

USP <232>/<233> and ICH Q3D Elemental Impurities Analysis: The Agilent ICP-MS Solution



Elemental Impurity Analysis Requirements

Worldwide, regulatory authorities are responsible for ensuring that pharmaceutical products are both effective and safe. Potentially toxic and harmful contaminants—including elemental impurities—must be identified, and limits defined for the maximum levels that a patient should be exposed to. In February 2017, new procedures for the analysis of elemental (inorganic) impurities in pharmaceutical products and ingredients were finalized. Existing wet chemical and colorimetric tests, such as European Pharmacopoeia Heavy Metals chapter 2.4.8 and United States Pharmacopoeial Convention (USP) General Chapter <231>, have been replaced with instrumental methods. These methods provide specific, quantitative determination of individual elemental impurities in drug products and ingredients.

The USP, in parallel with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), has revised the standards for measuring inorganic impurities in pharmaceuticals and their ingredients. The updated USP General Chapters USP<232> (Elemental Impurities – Limits)(1) and <233> (Elemental Impurities – Procedures)(2) were implemented in January 2018. The equivalent ICH method is defined in the Guideline for Elemental Impurities (Q3D)(3). ICH-Q3D has been in effect since June 2016 for new marketing authorization applications and has applied to previously authorized medicinal products since December 2017.

The latest ICH Q3D and USP<232> chapters include catalyst elements, and other inorganic contaminants that may enter a drug product. Such contaminants can come from raw materials, the manufacturing process, the environment, packaging, and container closure systems (CCS). The maximum exposure limits are defined according to each impurity's toxicity and route of administration, rather than method capability, as was the case for the old colorimetric sulfide precipitate test in USP<231>.

USP<233> recommends the use of modern instrumental techniques (Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) or ICP-Mass Spectrometry (ICP-MS)), in place of the colorimetric test used in USP<231>. Alternative procedures may be used, provided they can be demonstrated to meet the performance requirements defined in the chapters. USP <233> also recommends the use of closed vessel sample digestion for solid samples, to ensure the quantitative recovery of all the regulated analytes, including volatile elements such as mercury.

China's equivalent method for analyzing pharmaceutical materials (including traditional Chinese medicines – TCM) is defined in the China Pharmacopoeia (ChP) 2020 Edition. This edition, which was approved in April 2020 and came into effect on December 30 2020, also includes ICP-MS as the recommended analytical technique for determining elemental impurities in pharmaceutical products.

Elemental Impurity Limits

The permitted daily exposure (PDE) limits for elemental impurities in drugs intended for oral, parenteral, and inhalational routes of administration, as per the ICH and USP chapters, are shown in Table 1.

The potential toxicity of an elemental impurity is different depending on the route of administration. Elemental impurities must be considered in a product risk assessment, appropriate for the intended route of administration of the final drug product. The likelihood of the element being naturally present (e.g. elements associated with a mineral-based raw material) or intentionally or unintentionally added (e.g. as a catalyst in chemical reactions, or via contamination from process equipment) must also be considered. The most toxic and ubiquitous Class 1 elements (Cd, Pb, As, and Hg) must be considered in the risk assessment for all drug products. Other elements, such as the Class 3 impurities, may need to be considered only if the drug is intended for parenteral or inhalational administration. The three classes are defined based on the toxicity of the elements and the likelihood of them occurring in drug products intended for each route of administration.

USP General Chapter <232> provides guidance on how a manufacturer should conduct the risk assessment to demonstrate compliance with the regulated limits for any given pharmaceutical product. Options include:

- Direct analysis of the final drug formulation
- Measurement of the level of impurities in each of the component materials used in the drug material
- Review of test data, or
- A risk assessment provided by a qualified raw material supplier.

If a risk assessment is performed, it must follow the guidelines defined in USP<232>, summarized in Table 1.

Table 1. The permitted daily exposure (PDE) limits for elemental impurities in drug products, according to their route of administration. Elements shaded in the table should be considered in product risk assessment. All elements listed should be included in risk assessment if naturally present or if intentionally or unintentionally added.

ICH/USP Class	Element	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalational PDE (µg/day)
Class 1	Cd - Cadmium	5	2	2
	Pb - Lead	5	5	5
	As - Arsenic (inorganic)	15	15	2
	Hg - Mercury (inorganic)	30	3	1
Class 2A	Co - Cobalt	50	5	3
	V - Vanadium	100	10	1
	Ni - Nickel	200	20	5
Class 2B	Tl - Thallium	8	8	8
	Au - Gold	100	100	1
	Pd - Palladium	100	10	1
	Ir - Iridium	100	10	1
	Os - Osmium	100	10	1
	Rh - Rhodium	100	10	1
	Ru - Ruthenium	100	10	1
	Se - Selenium	150	80	130
	Ag - Silver	150	10	7
	Pt - Platinum	100	10	1
	Class 3	Li - Lithium	550	250
Sb - Antimony		1200	90	20
Ba - Barium		1400	700	300
Mo - Molybdenum		3000	1500	10
Cu - Copper		3000	300	30
Sn - Tin		6000	600	60
Cr - Chromium		11000	1100	3

The J-value

The maximum level of elemental impurities in finished drug products is expressed as a maximum permitted daily exposure (PDE). This limit considers the concentration of the element present in the drug product, and the maximum recommended daily dose for the medicine.

Some materials require digestion or dilution in a solvent before analysis. For these materials, the PDE limit (in µg/day) must be converted to a concentration limit (in µg/L) as measured in the prepared sample. This conversion takes into account the dilution required to bring the analytes within the analytical range of the instrument and the maximum daily dosage.

The Target Concentration value in the prepared sample, referred to as the “J-value”, defines the maximum permitted concentration limit for the analyte in that sample.

The J value is calculated from:

$$J = \frac{PDE}{\text{Total Dilution} \times \text{Max Daily Dose}}$$

The Agilent ICP-MS MassHunter software calculates the J-values for each analyte. This calculation includes the final dosage form of the drug material being analyzed and the dilution factor applied. The calculation is illustrated in Table 2 for the Class 1 elements Cd, Pb, As, and Hg. The calculation uses a maximum dosage of 1 g/day and dilution factors of 250 x (e.g. 0.2 g in 50 mL) and 1000 x (e.g. 0.1 g in 100 mL). Typical instrumental detection limits (IDLs) for the Agilent 7850 ICP-MS are also shown, for comparison. Similar or slightly lower limits would be achieved using the Agilent 7900.

Table 2. Example J value calculation and comparative ICP-MS instrument detection limits (IDLs).

Element	Oral Dose PDE (µg/day*)	J-value @ 250x Dil. (µg/L)	J-value @ 1000x Dil. (µg/L)	Agilent 7850 ICP-MS IDLs (µg/L)
Cd	5	20	5	0.0001
Pb	5	20	5	0.0002
As**	15	60	15	0.005
Hg**	30	120	30	0.001

* Values apply to oral dose drugs with a daily dose of ≤ 10 g.

** Inorganic forms

The J-value is also used to define the calibration levels and QC concentrations. For example; calibrations must be prepared at concentration levels between 0.5 and 1.5 J. Detectability (for Limit procedures) must be demonstrated using a sample spiked at 80% of the J value (0.8 J). Spike recovery tests must also be performed at concentrations ranging from 50 to 150% of the J value (i.e. between 0.5 and 1.5 J).

The Complete Agilent Workflow Solution for Implementing an Elemental Impurities Testing Capability

Sample preparation

The USP<233> chapter references several methods that can be used for the preparation of samples for analysis by the compendial procedures ICP-MS and ICP-OES. These include:

- Direct analysis
- Dilution/solubilization in a suitable aqueous solvent, such as water or dilute acid
- Dilution/solubilization in a suitable organic solvent, such as 2-butoxyethanol:water (25:75), DMSO, or DGME
- Indirect solution, preferably using closed-vessel microwave digestion with strong acids

Most solid pharmaceutical materials can be digested using closed-vessel microwave digestion in nitric and hydrochloric acid. This procedure provides a sample digest in which all the regulated elements are stabilized in solution, ready for analysis by ICP-MS or ICP-OES, after appropriate dilution. The inclusion of at least 0.5% HCl is strongly recommended for stabilization of all samples, as it ensures that elements such as Hg remain in solution. Addition of HCl is essential when platinum group elements (PGEs) such as Pt, Pd, and Os are included in the analysis. A higher level of HCl may be required for long-term stability of these elements.

Agilent works closely with the leading microwave oven suppliers around the world. These collaborations ensure that pharmaceutical laboratories can select the most appropriate microwave to install, depending on their method requirements and the microwave oven supplier's local support capabilities.

Agilent ICP-MS instruments tolerate all common acid and organic solvent matrices (4), as well as other complex matrices, e.g. those produced by dissolving solid samples. Most sample types can be measured without requiring high dilution factors (5, 6). Agilent ICP-MS systems have a robust, high temperature (low CeO/Ce) plasma, ensuring good ionization and high sensitivity for all analytes. The plasma performance is important for poorly-ionized elements such as As, Cd, Hg, and several of the platinum group elements.

ICP-MS can suffer from errors caused by polyatomic interferences. Agilent single quadrupole ICP-MS instruments (the Agilent 7850 and 7900) ensure accurate results by removing interferences using a proprietary ORS⁴ collision/reaction cell operating in helium (He) collision mode. Method development and routine operation are simplified as He cell mode can be applied to all analytes in all typical sample types. This broad applicability means that consistent conditions can be used, whatever the sample type being analyzed or the elements being determined.

Agilent ICP-MS systems can measure elements that are present at high concentrations (major elements) and low concentrations (minor and trace elements) in a single analytical run. This capability is possible due to the instrument's wide dynamic range of up to 11 orders of magnitude. For the analyst, less sample preparation time is required (e.g. diluting samples to bring major elements into range), and there is less likelihood of sample remeasurement being needed due to an over-range result.

The standard sample introduction configuration of Agilent ICP-MS systems tolerates a wide range of aqueous and acid stabilized sample types, including those containing high levels of dissolved solids. For samples containing an organic solvent, such as hexane, DMSO, or DGME, a solvent-resistant sample introduction system, Pt-tipped interface cones, and option gas controller can be added to the ICP-MS.

Similarly, for the analysis of samples that require the addition of hydrofluoric acid (HF) to ensure complete digestion, an inert (PFA) sample introduction system is used. Such samples are unusual in most pharmaceutical laboratories, but this requirement may apply to some mineral-based excipients.

Understanding Instrument Performance and Suitability

USP General Chapter <233> (Elemental Impurities – Procedures) recommends the use of either ICP-MS or ICP-OES to measure the levels of elemental impurities in drug products and ingredients. An alternative technique, such as Flame Atomic Absorption Spectroscopy (FAAS), may only be used if it has been validated and meets the acceptance criteria. FAAS may be appropriate for characterizing a few high concentration elements in raw materials. But it is unlikely FAAS will be suitable for final drug product testing, where the analyte levels are too low to be accurately determined with the technique. For most pharmaceutical laboratories, a fast, multielement ICP technique will be preferred.

Selecting the most appropriate technique for elemental impurities testing will depend on the laboratory's specific requirements. The decision may start with whether to outsource the analysis to a qualified contract laboratory or bring the testing in-house. If you are evaluating and purchasing new instrumentation for this analysis for the first time, you will need to understand the performance capabilities of the instrumentation relative to the method requirements. Budget considerations may also be a factor, as will the skills and experience of the analysts in your lab.



Figure 1. The Agilent 7850 ICP-MS.



Figure 2. The Agilent 5800 ICP-OES.

ICP-OES or ICP-MS?

The key performance differentiators between ICP-OES and ICP-MS are:

Detection limits

ICP-MS has detection limits (DLs) that are around three orders of magnitude lower than ICP-OES for most elements. This difference is partly offset by the better matrix tolerance of ICP-OES, which means samples may not need to be diluted as much before ICP-OES analysis. ICP-OES DLs may be sufficient for analysis of ingredients such as bulk raw materials (fillers, binders, and so on) and for oral medicines, where the PDE limits are higher. ICP-MS instruments achieve detection limits in the low parts per trillion range for all the regulated elements. These limits allow accurate determination of all required elements in all dosage forms, including parenteral or inhalation drugs, where the PDE levels are lower than for oral medicines. For manufacturing facilities that produce a range of products, ICP-MS offers the flexibility to achieve the required limits for all regulated elements in all sample types.

Dilution

Dilution levels applied during sample preparation must also be considered. If only small quantities of sample are available, such as for some active pharmaceutical ingredients (APIs), a large dilution may need to be applied to give sufficient sample volume for analysis. Applying a large dilution reduces the Target Concentration (J value) in solution, so lower DLs are required for the analysis. Similarly, samples that contain high levels of dissolved solids must be diluted before analysis, with greater dilution being required for analysis by ICP-MS than by ICP-OES. The lower DLs of ICP-MS do however allow greater flexibility to choose a dilution level appropriate to the material and the sample preparation procedure.

Ability to handle dissolved solids

Agilent ICP-MS systems with Ultra High Matrix Introduction (UHMI) capability can handle samples that contain up to ~25% total dissolved solids (TDS). This is about 100 x higher than is typical for non-Agilent ICP-MS systems, which are usually limited to matrix levels of around 0.2%. Agilent ICP-OES instruments can also tolerate high levels of dissolved solids with extended analysis being handled more easily than on ICP-MS. The Agilent 5800 ICP-OES can routinely measure samples with up to 25% total dissolved solids, so is a good choice for laboratories that only measure bulk raw materials used in oral medicines, where higher PDE limits apply.

Speciation

For some elements, bio-availability and toxicity are highly dependent on the chemical form (oxidation state, organometallic complex, and so on) of the element. Of the analytes listed in the ICH/USP regulations, arsenic and mercury are of particular concern, and both are required analytes in all pharmaceutical products. For these two elements, the PDE limit refers to the inorganic form, because inorganic arsenic is the most toxic form, and inorganic mercury is considered the most likely form to be present in pharmaceutical materials.

If the measured concentration of arsenic (total of all forms) exceeds the Target Concentration, USP<232> suggests that a speciation analysis is performed to allow independent quantification of the inorganic As. If the inorganic As is found to be below the limit, the material would be considered to be compliant, even if the total As concentration exceeds the limit. The speciation of mercury should be established if the test material is likely to contain the more toxic methyl mercury species, which would normally be derived from marine material—fish, seaweed, etc. Otherwise, compliance is established by determination of the total level of Hg, which is most likely to be in the inorganic mercuric (2⁺) form.

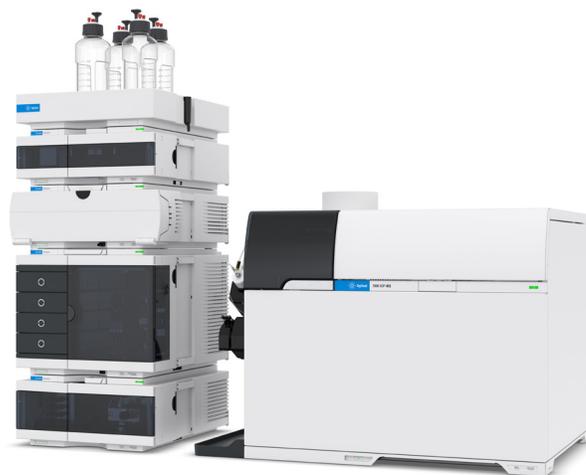


Figure 3. An Agilent LC can be integrated with an Agilent ICP-MS to create a complete system for routine speciation analysis.

Speciation analysis is performed using a chromatographic separation technique such as liquid chromatography (LC), coupled to the ICP-MS. Agilent LC-ICP-MS systems (Figure 3) are widely used and fully integrated, allowing a simple and reliable approach to routine speciation of arsenic and mercury in pharmaceutical materials. Data analysis for speciation uses the same intuitive, interactive data batch table view as for conventional total concentration measurements. The integrated chromatogram and calibration panes for inorganic As analysis are as illustrated in Figure 4.

Speed of analysis

ICP-OES is a fast technique, providing about twice the sample throughput of ICP-MS; ICP-OES can measure up to 2500 samples per 24 hours, compared to a maximum of around 1200 samples for ICP-MS. ICP-OES is the most suitable technique for laboratories that measure extremely high numbers of samples related to oral dosage medicines and where large dilution factors are not required.

Cost and ease of operation

ICP-OES instruments are a lower capital cost for the laboratory and maintenance costs are also somewhat lower than for ICP-MS. There are generally fewer method variables to setup on ICP-OES, and experienced operators are more widely available. However, Agilent ICP-MS systems such as the 7850 are provided with built in methods, automated optimization routines, and simplified workflows that enable novice operators to quickly learn the system.

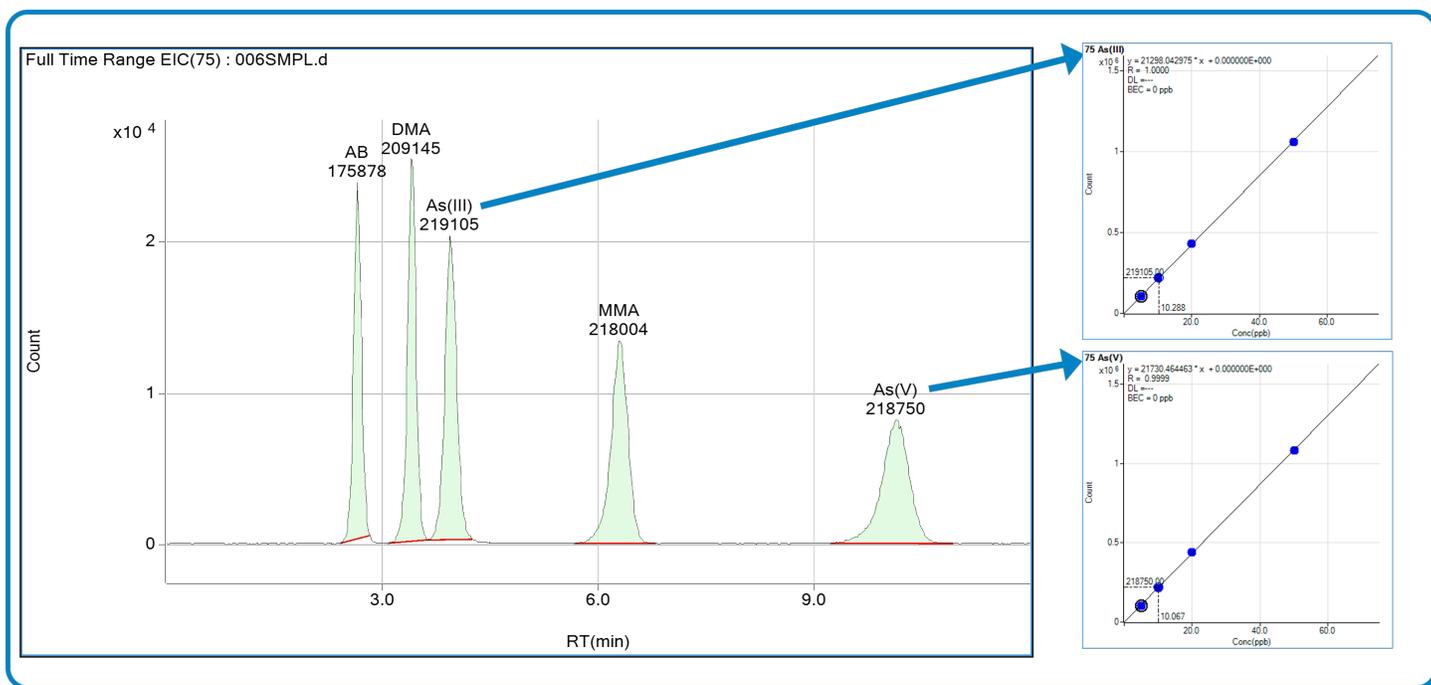


Figure 4. Speciation data analysis is integrated in ICP-MS MassHunter.

Why choose an Agilent ICP-MS?

Implementing the USP/ICH procedures could present a challenge for pharmaceutical laboratories with limited experience in metals analysis and ICP techniques. The Agilent 7850 or 7900 ICP-MS provides a simple, complete, workflow-based solution for labs that need to implement the latest procedures, with:

- Hardware features that minimize sample preparation and simplify calibration, including:
 - Robust, low CeO/Ce plasma, and Ultra High Matrix Introduction (UHMI) system to allow higher matrix level samples to be run routinely
 - Helium cell mode with kinetic energy discrimination (KED) for reliable removal of all common spectral interferences, ensuring accuracy and allowing access to qualifier isotopes for unequivocal analyte identification and quantification
 - 10 or 11 orders dynamic range detector to measure major and trace elements, and high- and low-concentration level samples in the same sample run
- Software tools that ensure consistent performance by automating system optimization and tuning, including automatically and consistently applying the selected UHMI dilution factor

- Pre-set methods that predefine the settings required for the USP/ICH/ChP methods, including operating conditions, analyte masses, integration times, and internal standard assignments
- Built-in templates for system suitability test reports
- A detailed standard operating procedure (SOP) template you can use as the basis for your laboratory's SOP. The SOP includes stepwise instructions for ICH Q3D and USP<232> method setup and operation.

The Agilent 7850 ICP-MS instrument provides a streamlined solution for low-level analysis of elemental impurities in pharmaceutical products and raw materials. With an Agilent ICP-MS, elemental impurity analysis is easier to implement and simpler to run routinely.

For laboratories that run applications other than routine elemental impurity analysis, e.g. pharmaceutical R&D, the Agilent 7900 ICP-MS provides lower detection limits, wider dynamic range, and greater flexibility for advanced applications. For laboratories addressing the most demanding applications, Agilent also offers the 8900 triple quadrupole ICP-MS (ICP-QQQ), which provides MS/MS operation to handle the most challenging analyses.

Installation and operational qualification

While vendor and instrument selection is the first step in establishing a new analytical capability, the vendor's ability to deliver, install, and commission the instrument is also a key factor in ensuring a smooth implementation. Qualification services (Installation Qualification (IQ) and Operational Qualification (OQ)), method setup and optimization, standard operating procedure (SOP) documentation, and operator training are essential steps in implementing an analytical facility in a regulated industry. After an instrument has been commissioned, Agilent provides applications expertise and documentation to ensure that the instrument is ready to go into production as quickly as possible.

Qualification services

Agilent provides a complete package of support services for pharmaceutical laboratories setting up an elemental impurities testing capability.

Our high levels of manufacturing quality control, combined with a worldwide organization of factory-trained support engineers, ensures fast installation and consistent, reliable instrument performance.

Once your instrument is installed, the Agilent CrossLab automated compliance engine (ACE) delivers instrument qualification services, IQ/OQ. These services follow an automated, paperless Analytical Instrument Qualification (AIQ) process.

ACE provides fully traceable, audit-ready approval documents and equipment qualification reports (EQRs), reducing the risk of noncompliance, see Figure 6.

Method Set Up and Documentation

The Solution-Ready Agilent 7850 and 7900 ICP-MS include pre-set methods and predefined report templates to help you to set up your new elemental impurities method.

The ICP-MS MassHunter software uses a streamlined workflow to guide new users through the process of setting up methods, defining sample analysis batches, and processing, approving, and reporting results. Many parameters are pre-defined, and system setup uses robust auto-optimization tools and status monitoring to ensure consistent high performance, regardless of operator experience.

ICH-Q3D, USP <232>/<233>, and ChP elemental impurity methods can simply be loaded and run. Settings—from plasma conditions to analyte isotopes, integration times, and internal standards—are predefined in a pre-set method supplied with the software.

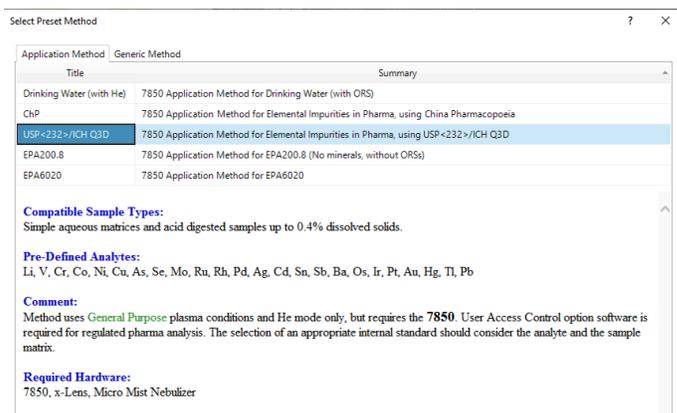


Figure 7. Agilent ICP-MS MassHunter software includes pre-set methods for elemental impurities analysis using ICH/USP and China Pharmacopoeia (ChP) methods.

If your laboratory has different requirements—for example you always measure a specific subset of the regulated analytes—the pre-set method can be modified and saved as a new, custom method template.

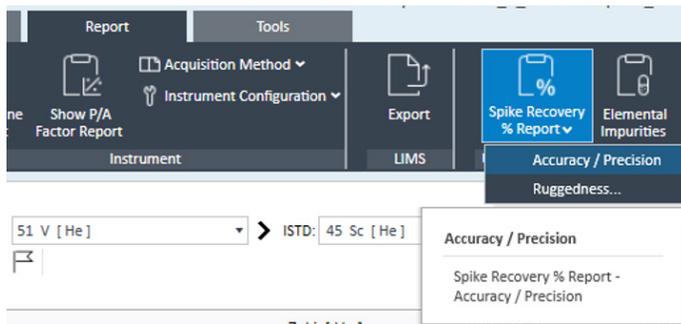
	Outlier	Method		
		Minimum Value	Maximum Value	Reference
Calibration Curve Fit R		0.95		
Relative Standard Error %				
Relative Error %				
ISTD Recovery % [compared with CalBlk]		60	125	
Spike Recovery % [compared with SpikeRef]				Spike Ref
QC Sample Conc Stability % [use 'QC1' Sample]		90	110	Oral (QC 1) (QC1)
QC Sample Conc Stability % [use 'QC2' Sample]		90	110	Parenteral (QC 2) (QC2)
QC Sample Conc Stability % [use 'QC3' Sample]				Inhalational (QC 3) (QC3)
QC Sample Conc Stability % [use 'QC4' Sample]				QC4
QC Sample Conc Stability % [use 'QC5' Sample]				QC5
Count RSD %			5	>= 10000 cps
Blank Conc Level % [use 'BlkVrfy' Sample]			100	BlkVrfy
Out of Calibration Curve Concentration Range %			110	

Analyte	Mass	Name	Curve Fit	Units	QC		
					L Oral (QC 1) (QC1)	Parenteral (QC 2) (QC2)	Inhalational (QC 3) (QC3)
1	7	Li	Linear	ppm	0.1	250	25
2	51	V	Linear	ppm	100	10	1
3	52	Cr	Linear	ppm	11000	1100	3
4	53	Cr	Linear	ppm	11000	1100	3
5	59	Co	Linear	ppm	50	5	3
6	60	Ni	Linear	ppm	200	20	5
7	62	Ni	Linear	ppm	200	20	5
8	63	Cu	Linear	ppm	3000	300	30
9	65	Cu	Linear	ppm	3000	300	30
10	75	As	Linear	ppm	15	15	2

Figure 8. QC checks evaluate whether each analyte complies with the concentration limits derived from the Permitted Daily Exposure for each route of exposure.

The ICP-MS MassHunter software also includes QC checks to evaluate whether each analyte complies with the J-value concentration limits derived from the Permitted Daily Exposure (PDE). Flags are displayed in the data table to highlight any analytes that are above the permitted level – different limits apply to drug products intended for different routes of administration.

ICP-MS MassHunter also includes pre-defined report templates for the Accuracy (spike recovery), and Precision (Repeatability and Ruggedness) checks defined in USP<233>.



Sample Name	111_Cd [He]		114_Cr [He]		118_Sn [He]		121_Sb [He]	
	Conc. (ppb)	Recovery (%)						
1 SATED NOSPK	0.011		0.003		0.265		0.038	
Mean	0.011		0.003		0.265		0.038	
3 SATED 1.0l	7.749	96.7	7.922	99.0	2376.230	99.0	362.459	100.7
4 SATED 1.0l	7.548	94.2	7.827	97.8	2352.859	98.0	357.301	99.2
5 SATED 1.0l	7.580	94.6	7.900	98.7	2394.578	99.8	363.020	100.8
6 SATED 1.0l	7.791	97.2	8.054	100.6	2420.406	100.8	368.985	102.5
7 SATED 1.0l	7.770	97.6	8.021	100.2	2420.879	100.9	366.827	101.9
8 SATED 1.0l	7.638	95.3	7.892	98.6	2398.333	99.9	361.043	100.3
Mean	7.679	95.8	7.936	99.2	2393.881	99.7	362.278	100.9
RSD of Conc. (%)	1.4		1.1		1.1		1.1	

Sample Name	135_Ba [He]		137_Ba [He]		138_Ba [He]		188_Op [He]	
	Conc. (ppb)	Recovery (%)						
1 SATED 1.0l	2774.191	99.1	2774.648	99.1	2800.978	100.0	39.023	97.5
2 SATED 1.0l	2723.445	97.3	2715.472	97.0	2750.059	98.2	39.328	97.3
3 SATED 1.0l	2793.643	99.8	2783.742	99.4	2788.082	99.6	39.226	98.0
4 SATED 1.0l	2809.762	100.3	2814.682	100.5	2817.966	100.6	39.563	99.8
5 SATED 1.0l	2804.823	100.2	2800.133	100.0	2810.305	100.4	39.637	99.0
6 SATED 1.0l	2782.058	99.4	2759.069	98.5	2769.389	98.9	39.268	98.1
Mean	2781.320	99.4	2774.624	99.1	2789.453	99.6	39.274	98.1
RSD of Conc. (%)	1.1		1.3		0.9		0.7	

Figure 9. The ICP-MS MassHunter software provides report templates that include the accuracy and precision checks defined in USP<233>.

Creating procedures and training operators

Agilent ICP-MS instruments can be supplied with a detailed Standard Operating Procedure (SOP) template for elemental impurity analysis that includes:

- Method summary and analyte list
- Sample preparation details
- Calibration and interferences
- Pre-set method parameters
- USP<233>/ICH method validation and reports
- Troubleshooting guide

Step-by-step instructions are included for the instrument and method setup, acquisition, data analysis, and reporting processes. The SOP can be used as the basis for creating your own elemental analysis SOP, saving you considerable time in getting your Quality documentation in place. Agilent ICP-MS instruments are delivered with a set of user manuals and a software Help and Learning Center containing interactive video tutorials on setup, operation, and instrument maintenance.



Figure 10. A detailed SOP template is supplied with the Agilent ICP-MS instrument, expediting development of your own elemental impurities analysis SOP.

Ensuring Data Quality with Certified and Traceable Standards

The ability to validate the quality of analytical results is a critical GMP requirement. Demonstrating data quality depends on the quality of the standards and reference materials used to calibrate the analytical equipment and confirm instrument performance using system suitability testing and ongoing analytical quality control (QC) solutions.

Agilent ICH/USP certified reference materials (CRMs) are pre-mixed blends of elements at the appropriate relative concentrations for the oral PDE limits defined in the ICH/USP methods (more CRMs are under development). The CRMs are traceable to NIST, giving a high level of confidence in the quantitative results generated by your Agilent ICP-MS. Agilent premixed standards save you time and reduce errors by eliminating the need for you to prepare your own standards from single element stocks.



Figure 11. Agilent ICH/USP elemental impurities kit contains standards covering all regulated elements.

Agilent CRMs for elemental impurity analysis are available as a kit containing five separate standards (including an internal standard mix) covering the full suite of regulated elements. Alternatively, each of the five solutions can be purchased separately, for example if only the Class 1 elements are being measured.

The standards are manufactured in an ISO Guide 34 compliant facility and certified in an ISO/IEC 17025 testing laboratory.

Table 3. The concentrations of elements in Agilent CRM standards for oral dosage drug products.

ICH/USP Class	Element	Oral PDE (µg/day)	Conc in Stock (µg/mL)
Class 1	Cd	5	5
	Pb	5	5
	As (inorganic)	15	15
	Hg (inorganic)	30	30
Class 2A	Co	50	50
	V	100	100
	Ni	200	200
Class 2B	Tl	8	8
	Au	100	100
	Pd	100	100
	Ir	100	100
	Os	100	100
	Rh	100	100
	Ru	100	100
	Se	150	150
	Ag	150	150
	Pt	100	100
Class 3	Li	550	550
	Sb	1200	1200
	Ba	1400	1400
	Mo	3000	3000
	Cu	3000	3000
	Sn	6000	6000
	Cr	11000	11000
	ICH/USP Target Elements Standard A		
	ICH/USP Target Elements Standard B		
	ICH/USP Target Elements Standard C		
	ICH/USP Target Elements Standard D		

Complying with Electronic Records and Electronic Signatures (ERES) Regulations

The US FDA has regulations in place to ensure the security, integrity, and traceability of electronic records. The FDA provides guidelines covering the criteria that they will use to judge whether electronic records and e-signatures can be accepted as equivalent to paper records and printed (handwritten) signatures. The regulations are described in Part 11 of Title 21 of the Code of Federal Regulations (21 CFR Part 11). The European Commission has similar regulations in place, as described in Annex 11: Computerized Systems of their Good Manufacturing Practice (GMP) rules.

Equivalent regulations that apply in other jurisdictions are described in the Pharmaceutical Inspection Convention/ Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMPs, China's GMPs and the chapter on computer systems of the Brazilian GMPs.

Agilent has a range of software solutions to help laboratories comply with Part 11, Annex 11, and equivalent regulations. Compliance products are available to suit any size of laboratory, from a lab with a single ICP-MS instrument, to a global enterprise with multiple sites and dozens or hundreds of instruments.

Access control

The ICP-MS MassHunter software integrates with Agilent User Access Control (UAC) module and OpenLab Shared Services (OLSS) to provide:

- Configurable password protection for user access to the workstation PC and ICP-MS software
- Flexible, configurable, user management tools, with multilevel access to software functions
- An audit trail—a record of user's logon/logoff to the workstation and ICP-MS MassHunter application, and user actions within ICP-MS MassHunter.
- Electronic signature protocols (user verification and reason) for specific actions, as defined in the Audit Trail Map (ATM)

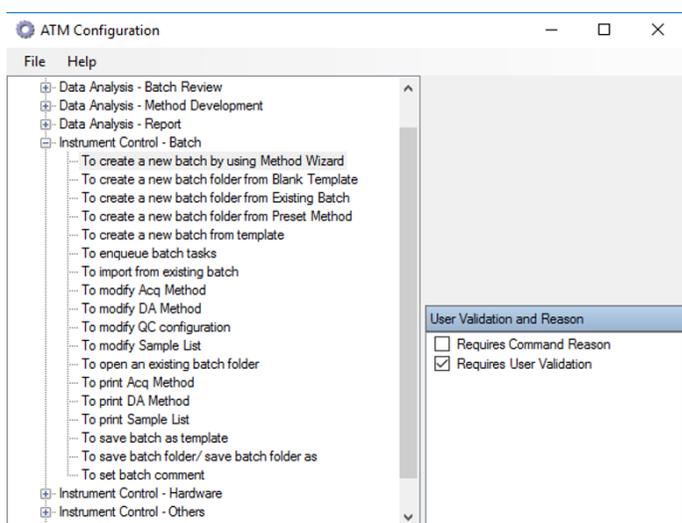


Figure 12. Electronic signature protocols (user verification and reason) for specific actions are defined in the Audit Trail Map (ATM) section of the Agilent ICP-MS MassHunter User Access Control (UAC) module.

To support multiuser and shift-based working, UAC/OLSS also allows a change of user during automated sequencing or other long operations, without affecting the electronic link between user and data.

Electronic records

Secure storage of electronic records, including version control, is provided by a range of Agilent compliance software products. Three options are available, to provide the perfect fit for your laboratory.

1. **Agilent Spectroscopy Database Administrator (SDA)** gives secure database storage of data collected on a single Agilent ICP-MS. The SDA software and free Microsoft SQL Server Express database are installed on the instrument workstation PC to minimize setup costs. A version of SDA is also available for the Agilent ICP Expert software for ICP-OES installations.
2. **Agilent OpenLab Server/ECM XT** provides the flexibility of an expandable solution, storing data for up to 100 instruments. These instruments can include Agilent ICP-MS systems operating with ICP-MS MassHunter, Agilent and non-Agilent LCs and GCs, and Agilent single quadrupole LC/MS and GC/MS instruments running OpenLab CDS software. OpenLab Server is installed on a separate server, allowing the use of RAID architecture for added security and data backup.
3. **Agilent OpenLab ECM**, also server based, supports an unlimited number of instruments, and includes multivendor support and PDF signatures.

Getting Support

Agilent ICP-MS systems include detailed operator training and documentation on key operations, workflows, and maintenance tasks, supporting Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) requirements. Extra application-specific training can be provided as part of the implementation package associated with setting up analysis methods following the Agilent elemental impurities SOP.

With our global network of Agilent offices and distributors, we have the capabilities to support even the most geographically diverse of pharmaceutical materials manufacturers. Whether you need support for a single instrument or multiple labs, Agilent can provide telephone support or onsite service to help you solve problems quickly, increase uptime, and maximize the productivity of your team with:

- Onsite maintenance, repair, and qualification/ requalification services.
- Service agreements for all your systems and peripherals.
- Application training and consulting from our dedicated, worldwide network of specialists.
- Service plans to optimize instrument utilization and maximize productivity

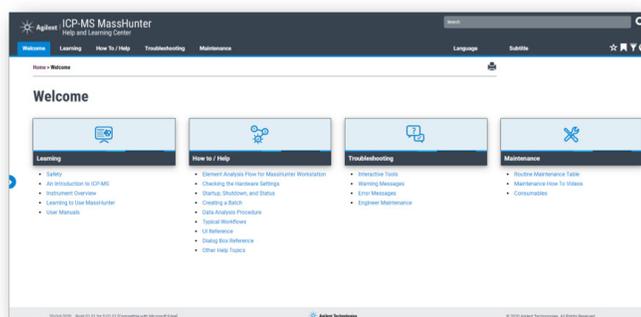


Figure 13. The Agilent ICP-MS Help and Learning Center includes user guides, tutorials, interactive videos, and manuals.



Figure 14. Agilent ICP-MS Help and Learning Center includes troubleshooting tips and guides covering common ICP-MS MassHunter workflows and ICP-MS maintenance tasks.

ICP-MS MassHunter software is provided with an extendable one year Software Maintenance Agreement (SMA), which provides unlimited access to phone support and free software updates during the warranty period.

The Agilent Service Guarantee provides the most secure guarantee in the industry. If your Agilent instrument requires service while covered by an Agilent service agreement, we guarantee repair or we will replace your instrument for free. No other manufacturer or service provider offers this level of commitment to keeping your lab running at maximum productivity.

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