

Ultrapure Water for Determination of Elemental Impurities per USP

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Abstract

This paper demonstrates the suitability of fresh ultrapure water produced using Milli-Q® water purification systems for analyses of elemental impurities according to General Chapters USP <231>; <232>; and <233>.

Key words or phrases

trace elements, metals, ICP-MS, BEC, LOD, water quality, interferences, pharmacopeia, USP, elemental impurities, General Chapter <231> - Heavy Metal Limit Test, General Chapters: USP <232> and USP <233>

Introduction and Water Quality Requirements

In the pharmaceutical industry, it is crucial to monitor and control inorganic impurities in pharmaceuticals because some metals are used as reagents and catalysts during production and formulation processes. Moreover, metal impurities can be introduced into pharmaceutical products non-intentionally through contaminated reagents, or when products are in contact with pharmaceutical packaging or with metal surfaces during the development process. This is why the United States Food and Drug Administration (FDA) and similar international health agencies have had long-standing regulations in place for controlling harmful impurities in pharmaceutical products marketed for human consumption. Historically, four heavy metals, or the “Big Four”, were required to be tested according to the United States Pharmacopeial Convention (USP) General Chapter <231> “Heavy Metal Limit Test”. However, new mandatory guidelines to control potential toxic impurities in drugs were recently established in two USP General Chapters <232>¹ and <233>.²

These new Elemental Impurities chapters in the USP subdivide the metals desired for analyses into several groups. In this application note, the first and the second groups comprising 15 metals (cadmium, lead, arsenic, mercury, iridium, osmium, palladium, platinum, rhodium, ruthenium, chromium, molybdenum, nickel, vanadium and copper) are addressed. Other elemental impurities listed in the FDA’s *Guidance for Industry to Q3D Elemental Impurities*³ and in the European Medicine Agency’s (EMA) *Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents*⁴ are addressed in an extended ICP-MS application note for pharma.

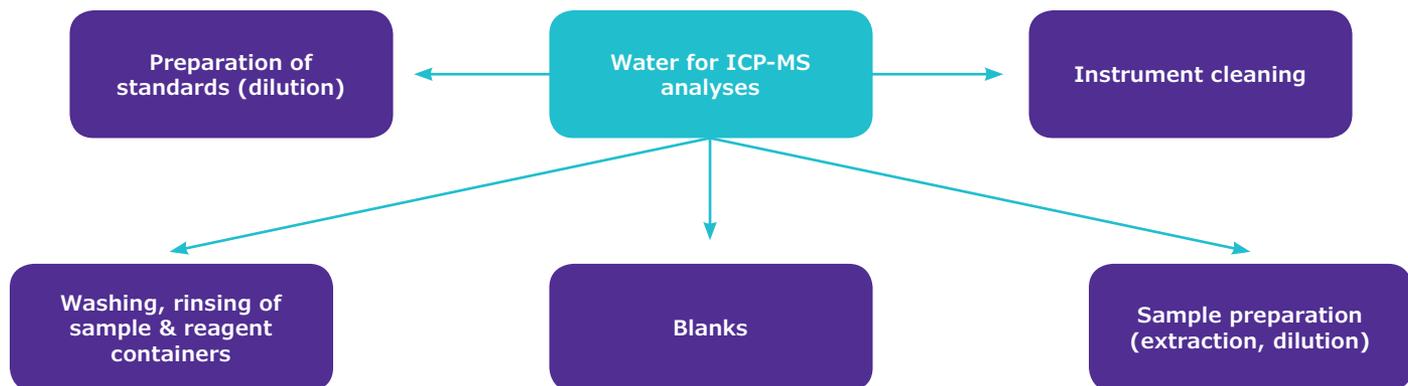


Figure 1. Different types of uses for ultrapure water in ICP-MS analysis.

Inductively coupled plasma–mass spectrometry (ICP-MS) is a sensitive technique for analyses of elemental impurities.² Ultrapure water is a main reagent in ICP-MS and is used extensively from sample preparation to analytical instrument cleaning (**Figure 1**). In the pharmaceutical industry, the choice of water quality is dictated by its intended use. Milli-Q[®] ultrapure water purification systems are designed to be compliant* with water quality standards described in various pharmacopeias. However, water selected as a reagent must not only comply with specific pharmacopeial standards, but must also meet the requirements of modern instrumentation to ensure the best performance of ICP-MS instrumentation.⁵ Thus, reagent water of very high quality must be selected to avoid sample and analytical instrument contamination.⁶ The aim of this study was to evaluate the suitability of fresh ultrapure water produced using Milli-Q[®] ultrapure water purification systems for use in ICP-MS trace element analyses.

Results and Discussion

In the pharmaceutical industry, element analyses are performed in the range of mg/L (ppm) to sub- $\mu\text{g/L}$ (sub-ppb) levels. As sensitivity, accuracy, precision and recovery must be appropriately demonstrated during the method validation process, achieving a low and stable background equivalent concentration (BEC) as well as low and consistent detection limits is critical. **Table 1** presents the BEC and limit of detection (LOD) in Milli-Q[®] ultrapure water for each element in ng/L (ppt) level.

Element	BEC (ppt)	LOD (ppt)
⁵¹ V	0.72	0.39
⁵² Cr	2.10	0.37
⁵⁸ Ni	0.76	0.14
⁶³ Cu	0.19	0.18
⁷⁵ As	3.10	0.11
⁹⁵ Mo	0.62	0.72
¹⁰¹ Ru	0.69	0.36
¹⁰³ Rh	0.16	0.19
¹⁰⁵ Pd	0.07	0.26
¹¹¹ Cd	0.06	0.06
¹⁸⁹ Os	0.28	0.20
¹⁹³ Ir	0.08	0.12
¹⁹⁵ Pt	0.29	0.19
²⁰² Hg	0.49	0.25
²⁰⁸ Pb	1.37	0.33

Table 1. The levels in ng/L (ppt) of elemental impurities in freshly produced ultrapure water from a Milli-Q[®] system measured under normal laboratory conditions (not in a clean room).

* Compliance reports are available on demand.

From **Table 1**, it can be observed that certain elements are present in slightly higher levels than sub-ppt. This can be explained by contamination coming from the laboratory environment, since the present analyses were performed under normal laboratory conditions.⁷ In case there is a need to achieve significantly lower levels of elements, it is reasonable to apply an additional polishing step, such as a Q-POD® Element unit which makes it possible to obtain BECs at sub-ppt and ppq levels in a clean room or metal-free laboratory environment.^{8,9}

Experimental

Ultrapure water samples from a Merck Milli-Q® Advantage A10 water purification system, equipped with Q-Gard® and Quantum® TEX cartridges, Millipak® final filter, and fed by an Elix® Essential 5 water purification system, were analyzed for the levels of V, Cr, Ni, Cu, As, Mo, Cd, Pd and Pb using an Agilent® 7700s ICP-MS instrument, and for the levels of Ru, Rh, Os, Ir and Pt using an Agilent® 7500s ICP-MS instrument. Ultrapure water samples from a Merck Milli-Q® Direct water purification system, equipped with Q-Pak® TIX cartridge and Millipak® final filter, were analyzed for Hg levels using an Agilent® 7500s ICP-MS instrument. All experiments were performed under regular laboratory conditions (not in a clean room).

Agilent® 7700s instrumental details and parameters: PFA-50 nebulizer, PFA spray chamber, sapphire inert torch, quartz 2.5 mm i.d. torch injector, platinum sample and skimmer cone, RF power 600/1600 W, sampling position 12 / 8 mm, carrier gas flow 0.90 L/min, makeup gas flow 0.32 / 0.51 L/min, auto detector mode, calibration through 1, 5, 10, 50 ng/L.

Agilent® 7500s instrumental details and parameters: quartz nebulizer, quartz spray chamber, quartz i.d. torch injector, nickel sample and skimmer cone, RF power 1300/1550 W, sampling position 8 mm, carrier gas flow 0.96 L/min, makeup gas flow 0.23 L/min, auto detector mode, calibration through 1, 20, 50, 100 ng/L.

The calibration standards used in experiments with the Agilent® 7700s were a mixture of Agilent® and SPEX CertiPrep®, and with the Agilent® 7500s, ROMIL PrimAg®-xtra was used. Containers were all PFA pre-cleaned with ultrapure water. All ultrapure water samples (resistivity of 18.2 MΩ·cm and TOC below 5 ppb) from Milli-Q® water purification systems were analyzed immediately after water collection.

Conclusion

Low levels of elemental impurities in ultrapure water produced by Milli-Q® ultrapure water purification systems were demonstrated. Laboratories in the pharmaceutical industry performing trace element analyses can rely on Milli-Q® water purification systems to meet their stringent requirements for the highest purity water for their experiments. Choosing ultrapure water from Milli-Q® water purification systems for element analyses will help to ensure the generation of high quality data.

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