Agilent

Trusted Answers

Measuring Elemental Impurities in Pharmaceutical Materials

Agilent Atomic Spectroscopy Solutions



USP <232>/<233> & ICH Q3D(R2)/Q2(R1)

Implementing Elemental Impurities Tests in the Pharmaceutical Industry

Worldwide regulations for pharmaceutical materials

Worldwide pharmacopeias have introduced revised standards for controlling elemental impurities in drug products and ingredients. The current USP and ICH chapters require more elements to be monitored at lower levels than previously and recommend modern instrumental analytical procedures to determine the concentration of elemental impurities. Sample preparation approaches are also described with closed vessel microwave digestion being recommended for acid solubilization of solid materials.

Limits for elemental impurities

Analytical requirements for the USP/ICH chapters depend on the type of sample and the manufacturing processes. The permitted daily exposure (PDE) limits specified for each element are based on the intended route of administration (refer to table, opposite).

Elements listed in Class 1 and Class 2A must be considered in all product risk assessments. Additional elements, highlighted in blue in the table, should also be considered, depending on the route of administration of the final drug product. All USP/ICH elements should be included in the assessment if they are likely to be naturally present or have been intentionally or unintentionally added.

Manufacturers must be able to demonstrate that their drugs comply with the limits for the listed elements in their final drug formulation. They can either test the final product, test each component of the product, or use impurity data from a qualified component supplier.

Element	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalational PDE (µg/day)	Cutaneous PDE (µg/day)
ICH/USP Class 1				
Cd - Cadmium	5	2	3	20
Pb - Lead	5	5	5	50
As - Arsenic (inorganic)	15	15	2	30
Hg - Mercury (inorganic)	30	3	1	30
ICH/USP Class 2A				
Co - Cobalt	50	5	3	50 (35)*
V - Vanadium	100	10	1	100
Ni - Nickel	200	20	6	200 (35)*
ICH/USP Class 2B				
Tl - Thallium	8	8	8	8
Au - Gold	300	300	3	3000
Pd - Palladium	100	10	1	100
Ir - Iridium	100	10	1	100
Os - Osmium	100	10	1	100
Rh - Rhodium	100	10	1	100
Ru - Ruthenium	100	10	1	100
Se - Selenium	150	80	130	800
Ag - Silver	150	15	7	150
Pt - Platinum	100	10	1	100
ICH/USP Class 3				
Li - Lithium	550	250	25	2500
Sb - Antimony	1200	90	20	900
Ba - Barium	1400	700	300	7000
Mo - Molybdenum	3000	1500	10	15000
Cu - Copper	3000	300	30	3000
Sn - Tin	6000	600	60	6000
Cr - Chromium	11000	1100	3	11000

Permitted daily exposure (PDE) limits for elemental impurities according to each route of exposure. Blue shaded cells indicate where an elemental impurity should be included in the risk assessment, even if not intentionally added.

**Lower value applies for sensitizers*

The Complete Agilent Solution

Supporting your lab every step of the way



Where do you get applications support and instrument services?

We have a global team of industry and technical experts to provide training and support.



What sample preparation is needed?

We have the expertise and relationships with vendors around the world to help you select the best sample preparation equipment.



Which instrument best meets your needs?

We can help you choose the most appropriate technique for your lab's requirements.



Is the instrument installed and operating correctly?

We have complete services to install, commission, and qualify your new instrument.



Agilent can help you successfully implement a compliant and effective elemental impurities testing capability



Are you meeting Part 11 & Annex 11 regulatory requirements?

We offer a range of compliance software options, suitable for any size and type of lab.



Where do you obtain reliable standards and consumables?

We offer premixed USP/ICH CRM stock solutions as well as consumables and parts for your system.



Do you have procedures and trained operators to meet analytical and regulatory requirements?

We have SOP templates and documentation to help you implement best practice, and can provide training for analysts.



How can you set up a method to meet the requirements?

We supply predeveloped methods for USP <232>/<233> & ICH Q3D(R2)/Q2(R1) to quickly get you operational.

Agilent Instrumentation for Elemental Impurities Analysis

Agilent 5800 VDV and 5900 SVDV ICP-OES

The Agilent 5800 and 5900 ICP-OES are ideally suited for analyzing elemental impurities in bulk ingredients (e.g., raw materials and excipients) or oral dosage final products that require the fast analysis of many samples. It can measure all 24 of the regulated elements down to parts-per-billion levels and can handle samples containing up to 25% total dissolved solids, e.g., sodium carbonate.

The 5800 and 5900 ICP-OES deliver high speed and reduced cost-per-analysis, making it ideal for those labs offering contract pharmaceutical analysis services.

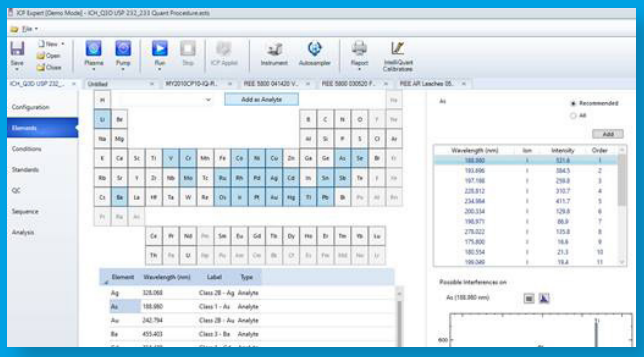
The 5800 and 5900 ICP-OES enable you to:

- Achieve reproducible results for long periods without cleaning—even with high matrix samples—with the vertically mounted torch.
- Add confidence to analysis accuracy with fast measurement of the whole wavelength range, allowing the comparison of concentrations determined from multiple emission lines for each element—without a time penalty.
- Simplify method setup and your analysis with automated software algorithms like fitted background correction and FACT spectral deconvolution.
- Simplify instrument setup, sample analysis, and maintenance activities with intuitive software and plug-and-play hardware components.



Quick Start Methods

The USP<232>/<233> and ICH Q3D method template provided with the 5800 and 5900 ICP-OES includes optimum wavelengths for the 24 elements and appropriate quality controls. It's a great headstart for an analyst setting up these methods for the first time.



*The elemental impurities methods are performance based so any procedure that has been validated and meets the acceptance criteria can be used.
Agilent offers both flame and furnace atomic absorption instruments that may be used, depending on the regulated limits of the elements to be measured.

Agilent 7850 ICP-MS

The Agilent 7850 ICP-MS* is perfect for analyzing a wide range of drug products and ingredients. The 7850 can easily measure all 24 USP/ICH elements at the low levels required in parenteral and inhalational medicines as well as oral and cutaneous dosage forms. The 7850 ICP-MS is also ideal when limited sample is available or a high matrix level necessitates a large dilution.

Easy method setup and the ability to handle samples with varying matrices or a wide range of concentrations make the 7850 a highly productive system for a contract lab.



The 7850 ICP-MS enables you to:

- Measure the widest range of sample types using the robust, high temperature plasma ion source with Ultra High Matrix Introduction (UHMI) capability.
- Remove all common polyatomic interferences using a single, simple, helium cell-mode ORS[4] collision/ reaction cell.
- Simplify method setup, minimize re-runs due to over-range results, and measure high- and low-concentration analytes in the same run, with the 10 orders dynamic range detector.
- Extend the range of your analytical capabilities with flexible sample introduction options for organic solvents, speciated analysis of As and Hg, and auto-dilution/standard preparation.

Agilent 9500 Triple Quadrupole ICP-MS

The Agilent 9500 delivers true ICP-MS/MS performance without the complexity. Its proprietary Dual-Cell System, with Advanced Helium Mode and Air cell mode, enables powerful interference removal across complex matrices. OpenLab ICP-MS software simplifies method setup and routine analysis.

The 9500 ICP-MS enables you to:

- Resolve difficult interferences on elements such as As and Se using Air mode, which uses ambient air without an oxygen cylinder.
- Reduce acquisition time by >33% for routine analysis with Advanced Helium Mode, which replaces multiple tune modes with one.
- Simplify method development with preset USP <232>/ ICH Q3D methods and Method Advisor in OpenLab ICP-MS, with dedicated elemental impurity reporting.

SOPs Made Easy

The 7850 ICP-MS includes predeveloped methods for USP<232>/ICH Q3D and the Chinese Pharmacopoeia, built-in USP calculations and reports, and a standard operating procedure template to expedite development of your own SOPs.These tools streamline setup and suitability testing and ensure fast and reliable system implementation.



*The Agilent 7900 ICP-MS and 8900 ICP-QQQ are also suitable for elemental impurity testing in pharmaceutical materials. Contact your Agilent representative for full details.

Compliance Across the Analysis Lifecycle

Agilent offers a range of software solutions, reference materials, and services

Instruments manufactured to comply

Agilent has a strong focus on regulatory compliance with a Quality Management System, product lifecycle documentation, and declarations of product validation for software development all in place.



An example of the Declaration of Software Quality delivered with the OpenLab ICP-MS software (left) and the ICP Expert 21 CFR Part 11 software kit (right).

System qualification in your lab

After the arrival of your new instrument, Agilent CrossLab instrument qualification services can help you confirm that it has been installed correctly and is operating as intended.

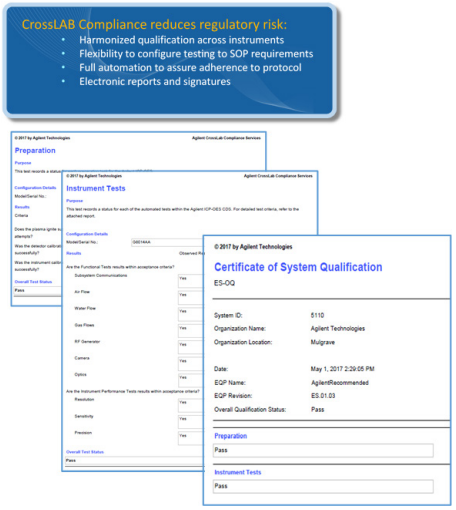
Using their Automated Compliance Engine (ACE), CrossLab field technicians deliver consistent Installation Qualification (IQ) and Operational Qualification (OQ) services for a wide range of Agilent instruments, including the 7850 and 7900 ICP-MS, the 9500 and 8900 ICP-QQQ, and the 5800 and 5900 ICP-OES.

CrossLab Installation Qualification confirms that the purchase order and certification is complete and correct and checks that the system and operating software are installed correctly prior to initial utilization.

CrossLab Operational Qualification includes a set of standard operational/performance tests; results are compared to the specifications for parameters such as sensitivity, stability, resolution, etc.

The CrossLab qualification service reduces regulatory risk by providing:

- Harmonized qualification process and reports across instruments
- Flexibility to configure testing to your SOP requirements
- Full automation to ensure adherence to protocol
- An audit-ready Equipment Qualification Report (EQR)



Agilent ACE software provides a detailed, audit-ready Equipment Qualification Report (EQR) after IQ/OQ are complete, certifying product performance.

21 CFR Part 11 and EU Annex 11 compliance software

Agilent provides a variety of software solutions and documentation to support compliance with the 21 CFR Part 11 and Annex 11 regulations on electronic records and electronic signatures. An Agilent compliance solution helps you to ensure the security, integrity, and traceability of your analytical data.

We can guide you through the software selection and implementation process to ensure you have the right systems and processes in place to meet your analytical needs and meet regulatory requirements.



Continuing compliance with Certified Reference Materials (CRMs)…

Agilent has a suite of CRMs to simplify testing of elemental impurities in pharmaceutical products to ICH Q3D and USP<232> requirements.

The Agilent ICH/USP elemental impurities kits for oral and parenteral limits include CRMs containing the required elements at the appropriate relative concentrations and separated by ICH/USP class, plus an internal standard mix. The individual standards in each kit can also be ordered separately. These CRMs are manufactured in an ISO Guide 34 facility and certified in an ISO/IEC 17025 testing laboratory. They include a Certificate of Analysis confirming actual concentrations, measurement uncertainty, and NIST traceability.



…and ongoing support

Agilent CrossLab service experts can support your continuing analytical and compliance needs with industry and method expertise, application consulting, preventive maintenance and repairs, compliance verification and periodic requalification, and ongoing education.

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