Application Note 43149

Analysis of elemental impurities in drug products using the Thermo Scientific iCAP 7600 ICP-OES Duo

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Key Words
USP 232, USP 233, USP 2232, ICH Q3D, ICP-OES, Pharmaceutical, DMSO, iTEVA Security

Goal

The detection of trace elemental impurities in pharmaceutical products is of great importance. Using the Thermo Scientific™ iCAP™ 7600 ICP-OES Duo and Thermo Scientific™ Qtegra™ Intelligent Scientific Data Solution™ allows analysts to meet the stringent requirements imposed by regulatory bodies such as the United States Food and Drug Administration (FDA). The work described here demonstrates compliance with 21 CFR Part 11 and analysis according to USP <232>, <233> and <2232>, as described in USP 37-NF-32.

Introduction

Impurities in pharmaceutical products are of great concern not only due to the inherent toxicity of certain contaminants, but also due to the adverse effect that contaminants may have on drug stability and shelf-life. This necessitates the monitoring of organic and inorganic impurities throughout the pharmaceutical manufacturing process, from raw ingredients to final products.

Many readers are already familiar with pharmaceutical testing methodologies governed by The United States Pharmacopeia (USP). USP recently announced measures to modernize (and replace) the USP General Chapter for Heavy Metals <231> by proposing two new General Chapters and one Supplemental General Chapter:

<232> Elemental Impurities – Limits (1)

<233> Elemental Impurities – Procedure (2)

<2232> Elemental Contaminants in Dietary Supplements (3)

The rationale behind introducing the new chapters was to provide a modern equivalent to USP General Chapter <231>, which is based on a hundred-year-old colorimetric test ('heavy metals test') involving the precipitation of ten sulfide-forming elements and visually comparing the color of the resulting precipitate to that of a 10 ppm lead standard. There are several known deficiencies with the method including: the inability to differentiate between the levels of individual contaminants, use of potentially hazardous solvents such as thioacetamide and the use of a furnace during the preparation of certain samples, which results in significant loss of volatile contaminants such as tin and mercury.

The Second Supplement to USP 35-NF 30 June 1, 2012, with an official date of December 1, 2012 approved changes to heavy metals testing procedures for pharmaceuticals and dietary supplements. USP General Chapter <232> sets out the permissible levels of fifteen elements in final drug products. Toxicological data is used to set the limits, which are then expressed in terms of a permissible daily exposure (PDE) limit. The route of administration (oral, parenteral, or inhalation) is taken into account when setting the PDE, with orally administered drugs having a higher permissible limit than drugs that are delivered parenterally or by inhalation.

With the exception of mercury, the limits set out in Chapter <232> are consistent with the International Conference on Harmonization's (ICH) Q3D Elemental Impurities Working Group pre-Stage 2 draft guidelines (4). The ICH Q3D guideline are currently being reviewed and are likely to expand to cover more elements and it has been decided that a review of Chapter <232> will happen after the deliberations on ICH Q3D guidelines have been completed. Following the review, Chapter <232> may be expanded to cover more elements, or an informational chapter may be incorporated to cover elements of low toxicity and bring it in line with ICH Q3D.

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The USP–NF is a combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). The current version of USP–NF standards is deemed official by USP and is enforceable by the U.S. Food and Drug Administration. The General Notices provision, which instigates changes applicable to all USP–NF articles, will be part of a General Notices revision that is scheduled to appear in USP 37–NF 32. The official date for this is May 1, 2014 and marks the date on which <232>, <233> and <2232> will be mandatory, despite their implementation date of December 2, 2012. A further consequence of the implementation process for general chapters <232> and <233>, will be the complete removal of USP General Chapter <231> Heavy Metals from the compendia on May 1, 2014. Past May 1, 2014 Chapter <231> will no longer be valid and testing must instead conform to the limits set out in Chapter <232>, using the procedures set out in Chapter <233> (analysis by ICP-OES or ICP-MS).

In future all drug products produced and sold in the U.S. must comply with the limits set by USP<232>. Drug substances and excipients will be tested and reported for elemental impurities. Similarly, nutraceutical products must comply with the limits set by USP<2232>, which extends only to arsenic, mercury, cadmium and lead. Speciation of organic and inorganic elemental forms is critical for the analysis of Dietary Supplements.

Instrumentation

The Thermo Scientific iCAP 7600 ICP-OES Duo and associated Thermo Scientific Qtegra Intelligent Scientific Data Solution (ISDS) was used for the analysis. The iCAP 7600 ICP-OES Duo is well suited to this type of application due to its low detection capabilities for the elements of interest, as well as for its ability to resolve complex spectra. Both of these points are critical in relation to the low limits stipulated for elements such as arsenic and mercury. In addition, elements such as Pd, Pt, Os and Ir produce many emission lines when excited in the plasma, which need to be resolved effectively to avoid spectral interferences. The Qtegra ISDS and Thermo Scientific iCAP Validator Kit were used to ensure that the analysis can meet the requirements of the United States Food and Drug Administration (FDA) 21 CFR Part 11 regulations relating to the use and control of electronic records.

Sample and standard preparation

Two over the counter drugs: an anti-inflammatory drug (Drug 1) and an antihistamine drug (Drug 2) were obtained to demonstrate the capability of the instrumentation for the application. The samples were prepared by dissolving 0.5 g of drug in 20 g of dimethyl sulfoxide (DMSO, ≥ 99.8% Certified Analytical Reagent, Fisher Scientific™, Loughborough, UK), sonicating the mixture for 10 minutes before making up to a final weight of 25 g with DMSO. The polar aprotic solvent DMSO is a very powerful solvent with high boiling point. The high boiling point is convenient as it allows samples prepared in DMSO to be run using the standard aqueous sample introduction kit. However, the aggressive nature of DMSO does necessitate the use of silicone pump-tubing.

All standards were prepared in DMSO from 1000 mg/L single element solutions (Fisher Scientific, Loughborough, UK). Concentrations were prepared to cover the expected range of the elements in the sample and to cover the limits specified by the chapters. Analysis was performed in accordance with USP Chapter <233> Elemental Impurities – Procedures. Firstly, three standards were prepared by spiking pure DMSO with the single element solutions at a level of 0, 0.5J and 2J, where J indicates the Target Limit, which is calculated in Table 1. Target Limits were calculated by dividing the Daily Dose PDEs by the maximum daily dose. For both drugs, the maximum daily dose was 2 g. Next, a dissolved sample of each drug was spiked with 0.5J, and 1.5J respectively. Finally, six independent samples of the material under test were spiked at 1J. Finally, the prepared samples were analyzed directly. Drift was monitored by measuring the 2J standard before and after the sample run.

Table 1. Target Limits, J, for the fourteen elements specified in USP ‹232› with an oral PDE. Chromium is not included in this list as only an inhalation PDE is specified by USP ‹232›

Elements	Oral daily dose PDE* (µg/day)	Target limit J (µg/day)
Cadmium	25	12.5
Lead	5	2.5
Inorganic arsenic	1.5	0.75
Inorganic mercury	15	7.5
Iridium	100	50
Osmium	100	50
Palladium	100	50
Platinum	100	50
Rhodium	100	50
Ruthenium	100	50
Molybdenum	100	50
Nickel	500	250
Vanadium	100	50
Copper	1000	500

* PDE = permitted daily exposure based on a 50 kg person

Taking into account Target Limits and noting that the samples were diluted fifty-fold, calibration standards were prepared at the concentrations given in Table 2.

Table 2. Calibration standards used for analysis; dilution factors were taken into account

Elements	0.5J (µg/kg)	2J (µg/kg)
Cadmium	125	500
Lead	25	100
Inorganic arsenic	7.5	30
Inorganic mercury	75	300
Iridium	500	2000
Osmium	500	2000
Palladium	500	2000
Platinum	500	2000
Rhodium	500	2000
Ruthenium	500	2000
Molybdenum	500	2000
Nickel	2500	10000
Vanadium	500	2000
Copper	5000	20000

Method development

The wavelengths of interest were selected based on the relative intensity and potential inferences from elements that may be present in the sample. To optimize the instrument, a typical sample spiked with the elements of interest was analyzed whilst carrying out the Optimize Source function of the Qtegra ISDS. The routine determined the optimal plasma and sample introduction settings, shown in Table 3, required to produce the lowest detection limits. The instrument was calibrated and a typical sample was analyzed. The sub-array plots for the wavelength were examined and the background positions optimized. Representative calibration plots are shown in Figure 1 for lead and Figure 2 for iridium.

Table 3. Sample introduction and plasma parameters used during the analysis

Parameter	Setting
Sample/Drain Tubing	1.016 mm Silicon, 1.524 mm Silicon
Pump Speed	50 rpm
Nebulizer Gas Flow	0.5 L/min
Auxiliary Gas Flow	0.5 L/min
Coolant Gas Flow	12 L/min
RF Power	1150 W
High/Low Integration Time	5/10 s
Spray Chamber	Glass Cyclonic
Nebulizer	Glass V-groove
Center Tube	2 mm Internal Diameter
Torch	EMT

Calibration curves

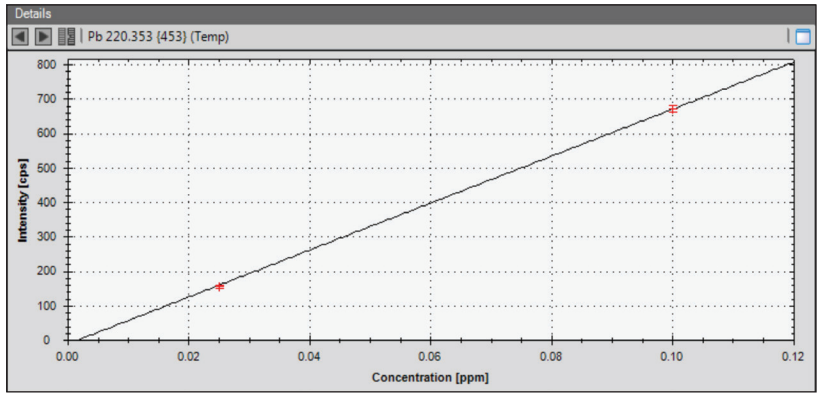

Figure 1. Calibration plot for Pb using the 220.353 nm optical emission line, measured at 0J, 0.5J and 2J

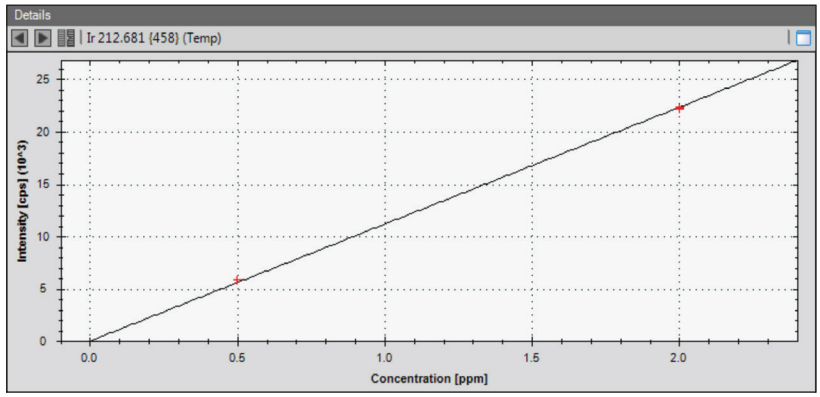

Figure 2. Calibration plot for Ir using the 212.681 nm optical emission line, measured at 0J, 0.5J and 2J

Method detection limits were obtained for all the elements and are presented in Table 4. The method detection limits (MDL) obtained for elements in the solid drug samples are all at least an order of magnitude lower than the Target Limit.

Table 4. Method detection limits for the solid samples compared to the calculated target limit

Elements	Wavelength (nm)	MDL (µg/g)	Target limit J (µg/g)
Cadmium	214.438	0.004	12.5
Lead	220.353	0.062	2.5
Inorganic arsenic	189.042	0.070	0.75
Inorganic mercury	184.950	0.050	7.5
Iridium	212.681	0.034	50
Osmium	225.585	0.031	50
Palladium	340.458	0.055	50
Platinum	203.646	0.085	50
Rhodium	343.489	0.095	50
Ruthenium	240.272	0.051	50
Molybdenum	202.030	0.022	50
Nickel	221.647	0.015	250
Vanadium	309.311	0.012	50
Copper	324.754	0.008	500

The measured concentration, over three repeats, for each target element in both drug samples was then determined and found to be above the method detection limit, as shown in Table 5.

Table 5. The table shows that the concentration for each target element was above the method detection limit

Elements	Drug 1 (µg/g)	Drug 2 (µg/g)	Target limit J (µg/g)
Cadmium	< MDL	< MDL	12.5
Lead	< MDL	< MDL	2.5
Inorganic arsenic	< MDL	< MDL	0.75
Inorganic mercury	< MDL	< MDL	7.5
Iridium	< MDL	< MDL	50
Osmium	< MDL	< MDL	50
Palladium	< MDL	< MDL	50
Platinum	< MDL	< MDL	50
Rhodium	< MDL	< MDL	50
Ruthenium	< MDL	< MDL	50
Molybdenum	< MDL	< MDL	50
Nickel	< MDL	< MDL	250
Vanadium	< MDL	< MDL	50
Copper	< MDL	< MDL	500

Analysis and results

Instrumental drift was determined by comparing the results obtained from measuring the 2J standard before and after the sample run. The results presented in Table 6 conform to the acceptance criterion of < 20% for each element.

Table 6. Comparison of the measured concentration of the 2J standard, measured before and after sample analysis. The measured drift was 1 % compared with an acceptance criterion of <20%

Elements	2J (µg/L) Before samples	2J (µg/L) After samples	Measured Drift	Criteria	Test Result
Cadmium	501	500	1%	<20%	pass
Lead	101	99	1%	<20%	pass
Inorganic arsenic	30	29.5	1%	<20%	pass
Inorganic mercury	300	299	1%	<20%	pass
Iridium	2000	1985	1%	<20%	pass
Osmium	1995	1985	1%	<20%	pass
Palladium	1978	1942	1%	<20%	pass
Platinum	2000	1994	1%	<20%	pass
Rhodium	1977	1921	1%	<20%	pass
Ruthenium	1995	2001	1%	<20%	pass
Molybdenum	2000	1986	1%	<20%	pass
Nickel	9916	9848	1%	<20%	pass
Vanadium	2005	2013	1%	<20%	pass
Copper	19760	19620	1%	<20%	pass

As part of the validation procedure, accuracy was determined in accordance with USP <233> by measuring spike recoveries for three repeats of the two samples at the 0.5J and 1.5J spike levels. The recoveries are shown in Figure 2 and Figure 3 for the 0.5J and 1.5J test respectively. USP <233> states that the acceptance criterion is that recoveries should be between 70% and 150% for the mean of the three repeat analyses of each sample at both spike levels, this is clearly the case.

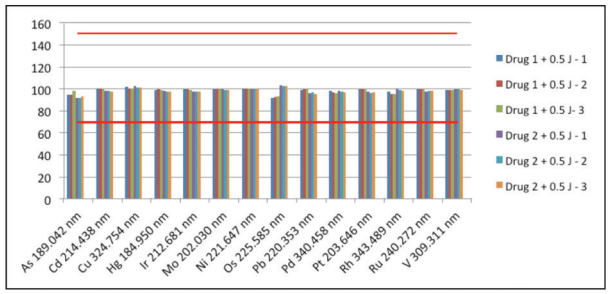

Figure 3. Recoveries for the 0.5J spike level. Red lines demarcate the 70% and 150% boundaries

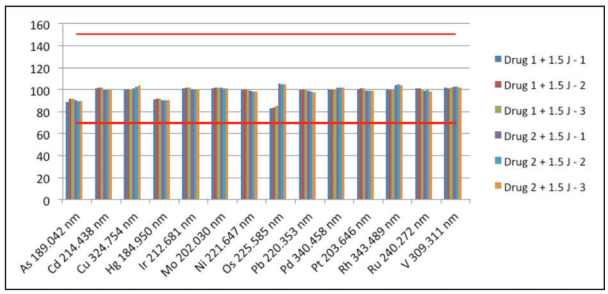

Figure 4. Recoveries for the 1.5J spike level. Red lines demarcate the 70% and 150% boundaries

Precision was determined by analyzing six individual samples of the material under test spiked with the element of interest at the target concentration (J). The acceptance criterion stipulates that the standard deviation should not exceed 20%. Results are shown in Table 7 for Drug 1 and Table 8 for Drug 2 and demonstrate conformance. Ruggedness was determined by re-running the samples using the same instrument the following day. The acceptance criterion of measurements not exceeding a relative percentage standard deviation of 25% was met.

Table 7. Measured concentrations for six repetitions of Drug 1 spiked with J

Elements	Drug 1 Run 1 (µg/L)	Drug 1 Run 2 (µg/L)	Drug 1 Run 3 (µg/L)	Drug 1 Run 4 (µg/L)	Drug 1 Run 5 (µg/L)	Drug 1 Run 6 (µg/L)	RSD (%)
Cadmium	232.4	232.7	234.7	239.1	235.6	229.9	1.4
Lead	45.9	45.2	44.6	47	46.6	43	3.2
Inorganic arsenic	12.1	12.7	12.8	14	12.9	11.4	6.9
Inorganic mercury	130.7	130.8	132.5	136.5	131.8	127.4	2.3
Iridium	944.5	941.3	948.2	963.7	950.9	924.5	1.4
Osmium	954.8	952.7	959	974.9	960.5	940	1.2
Palladium	918.8	914.7	914.6	928.6	929.4	890.6	1.5
Platinum	924.4	917.6	931.5	949.9	934.6	910.7	1.5
Rhodium	921.5	907.2	907.5	917.6	915.8	874.9	1.9
Ruthenium	955.5	966.5	953.6	972.8	967.5	932.7	1.5
Molybdenum	956.8	952	959.6	974	959.5	937.7	1.2
Nickel	4669	4666	4706	4787	4718	4610	1.3
Vanadium	962.5	952.9	945.5	960.1	961.7	928.9	1.4
Copper	9680	9590	9522	9666	9668	9318	1.5

Table 8. Measured concentrations for six repetitions of Drug 2 spiked with J

Elements	Drug 2 Run 1 (µg/L)	Drug 2 Run 2 (µg/L)	Drug 2 Run 3 (µg/L)	Drug 2 Run 4 (µg/L)	Drug 2 Run 5 (µg/L)	Drug 2 Run 6 (µg/L)	RSD (%)
Cadmium	236.1	234.3	238.2	238.9	233.4	231.8	1.2
Lead	44.5	42.6	45.4	45.7	43.7	44.5	2.6
Inorganic arsenic	15.6	14.8	15.2	15.1	14.8	13.5	4.8
Inorganic mercury	137.8	137.6	139.4	139.7	134.1	134	1.8
Iridium	951.1	946	956.5	960.4	937	933.1	1.1
Osmium	963.9	962.3	977.6	975.7	958.3	953.2	1
Palladium	953.5	949.8	963.8	986.7	948	937.1	1.8
Platinum	923.6	915.3	931.7	937.4	910.6	901.6	1.5
Rhodium	939.4	934	953.3	973.3	935.5	929	1.7
Ruthenium	979.7	953.6	966.9	1004	983.7	959	1.9
Molybdenum	965.1	964	979.8	982.4	960.7	956.7	1.1
Nickel	4773	4746	4816	4833	4720	4695	1.1
Vanadium	976.9	985.1	1002	1017	986.9	973.7	1.7
Copper	9902	9967	10140	10350	9996	9860	1.8

Conclusion

The Thermo Scientific iCAP 7600 ICP-OES Duo is well suited to the analysis of trace elements in pharmaceutical products, allowing users to meet the challenge of implementing the new USP Chapters <232> and <233>. The Thermo Scientific Qtegra software and Thermo Scientific iCAP Validator Kit enable the iCAP 7000 Series ICP-OES Duo to be used in an FDA CFR 21 Part 11 compliant laboratory.

References

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