.11.2 Label Claim

- If the specification is in %, then DM is 0.0000001.
- If the specification is in µg, then DM is the weight of a single dose or serving (formula weight, FW) in g divided by 1000. This typically only applies to finished products. FW is the average weight of at least 10 dosage units (fill material only for capsules). If testing a powder or liquid, use the FW from the Product Profile.
- If the specification is in mg, then DM is the FW in g divided by 1,000,000.

11.23.12 If the plasma will need to be shut down automatically at the end of the run (overnight run), delete the pauses at the end of the unknown samples.

11.23.13 Click Validate Method. If any errors are displayed in the Method Error List pane, double-click the error message to view the line in the Method Table pane that contains the error. Fix the problem and click Validate Method again.

11.23.14 Place the samples in the Autosampler. The blank (Diluent) is always in position 3101, and standards are always in positions 3102 – 3106 (low to high conc) for EI or positions 3102 – 3107 (low to high conc) for LC.

11.23.15 Click Add to Queue. The acquisition starts automatically if no other task is currently running.

11.23.16 The instrument will perform tuning before running the samples.

11.23.17 After tuning, the queue will pause and a performance report will be printed. Review the Performance Report, and ensure that the following tuning requirements are satisfied:

11.23.17.1 Mass 59 Count > 1000

11.23.17.2 Mass 89 Count > 500

11.23.17.3 Mass 205 Count > 2500

11.23.17.4 Oxide NMT 0.35%

11.23.18 If the system meets the tuning requirements, proceed to step 11.2.22.

11.23.19 If the system does not meet the tuning requirements, evaluate the root cause of tune failure and repeat the auto-tune:

11.23.19.1 Tuning failures are frequently caused by worn tubing or improper tension adjustment of the peristaltic pump.

- Replace tubing.
- Adjust tension on the peristaltic pump so that there is a smooth flow though the tubing.

11.23.19.2 Tuning failures are frequently caused by worn or dirty cones.

- Remove and inspect the sampler and skimmer cones. **Take great care not to damage the tip of the cones.**
- To clean dirty cones: sonicate for 5 min in a 1% aqueous citranox solution, sonicate for 5 min in deionized water, then rinse thoroughly with deionized water and dry using a gentle stream of argon gas.
- If the orifice of the sampler cone is > 1.1 mm or the orifice of the skimmer cone is > 0.42 mm, replace the cone.

11.23.19.3 Repeat the autotune:

- Click the Batch gadget.
- Click the Autosampler tab, and double click position 3.
- Wait 3 minutes for the tuning solution to equilibrate.
- Click Start Editing Mode.
- Click the Start Auto Tune tab.
- The instrument will perform an auto-tune and generate a performance report.
- Click End Editing Mode.

11.23.19.4 If the system meets the tuning requirements, proceed to step 11.2.20.

11.23.19.5 If the system still does not meet the tuning requirements, contact Perkin Elmer customer support.

11.23.20 Place the internal standard line in the internal standard solution. Wait for five minutes, then click the Queue drop down menu and select Resume.

11.23.21 The instrument will measure the 5% nitric acid solution. After measurement is complete, the queue will be paused.

11.23.22 Right-click on the Queue drop down menu and select Resume.

11.23.23 The calibration will be performed. After the calibration is complete, the queue will pause. Check the calibration for each target element in online data analysis:

11.23.23.1 Click on any column under the target element on any standard row. The calibration curve and table will be displayed in the bottom right pane.

11.23.23.2 In the calibration table, ensure that the concentration and measured concentration are in good agreement for all concentration levels.

11.23.23.3 Ensure that R is:

- EI: R is NLT 0.995
- LC: R is NLT 0.997

11.23.23.4 Ensure that the background equivalent concentration (BEC) for the elements to be quantified conform with the limits listed in Table 1:

Table 1: BEC Limits

Element	BEC Limit
As, Cd, Hg, Pb	0.03
B, Ca, Fe, K, Mg, Na, P, Zn	100
Cr, Cu, Mn, Mo, Se, V	2

11.23.23.5 If the calibration does not meet the requirements above, abort the run and prepare new standards and/or Diluent.

11.23.23.6 If the calibration meets the requirements, right-click on the Queue drop down menu and select resume.

11.23.24 The instrument will now run the samples.

11.23.25 To check the progress of the acquisition, click the Queue gadget on the Dashboard. The progress is displayed in the status bar in the lower right corner.

11.23.26 To modify a batch that is currently running in the queue:

11.23.26.1 Click the Batch gadget.

11.23.26.2 In the Batch pane, click on the Sample List tab.

11.23.26.3 Under Acquisition Order, select Unknown Samples.

11.23.26.4 Select the line just below the currently running sample.

11.23.26.5 Click Start Editing Mode on the toolbar in the Batch pane.

11.23.26.6 When all changes have been made, click End Editing Mode.

11.23.27 To automatically turn off the plasma when all queue items have been completed, select Plasma Off at the End on the toolbar in the Queue pane. All pauses at the end of the unknown samples must be removed, or the queue will not reach the plasma off directive. Note: The preferred method of instrument shut down is outlined in Section 11.5; however, using Plasma Off at the End is acceptable for overnight runs.

11.24 Generating the Report

11.24.1 The procedure for generating a report is the same in both Online and Offline Data Analysis.

11.24.2 Click the Report gadget on the ICP-MS Data Analysis window.

11.24.3 Select the samples for which a report is needed.

11.24.4 In the Generate Report dialog box, select the Ion Labs Report Template, Selected Samples, and To Printer.

11.24.5 Click Generate

11.24.6 Click the drop down menu of the Report Gadget, and select Print Calib Simple.

11.24.7 Click the drop down menu of the Report Gadget, and select Show Tune Report. When the Tune Report is displayed, right click on the report and select Print.

11.25 Reporting Requirements

11.25.1 Sample Report.

11.25.2 D-777-F1 Intermediate Standard Preparation Form

11.25.3 D-777-F2 Working Standard Preparation Form

11.25.4 D-777-F3 Sample Preparation Form (finished products only).

11.25.5 D-777-F4 Standard Concentration Calculations

11.25.6 D-777-F6 Raw Material Sample Preparation Calculations (only LC)

11.25.7 D-777-F7 Dilution by Weight Calculations (only for LC if dilutions performed by weight).

11.25.8 Lab notebook containing sample weights and dilutions (raw materials only).

11.25.9 Tuning Report.

11.25.10 Calibration Report.

11.25.11 D-777-F8, ICP Data Review Checklist

11.26 Electronic Data and Audit Trail Review

11.26.1 All results generated shall have the electronic data reviewed and compared to result reports. Review should include the following:

11.26.1.1 Standard Concentrations

11.26.1.2 Sample weights, multiplier, and dilutions

11.26.2 Audit trail shall be reviewed for traceability and completeness.

11.26.2.1 Testing present should align with documentation during audit trail review.

11.26.2.2 All creation and modification actions captured in the audit trail should align with normal practices.

11.27 Instrument Shutdown

11.27.1 Double click the Plasma gadget on the dashboard.

11.27.2 In the dialog box, click Yes.

11.27.3 Click the Batch gadget. Select the Autosampler tab, and double click Home.

11.27.4 **Close the Instrument Control window. If Instrument Control is not closed, other users will not be able to use the instrument.**

11.27.5 Close all sample and standard containers.

11.27.6 Release tension on the peristaltic pump tubing.

11.28 Digestion Vessel Cleaning

11.28.1 Soak vessels for at least one hour in a 1% citranox solution.

11.28.2 Rinse vessels with hot tap water. Be sure to pass water through the pressure release valve.

11.28.3 For difficult to remove contamination: add 4 mL of water and 3 mL of nitric acid to the digestion vessel. Perform a digestion cycle ramping the temperature to 180°C over 10 minutes and hold at 180°C for 10 minutes.

11.28.4 In some cases, a rinse with organic solvent (methanol or isopropanol) may be required to remove partially digested samples.

11.28.5 Only for extremely resistant residual contamination, a test tube brush may be used. Take extreme care not to scratch the Teflon vessel with the test tube brush.

11.28.6 Rinse vessels with DI water. Be sure to pass water through the pressure release valve.

11.28.7 Allow vessel to air dry before use.

12.0 Acquisition Method

12.1 Parameters Applicable to EI and LC

12.1.1 Peri-Pump Parameters

12.1.1.1	Uptake Speed	0.5 rps
12.1.1.2	Uptake Time	45 sec
12.1.1.3	Stabilize Time	30 sec
12.1.1.4	Probe Rinse Speed	0.5 rps
12.1.1.5	Probe Rinse Time Spl	20 sec
12.1.1.6	Probe Rinse Time Std	20 sec
12.1.1.7	Rinse Vial 1 Speed	0.5 rps
12.1.1.8	Rinse Vial 1 Time	60 sec
12.1.1.9	Rinse Vial 4 Speed	0.5 rps
12.1.1.10	Rinse Vial 4 Time	60 sec
12.1.1.11	Intelligent Rinse	Off
12.1.1.12	Preemptive Rinse	On
12.1.1.13	Start Rinse Before Acq Complete	30 sec

12.1.2 Internal Standards

Table 2: Internal Standard Masses Monitored

Element	Monitored Mass	Integ Time
Sc	45	1.5
Ge	72	1.5

Y	89	0.3
Bi	209	0.3

12.2 EI Specific Parameters

12.2.1 Acq Parameters

12.2.1.1 Acq Mode Spectrum

12.2.1.2 Peak Pattern 3 Point

12.2.1.3 Replicates 3

12.2.1.4 Sweeps/Replicate 100

12.2.2 Tune Parameters

12.2.2.1 Use Gas Yes

12.2.2.2 He Flow On

12.2.2.3 He Flow Rate 4.8

Table 3: Target Element Masses Monitored for Elemental Impurities

Element	Monitored Mass	Internal Std	Integ Time	Element	Monitored Mass	Internal Std	Integ Time
Li	7	45	6.0	Ag	107	89	0.5
V	51	45	0.5	Cd	111	89	1.0
Cr	52	45	0.5	Sn	118	159	0.3
Co	59	45	0.3	Sb	121	159	0.3
Ni	60	45	0.5	Ba	137	159	0.3
Cu	63	72	0.3	Os	189	159	0.5
As	75	72	3.0	Ir	193	209	0.5
Se	78	72	3.0	Pt	195	209	0.5
Mo	95	89	0.3	Au	197	209	0.5
Ru	101	89	0.3	Hg	202	209	2.0
Rh	103	89	0.3	Tl	205	209	0.3
Pd	105	89	0.3	Pb	208	209	0.3

12.3 Label Claim

12.3.1 Acq Parameters

12.3.1.1 Acq Mode — Spectrum

12.3.1.2 Peak Pattern — 3 Point

12.3.1.3 Replicates — 4

12.3.1.4 Sweeps/Replicate — 100

12.3.2 Tune Parameters

12.3.2.1 Use Gas — Yes

12.3.2.2 He Flow — On

12.3.2.3 He Flow Rate — 4.8

Table 4: Target Element Masses Monitored for Elemental Impurities

Element	Monitored Mass	Internal Std	Integ Time	Element	Monitored Mass	Internal Std	Integ Time
B	11	45	2.0	Cr	52	45	0.5
Na	23	45	0.3	Mn	55	45	0.5
Mg	24	45	0.5	Fe	56	45	0.5
P	31	45	0.3	Cu	63	45	0.5
K	39	45	0.3	Zn	66	72	2.0
Ca	44	45	2.0	Se	78	72	2.0
V	51	45	0.5	Sr	88	89	2.0
				Mo	95	89	0.5

13.0 ICP-MS Maintenance

13.1 Routine maintenance of the ICP-MS is documented in a laboratory notebook.

13.2 Perform maintenance as outlined in the Hardware Maintenance Manual or in the instructional videos located at D:/ICPMS Resources/Maintenance videos/index.html.

13.3 Recommended maintenance frequency:

13.3.1 Tubing — Replace weekly

13.3.2 Nebulizer — Clean if blocked or if memory effects are observed

13.3.3 Spray Chamber — Clean if memory effects are observed

13.3.4	Torch	Clean if deposits are observed, replace if damaged
13.3.5	Torch Shield Plate	Replace if corroded or deformed
13.3.6	Torch Bonnet	Replace if fractured, cracked, or chipped
13.3.7	RF Coil	Replace if corrosion or damage is observed
13.3.8	Sampling Cone	Replace if orifice is > 1.10 mm, deformed, or damaged
13.3.9	Skimmer Cone	Replace if orifice is > 0.42 mm, deformed, or damaged
13.3.10	Graphite Gasket	Replace if pitted, damaged, or worn
13.3.11	Ion Lens	Clean every three months
13.3.12	Vacuum Pump	Change pump oil every six months, check level monthly
13.3.13	Cooling Fluid	Replace yearly, check level monthly

14.0 Consumables List

14.1 Sample Tubing White/White SCP Science P# 022-133-009

14.2 Internal Standard Tubing Orange/Blue Agilent P# 5005-0021

14.3 Waste Tubing Santoprene Yellow/Blue SCP Science P# 022-033-419

14.4 MicroMist nebulizer Agilent P#G3266-80004 SCP Science P# 020-060-047

14.5 Torch, quartz, 2.5 mm i.d. Agilent P# G3280-80053 SCP Science P# 020-056-005

14.6 Shield plate Agilent P# G1833-65419 SCP Science P# 020-102-156

14.7 Bonnet Agilent P# G1833-65421 SCP Science P# 020-056-052

14.8 Nickel Sampling Cone Agilent P# G3280-67040 SCP Science P# 020-102-073

14.9 Nickel Skimmer Cone Agilent P# G3280-67041 SCP Science P# 020-102-074

14.10 Graphite Gasket for Sampling Cone Agilent P# G3280-67009

14.11 Extraction-Omega Lens Assembly Agilent P# G8400-67001

14.12 Vacuum Pump Oil Agilent P# X3760-64004

14.13 Oil mist filter element Agilent P# G1960-80039

15.0 Product Specific Method Validation

15.1 Product specific method validation is not required for finished products; however, validation is recommended in certain cases (see Section 9.4).

15.2 Validation will generally not be performed for raw materials.

15.3 The method validation requirements outlined herein are applicable to the majority of finished products at ION Labs. If a material has specific validation requirements due to its intended use, customer request, or any other reason, a separate validation protocol may be created for the product.

15.4 Product specific validations should not be performed concurrently with finished product or raw material release testing. Acquire validation results in a separate batch.

15.5 Do not use the finished product batch number as a sample name in validation batches. Instead, use the product formula number.

15.6 Validation requirements differ by use class as indicated below.

15.7 System Suitability:

15.7.1 The tuning requirements outlined in Section 11.2.17 are met.

15.7.2 The calibration requirements outlined in Section 11.2.23 are met.

15.8 Specificity: Detection by mass spectrometry is inherently specific. However, certain elements are subject to interferences from polyatomic species generated by other elements, matrix components, and plasma gasses as well as isobaric interferences from other elements which have isotopes at the same mass as the target element. As suggested in USP <233>, the use of a collision cell purged with an appropriate gas will be utilized to reduce polyatomic interferences. Isobaric interferences are mitigated by carful choice of the monitored isotope for each target element. Specificity is demonstrated by the assessment of accuracy as outlined below.

15.9 Precision (Repeatability):

15.9.1 Prepare replicate samples, and analyze them by the ICP-MS method. Calculate the %RSD for the measured concentrations of the replicate samples. Solid and liquid suspensions requiring digestion must be spiked prior to digestion if digestion is required.

15.9.2 The number of replicate samples depends on the use class of the material as follows:

15.9.2.1 Drug: Six replicate samples.

15.9.2.2 Dietary Supplement, Cosmetic, and Food: Three replicate samples.

15.9.2.3 If a material fits into multiple use classes, perform validation based on the most restrictive class.

15.9.3 The spike level and acceptance criteria depend on the analyte class as follows:

15.9.3.1 Elemental Impurities: Spiked at the limit level (1.00J). The %RSD is NMT 20%.

15.9.3.2 Label Claim Elements: Not spiked. In general, the %RSD should be NMT 10%. For label claim elements which are present at very low levels in the finished product (< 0.1%), an acceptance criteria of NMT 20% RSD is more appropriate.

15.10 Accuracy:

15.10.1 Prepare replicate samples spiked with the target elements and analyze them by the analytical procedure. Solid and liquid suspensions requiring digestion must be spiked prior to digestion if digestion is required. Evaluate the recovery of spiked elements.

15.10.2 The spike level and number of replicate samples depends on the use class and analyte type as follows:

15.10.2.1 Elemental Impurities

- Drug: Three replicate samples spiked at 0.5J, six replicate samples spiked at 1.0J, and three replicate samples spiked at 1.5J. Additionally, prepare triplicate unspiked samples as a control.
- Dietary Supplement, Cosmetic, and Food: Three replicate samples spiked at 1.0J. Additionally, prepare three replicate unspiked samples as a control.
- If a material fits into multiple use classes, perform validation based on the most restrictive class.

15.10.2.2 Macro-Elements

- All use classes: Three replicate samples spiked at one half of the label claim amount. Additionally, prepare three replicate unspiked samples as a control.

15.10.3 The acceptance criteria depends on the analyte class as follows:

15.10.3.1 Elemental Impurities: The average (mean) recovery of spiked elemental impurities in the replicate samples is 70% - 150%:

15.10.3.2 Label claim elements: In general, the average (mean) recovery of spiked label claim elements should be 90% - 110%. For elements which are present at very low levels in the finished product (< 0.1%), an acceptance criteria of 80% - 120% recovery is more appropriate.

15.11 **Linearity/Range:** Use the System Suitability requirements for validation of linearity.

15.12 **Quantitation Limit:** As discussed in USP <233>, sufficient sensitivity of the method (Quantitation Limit) is demonstrated by meeting the requirements for Accuracy.

16.0 Quality Assurance Activities

16.1 Each QC Laboratory analyst that performs testing by ICP-MS is required to participate in a quality assurance activity at least once annually.

16.2 Quality assurance activities which may satisfy this requirement include proficiency testing, inter-laboratory comparison, and intra-laboratory comparison.

16.3 Requirements for quality assurance activities are outlined in SOP D-118 Laboratory Quality Assurance Activities Plan (Proficiency Testing).

17.0 Documentation Requirements

17.1 All documentation will be completed as outlined in SOP A-106 Documentation Guidelines for cGMP Records.

17.2 All documentation will be distributed and maintained as outlined in SOP C-501 Document Control and SOP C-502 Record Storage, Retention, and Destruction.

18.0 Revision History

Revision	Date	Description of Changes	CCR #	By
0	05/23/19	New procedure.	N/A	S. Sassman
1	09/25/19	Increased internal standard concentration. Added expiration for standard solutions, change LC standard concentration for some elements, change diluent composition. Added specific instructions for various dosage forms. Modified procedure for more automated analysis. Added calculation and reporting instructions. Added instrument parameters. Added requirements for method validation. Added maintenance schedule.	19-0607	S. Sassman
2	10/07/20	Changed internal standard prep to eliminate interferences from carbon, change LC stock standard expiry to one month. Changed standard prep to increase the concentration for Mg, allow use of a blender for sample prep. Changed run name conventions for microwave. Changed tuning requirements. Added requirement for BEC. Updated formatting. Added prep/expiration date lines to solution prep form.	CC-20-0713	S. Sassman
3	12/20/22	Added forms for calculation of standard concentrations, calculation of validation parameters, calculation of raw material dilutions for label claim analysis, calculation of dilution factors for label claim analysis, and data review checklist. Modified sample preparation section to point to test details section of product profile for sample weight and dilutions. Added requirements for excluding finished products from validation. Simplified validation requirements.	CC-22-0478	S. Sassman
4	01/10/23	Increased BEC limits by factor of 1000 since the unit of measure was changed from ug/g to ng/g in revision 3. Added Tb in internal std table since it is being used, peak pattern for LC should be 3 point.	CC-23-0014	S. Sassman

5	05/19/23	Updated to accommodate analysis of finished products for LC without digestion. Updated D-777-F5 to accommodate analysis of finished products for LC without digestion. Removed requirement for product specific validation. Slightly increased internal standard solution concentration. Added troubleshooting for tuning failures. Updated D-777-F6 to allow different stock solution volumes. Added section 16.0 Quality Assurance Activities.	CC-23-0223	S. Sassman
6	08/31/23	Added Electronic Data and Audit Trail Review Requirements	CC-23-0438	J. Sassman
7	06/03/24	Added strontium as an element, allow use of weight variation to calculate dilution multiplier for elemental impurities.	CC-24-0242	S. Sassman
8	03/04/25	Updated He flow rate	CC-25-0053	A. Lukes