TECHNICAL GUIDE

How to Select Internal Standard Elements for ICP-MS

A technical guide to ICP-MS internal standard selection criteria, mass proximity, matrix effects, interference risk, and method-specific requirements.

About the Method Example Used in This Guide

The standards and technical principles discussed in this guide support a broad range of laboratory methods and applications. EPA Method 200.8 is referenced throughout as a practical, publicly available example of how an established ICP-MS method addresses internal-standard selection, concentration, addition, response monitoring and corrective action. These references are illustrative and do not mean that the discussion or the CPI products described are limited to testing performed under EPA Method 200.8.

Requirements can vary among regulatory methods, consensus methods, industry procedures and laboratory-developed methods. Laboratories should confirm product suitability and follow the analytical method, instrument instructions, validated SOPs, and quality-system requirements applicable to their work.

Quick Answers

Which elements make good ICP-MS internal standards? Elements that are absent or negligible in samples, chemically compatible with the matrix, stable in solution, free from significant interferences, and similar enough to assigned analytes in mass and/or ionization behavior to track response changes.

Should internal-standard mass be close to analyte mass? Usually yes, but mass proximity is not the only criterion. Ionization behavior, matrix behavior, interference risk, instrument conditions, and method requirements also matter.

What interferences matter? Interferences on the analyte and the internal standard both matter. Polyatomic, isobaric, oxide, doubly charged ion, matrix, memory, and physical sample-introduction effects can affect internal-standard selection.

Why Internal Standard Selection Matters

ICP-MS can measure trace elements across a wide analytical range, but signal response is not static. Sample introduction, plasma conditions, matrix loading, cone condition, instrument drift, and interferences can change measured response during an analytical sequence.

An internal standard is used to monitor those response changes and normalize analyte signals. When selected and applied correctly, internal standardization improves confidence in ICP-MS results. When selected poorly, it can hide problems, introduce bias, or create a false sense of control.

For example, EPA Method 200.8 defines an internal standard as a pure analyte added to a sample, extract, or standard solution in a known amount and used to measure relative responses of method analytes. The method also states that the internal standard must not be a sample component. [1]

This guide explains how to select internal standard elements for ICP-MS, with emphasis on method requirements, mass proximity, ionization behavior, matrix behavior, interference risk, and practical laboratory workflow.

What Is an ICP-MS Internal Standard?

An ICP-MS internal standard is an element added at a constant known level to blanks, calibration standards, QC samples, and unknown samples. The instrument measures the internal standard along with the target analytes.

The internal-standard response is then used to correct analyte response for changes that affect signal generation or transmission. These changes may include nebulization differences, physical matrix effects, ion transmission changes, or gradual instrument drift.

EPA Method 200.8 describes internal standardization as a required correction for instrument drift and physical interferences under that method. [1] The same principle is widely used beyond EPA 200.8, but laboratories should always follow the method, instrument software, and laboratory quality system that apply to their work.

Technical distinction

An internal standard is **not** a calibration standard, interference check solution, tuning solution, or second-source verification standard.

It is a response-correction tool added consistently across the analytical sequence.

What Makes a Good ICP-MS Internal Standard Element?

A good internal standard should behave similarly enough to the assigned analyte to track relevant response changes, but it should not interfere with the analyte or be present at meaningful levels in the sample.

In practice, selection requires balancing several criteria rather than relying on one rule.

Selection criterion	Why it matters
Absent or negligible in sample	The internal standard should not normally be present in the sample at a level that materially affects the added internal-standard signal.
Appropriate mass relationship	A nearby mass often tracks mass-dependent effects better than a distant mass, especially when space-charge or mass-dependent drift is important.
Similar ionization behavior	Elements with similar ionization characteristics may respond more similarly to plasma-condition changes.
Free from interference	The selected isotope should be free from significant isobaric, polyatomic, oxide, doubly charged, or matrix-derived interference under the method conditions.
Compatible chemistry	The element must remain stable in the standard matrix and be compatible with samples, calibration standards, and internal-standard delivery conditions.
Stable signal	The internal standard should produce adequate, stable counts without saturating the detector or adding unnecessary background.
Method accepted	For regulated work, the selected internal standard must comply with the applicable analytical method and quality program.

Start with the Method Requirement

Internal-standard selection should begin with the applicable method. For environmental trace-element analysis by EPA Method 200.8, the method provides specific internal-standard expectations and examples.

EPA Method 200.8 states that internal standardization must be used in all analyses to correct for instrument drift and physical interferences. For full mass-range scans, the method specifies a minimum of three internal standards and describes the use of scandium, yttrium, indium, terbium, and bismuth for general application. It also states that internal standards must be present in all samples, standards, and blanks at identical levels. [1]

Method 200.8 recommends an internal-standard concentration range of 20–200 µg/L for each internal standard, depending on instrument sensitivity. [1] That range is method-specific and should not be treated as a universal concentration requirement for every ICP-MS procedure.

If the laboratory is not following EPA Method 200.8, the method, instrument software, laboratory SOP, validation data, and quality requirements should determine the internal-standard set.

Method-specific warning

Do not copy an internal-standard mix from one method into another method without confirming suitability.

A mix that is appropriate for EPA Method 200.8 may not be appropriate for a different matrix, analyte list, instrument configuration, collision/reaction cell mode, or regulatory method.

Should Internal-Standard Mass Be Close to the Analyte Mass?

In many ICP-MS methods, mass proximity is a useful selection principle. If the internal standard is close in mass to the analyte, it may better track mass-dependent signal changes.

Mass proximity is especially relevant when signal suppression or enhancement varies across the mass range. Agilent ICP-MS documentation notes that internal standard elements should be selected to show similar behavior to the analytes, with mass number and/or ionization potential similar to the analyte. [2]

However, the closest mass is not always the best choice. A nearby isotope that suffers interference, is naturally present in the sample, or behaves differently in the matrix may perform worse than a more distant but cleaner internal standard.

Use mass proximity as a starting point, not the only rule

A practical selection sequence is:

1. Group analytes by mass range.
2. Identify candidate internal-standard elements near each group.
3. Check whether each candidate is expected in the sample matrix.
4. Check for isobaric, polyatomic, oxide, and doubly charged interferences.
5. Confirm compatibility with the acid matrix and instrument conditions.
6. Evaluate recovery, internal-standard response, and QC performance during method validation or verification.

Ionization Potential and Plasma Behavior

ICP-MS response is affected not only by mass but also by plasma behavior and ionization. Elements with similar ionization characteristics may respond more similarly when plasma conditions change.

Agilent documentation gives examples of selecting internal standards based on similar mass or ionization potential, noting that the analyte and internal standard should show similar behavior. [2]

This does not mean analysts should select solely by ionization potential. Instead, ionization behavior should be evaluated alongside mass, sample matrix, interferences, and observed method performance.

Avoid Internal Standards Present in the Sample

An internal standard should generally be absent from the sample, or present only at a level that is negligible compared with the added internal-standard concentration.

If the sample contains a significant amount of the internal-standard element, the measured internal-standard signal may reflect both the added internal standard and native sample content. That can distort the correction and bias analyte results.

EPA Method 200.8 defines the internal standard as an analyte that is not a sample component. [1] The method also notes that the internal-standard concentration should be high enough to minimize the possibility of correction errors if the internal standard is naturally present in the sample. [1]

For unknown or variable matrices, screening data, historical sample knowledge, or method-validation data can help determine whether candidate elements are suitable.

Check Interference Risk on Both Sides

Internal-standard selection must consider interference on the analyte and interference on the internal standard.

A clean analyte isotope paired with an interfered internal standard can still produce biased correction. Likewise, a clean internal standard cannot correct a direct spectral interference on the analyte unless the method includes an appropriate interference correction.

Interferences that can affect ICP-MS internal-standard selection

- **Isobaric interferences:** isotopes or ions with the same nominal mass-to-charge ratio.
- **Polyatomic interferences:** molecular ions formed from plasma gas, reagents, or matrix components.
- **Oxide interferences:** oxide species formed from matrix or analyte elements.
- **Doubly charged ion interferences:** ions with a two-plus charge appearing at half the mass-to-charge ratio.
- **Matrix effects:** suppression or enhancement caused by dissolved solids, acids, viscosity, salts, or other sample components.
- **Memory effects:** residual signal from previous samples, especially for elements prone to carryover.

EPA Method 200.8 identifies multiple ICP-MS interference types, including isobaric elemental interferences, isobaric polyatomic ion interferences, physical interferences, and memory interferences. [1] Its internal-standard table also lists possible limitations for several internal standards, including potential environmental presence and specific interference considerations. [1]

Common ICP-MS Internal Standard Elements

Common internal-standard candidates include elements such as lithium-6, scandium, yttrium, rhodium, indium, terbium, holmium, lutetium, and bismuth, depending on the method and instrument configuration.

EPA Method 200.8 lists internal standards and limitations of use in Table 3, including lithium-6, scandium, yttrium, rhodium, indium, terbium, holmium, lutetium, and bismuth. [1]

The following table is a practical planning aid. It is not a substitute for the applicable method, software setup, interference review, or validation data.

Candidate element	Typical role	Selection cautions
6Li	Low-mass analytes	May be present in environmental samples; enriched lithium-6 may be needed in some workflows.
Sc	Low-to-mid mass analytes	EPA 200.8 lists possible polyatomic ion interference.
Y	Mid-mass analytes	EPA 200.8 notes possible presence in environmental samples and possible oxide/hydroxide formation on some instruments.
Rh	Mid-mass analytes	Often useful when absent from sample and free from interference.
In	Mid-to-high mass analytes	EPA 200.8 notes possible isobaric interference by tin.
Tb	High-mass analytes	Useful high-mass option in many ICP-MS methods.
Ho	High-mass analytes	Useful high-mass option when method/instrument conditions support it.
Lu	High-mass analytes	Can be useful for high-mass correction; check sample presence and method suitability.
Bi	Very high-mass analytes	EPA 200.8 notes possible presence in environmental samples; often used near Pb/Tl/U mass range.

How Many Internal Standards Should Be Used?

The number of internal standards depends on the method, analyte mass range, instrument configuration, and sample matrix.

EPA Method 200.8 requires a minimum of three internal standards for full mass-range scans and describes a five-element internal-standard approach for general application. [1]

A small analyte list over a narrow mass range may require fewer internal standards than a broad multi-element method. A method covering low-, mid-, and high-mass analytes typically benefits from internal standards distributed across the mass range.

Using too few internal standards can leave some analytes poorly corrected. Using too many can increase method complexity and may introduce additional interference or contamination risks. The objective is coverage and performance, not maximum element count.

How Should Internal Standards Be Assigned to Analytes?

Internal-standard assignment should reflect how well each internal standard tracks each analyte under the method conditions.

A general workflow is:

1. **List analytes and isotopes.** Include target isotope, alternate isotope, expected concentration range, and known interferences.
2. **Group by mass range.** Low, mid, and high mass ranges often require different internal standards.
3. **Screen candidate internal standards.** Remove candidates present in the sample, unstable in the matrix, or interfered under the selected mode.

4. **Assign the best available internal standard.** Favor similar mass and/or ionization behavior when interference risk is acceptable.
5. **Verify performance experimentally.** Review internal-standard response stability, spike recovery, calibration verification, and sample/QC behavior.
6. **Document the assignment.** Record the internal standard used for each analyte in the method or instrument acquisition method.

Example assignment logic

Analyte group	Practical selection approach
Low mass analytes	Use a low-mass internal standard when clean and method-appropriate.
Mid mass analytes	Use a mid-mass element such as Sc, Y, Rh, or In depending on isotope, mode, and matrix.
High mass analytes	Use high-mass elements such as Tb, Ho, Lu, or Bi when clean and suitable.
Problem analytes	Review isotope selection, cell mode, interference correction, standard addition, dilution, or alternative internal-standard assignment.

How Are Internal Standards Added?

Internal standards can be added directly to each solution or introduced online through a separate pump channel, depending on the method and instrument configuration.

EPA Method 200.8 describes two approaches: direct addition to the calibration standard, blank, or sample solution; or online mixing before nebulization using a second peristaltic-pump channel and mixing coil. The method states that internal standards should be added to blanks, samples, and standards in a like manner so dilution effects from the addition may be disregarded. [1]

Consistent addition is critical. If internal standards are not added consistently, the correction can introduce error rather than reduce it.

Direct addition

- Internal standard is pipetted into each blank, calibration standard, QC sample, and unknown sample.
- Works well when preparation can be controlled carefully.
- Requires consistent volumetric technique and documentation.

Online addition

- Internal standard is mixed with sample flow before nebulization.
- Can simplify routine workflows and reduce manual additions.
- Requires stable pump tubing, correct flow balance, proper mixing, and verification that the internal-standard signal is stable.

CPI offers Internal Mixing Kits for ICP/ICP-MS instrumentation that support simultaneous introduction of samples and internal standards.

For laboratories that need a defined internal-standard mixture, CPI can also support Custom Inorganic Standards

requests with specified elements, concentrations, matrix, and volume.

What Internal-Standard Response Is Acceptable?

Internal-standard response limits should come from the applicable method, laboratory SOP, and instrument software configuration.

EPA Method 200.8 requires analysts to monitor internal-standard responses throughout the sample set. Under that method, the absolute response of any one internal standard must not deviate more than 60–125% of the original response in the calibration blank. If the response is outside those limits, the method provides specific investigation and corrective-action steps. [1]

Those limits are method-specific. Do not apply them universally without confirming that they are appropriate for the method being performed.

When an Internal Standard Fails

A failed or drifting internal-standard response is a signal that something in the measurement system may have changed.

Possible causes include:

- Partially blocked sampler or skimmer cone
- Changes in tuning condition
- Matrix suppression or enhancement
- Incorrect internal-standard addition
- Pump tubing wear or online mixing instability
- Contamination or native internal-standard contribution from the sample
- Incorrect internal-standard concentration
- Memory effects from a previous sample
- Nebulizer or spray-chamber instability

EPA Method 200.8 specifically directs the analyst to flush the instrument with rinse blank and monitor internal-standard responses in the calibration blank. If responses return within limits, the method describes further dilution and reanalysis of the sample; if responses remain out of limits, the analysis is terminated and the cause of drift is determined. [1]

In other methods, follow the applicable corrective-action procedure.

Internal Standards Do Not Correct Everything

Internal standardization is powerful, but it has limits.

Internal standards can help compensate for changes that affect the analyte and internal standard similarly. They do not automatically correct direct spectral interferences, poor calibration, incorrect dilution, contamination, poor sample digestion, or unstable standards.

For example, if a polyatomic ion directly overlaps the analyte isotope and the method does not correct for it, normalizing the analyte to an internal standard does not remove the overlap. The method may require isotope selection, mathematical correction, collision/reaction cell conditions, matrix separation, dilution, or another interference-control strategy.

Internal standardization should therefore be part of the overall ICP-MS quality-control system, not a substitute for calibration verification, interference evaluation, blanks, laboratory control samples, spike recoveries, or method validation.

Internal Standard Selection Checklist

1. Identify the analytical method and confirm whether internal standards are required.
2. List analytes, isotopes, expected concentration range, matrix, and instrument mode.
3. Identify internal-standard elements permitted or recommended by the method.
4. Exclude elements expected to be present in the samples at significant levels.
5. Select candidates with appropriate mass proximity and/or similar ionization behavior.
6. Check for isobaric, polyatomic, oxide, doubly charged, and memory-related interferences.
7. Confirm acid-matrix compatibility and solution stability.
8. Determine whether internal standards will be added directly or online.
9. Verify that all blanks, standards, QC samples, and unknowns receive internal standards consistently.
10. Set response monitoring limits according to the method and laboratory SOP.
11. Review recovery, precision, calibration verification, and internal-standard response data before routine use.

Frequently Asked Questions

Which elements make good ICP-MS internal standards?

Good internal standards are absent or negligible in the sample, stable in the solution matrix, free from significant interference, and able to track response changes for assigned analytes. Mass proximity, ionization behavior, and method requirements all matter.

Should the internal standard be close in mass to the analyte?

Mass proximity is often useful because it can help track mass-dependent response changes. However, it is not the only criterion. An element close in mass but subject to interference or naturally present in the sample may be a poor choice.

Can one internal standard correct every analyte?

Usually not for broad multi-element methods. A wide mass range often requires multiple internal standards distributed across low, mid, and high masses.

Can the internal standard be a target analyte?

Generally no. EPA Method 200.8 states that the internal standard must not be a sample component. If a candidate is present in the sample, the native contribution can interfere with the correction.

What concentration should an ICP-MS internal standard be?

The concentration should follow the applicable method or laboratory procedure. EPA Method 200.8 recommends 20–200 µg/L for each internal standard depending on instrument sensitivity, but that is not a universal requirement.

What if the internal-standard recovery is outside limits?

Follow the applicable method or SOP. Under EPA Method 200.8, analysts monitor internal-standard responses and investigate deviations from the specified response range with rinse, dilution, reanalysis, or termination of analysis depending on the result.

Do internal standards correct spectral interferences?

Not by themselves. They mainly normalize response changes. Direct spectral or mass interferences still require appropriate isotope selection, correction equations, cell conditions, sample preparation, dilution, or another method-specific interference-control approach.

CPI Support for ICP-MS Internal Standard Workflows

Selecting the right internal standards starts with the method, analytes, matrix, instrument configuration, and interference profile.

CPI International supports analytical laboratories with inorganic reference materials, ICP calibration and QC standards, custom inorganic standards, and ICP/ICP-MS accessories designed for routine laboratory workflows.

For laboratories developing or maintaining ICP-MS methods, CPI can help support:

- Custom inorganic standards with specified elements, concentrations, matrix, and volume
- ICP-MS and ICP-OES calibration standards
- ICP quality-control standards
- ICP tuning and setup solutions
- Internal mixing kits for simultaneous introduction of samples and internal standards

When the internal-standard mixture needs to match a specific method or laboratory workflow, a custom formulation can reduce manual preparation while keeping the analyte list, matrix, and concentration aligned with the method requirements.

Standardize Your Standards

References and Source Notes

[1] U.S. EPA. Method 200.8: Determination of Trace Elements in Waters and Wastes by Inductively Coupled Plasma–Mass Spectrometry, Revision 5.4. EPA page last updated April 8, 2026. https://www.epa.gov/esam/epa-method-2008-determination-trace-elements-waters-and-wastes-inductively-coupled-plasma-mass

[2] U.S. EPA. Method 200.8 PDF. Used for internal-standard definition, internal-standard stock solution, internal standardization, response limits, and Table 3 internal-standard limitations. https://www.epa.gov/sites/default/files/2015-06/documents/epa-200.8.pdf

[3] Agilent Technologies. ICP-MS Help: Internal Standard Method and Standard Addition Method. Used for general selection principles involving matrix effects, mass number, ionization potential, and candidate internal-standard elements. https://icp-ms.help.agilent.com/en/HowTo/Help/Reference/Internal_Standard_Method_and_Standard_Addition_Method.htm

Technical note: Method-specific requirements, acceptance criteria, internal-standard concentrations, and corrective actions should be verified against the current official method, laboratory SOP, instrument method, and quality system.