Application Note: 43059

Using ICP-OES to Meet the Requirements of Elemental Impurity Analysis in Pharmaceutical Products

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Key Words

- FDA
- iCAP Duo
- iTEVA Security
- USP 232
- USP 233
- 21 CRF Part 11

Benefits in brief

- High sensitivity to achieve the required detection for all elements in the proposed chapters – 232 and 233
- Validation and data security requirements achieved with field proven products

Introduction

The United States Pharmacopeia (USP) is in the process of introducing new chapters (232 and 233) to replace the current, "Heavy Metals, Chapter 231" which is based on total heavy metals by a sulfide precipitation. This method has been used for many years, however it is not able to detect some metals and has also been found to produce false results for others.

Two new chapters have been proposed for the monitoring of elemental impurities in pharmaceuticals:

- Chapter 232 Elemental Impurities – Limits, details the maximum permissible limits of different classes of elements in drug substances and drug products (including natural source and rDNA biologics)[1]. These limits are shown in Table 1.
- Chapter 233 Elemental Impurities – Procedures, details two referee procedures either for ICP-OES or ICP-MS analysis following microwave digestion[2].

The referee procedures in chapter 233 do not have to be used for the analysis, alternative methods of sample preparation and analysis can be used. However, any alternative method must be fully validated for each element and must meet the validation requirements in chapter 233, at which point they will be considered equivalent to the two referee procedures. Currently there is no proposal for the speciation of elements in pharmaceutical products.

Element	Component Limit µg/g	Oral Daily dose PDE* µg/g	Parenteral Component Limit µg/g	Parenteral Daily dose PDE µg/g
Class 1 elemental impurities analysis is required for all drug products				
Arsenic	1.5	15	0.15	1.5
Cadmium	0.5	5	0.05	0.5
Lead	1	10	0.1	1
Mercury	1.5	15	0.15	1.5
Class 2 elemental impurities analysis is only required if an element has been added during the manufacturing process				
Chromium	25	250	2.5	25
Copper	250	2500	25	250
Manganese	250	2500	25	250
Molybdenum	25	250	2.5	25
Nickel	25	250	2.5	25
Palladium	10	100	1	10
Platinum	10	100	1	10
Vanadium	25	250	2.5	25
Osmium Rhodium Ruthenium Iridium	10 (combination not to exceed)	100 (combination not to exceed)	1 (combination not to exceed)	10 (combination not to exceed)

Table 1: Class 1 and 2 elemental impurity limits in drug products.
*Permitted Daily Exposure

Instrumentation and software

The Thermo Scientific iCAP 6500 ICP-OES (Duo) and associated Thermo Scientific iTEVA Security Software was used for the analysis. The iCAP 6500 ICP-OES (Duo) was chosen for this analysis 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 proposed chapters because the expected levels of trace elements in the pharmaceutical products are likely to be low. In addition, some of the Class 2 elements (particularly 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 Thermo Scientific iTEVA Security Software was chosen to ensure that the analysis can meet the requirements of United States Food and Drug Administration (FDA) 21 CFR Part 11 regulations relating to the use and control of electronic records.

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Sample and standard preparation

An over the counter cold and flu medicine was obtained to demonstrate the capability of the instrumentation for the application. The medicine was in the form of a water soluble powder and is prepared for oral administration by addition of hot water (200 ml) to the contents of a sachet of the medicine (5 g).

The samples were prepared by dissolving the product (1 g and adding analyte spikes) in a 1% (v/v) nitric acid solution (25 g, Trace metals grade, Fisher Scientific, Loughborough, UK). The sample/acid mixture was then sonicated for 10 minutes and made up to final weight with 1 % (v/v) nitric acid (50 g total weight).

As per the validation requirements prescribed in USP Chapter 233 Elemental Impurities – Procedures, the following samples were prepared for analysis:

Accuracy samples;

- Control sample 1, 2 and 3 – Blank solutions spiked with 0.5 j, 1 j and 1.5 j of the limit respectively. Where j is the indicated limit.
- Test sample 1, 2 and 3 – Sample of the material under test spiked with the elements of interest with 0.5 j, 1 j and 1.5 j of the limit respectively. Where j is the indicated limit. These samples were prepared in triplicate.

Repeatability samples;

- Six independent samples of the material under test spiked with the elements of interest (1 j). Where j is the indicated limit.

Test samples;

- Triplicate samples of the product under test.

Standards;

Multi-element standards were prepared in 1 % nitric acid from 1000 mg/L single element solutions (Fisher Scientific, Loughborough, UK) with the exception of the osmium solution (Romil, Waterbeach, UK). Concentrations were prepared to cover the expected range of the elements in the sample and to cover the limits proposed by the chapters.

Methodology

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 iTEVA Security Software. This routine determines the optimum plasma and sample introduction settings (Table 2) 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.

When sub-array plots were examined it was noticed that there was a potential interference on the platinum wavelength selected for the analysis from an adjacent cadmium wavelength. The platinum wavelength selected for the analysis is the most sensitive and therefore, due to the low concentrations expected in the samples, it was decided to use this wavelength for analysis with the addition of an Inter-Element Correction (IEC). For more information on setting up IEC's within the iTEVA Software see the application note: Overcoming Interferences using iTEVA Software and the Thermo Scientific iCAP 6000 Series ICP-OES (Application note number AN40961).

Parameter	Setting
Sample/Drain Tubing	White Orange Tygon, White White Tygon
Pump Speed	45 rpm
Nebulizer Gas Flow	0.6 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 Concentric
Center Tube	2 mm Internal Diameter
Torch	EMT

Table 2: Sample introduction and plasma settings used for the analysis.

Samples were analyzed after an initial calibration and QC check to determine both accuracy and repeatability (in addition to analyzing triplicate samples of the product under test). This analysis was then repeated the following day to determine intermediate precision (intermediate precision is required to be measured by performing repeat sample analysis on a different day, on a different instrument or alternatively by a different analyst).

Results

The spike recovery of the samples described above must be within 80-150 % of the spiked levels and the relative standard deviation (RSD) of the samples must be lower than 20 %.

The results of the accuracy tests in which a blank sample (Figure 1) and a matrix sample (Figure 2) were spiked with the elements of interest, show that the spike recoveries were within limits set by Chapter 233 (80 to 150 % of the spiked values).

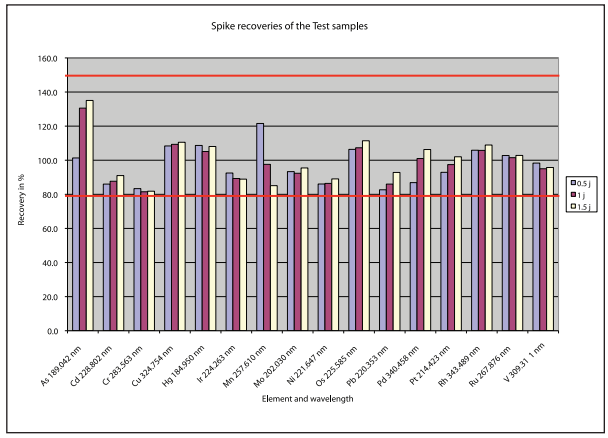

Figure 1: The spike recoveries of the control samples (without sample matrix) at different concentrations of the control limits set in Chapter 232. Acceptance criteria 80 – 150 % of the spiked value.

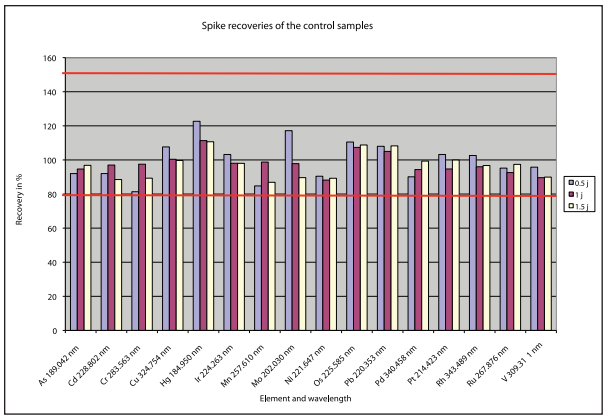

Figure 2. The spike recoveries of the test samples (with sample matrix) at different concentrations of the control limits set in Chapter 232. Acceptance criteria 80 – 150 % of the spiked value.

The RSD values derived from the six repeatability samples were calculated (Figure 3) and shown to be within the required acceptance criteria of Chapter 233 – which specifies mean RSD values derived from the six repeatability samples is less than 20 %. With the exception of the Pd, the RSD % of the six samples are all less than 2 %.

The intermediate precision test was performed by repeating the analysis of the six above described repeatability samples on two consecutive days. RSD values derived from sample analysis performed over the two day period (12 samples in total) were calculated and the results are shown below (Figure 3). Results derived from the intermediate precision test exhibit RSD % values of less than 16 % for each element. These results are acceptable on the basis of the Chapter 233 test criteria – which stipulate values to be less than 25 %.

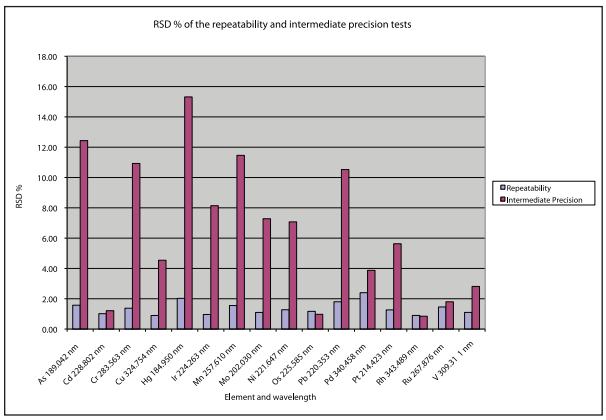

Figure 3: The RSD % of the six repeatability and 12 intermediate precision samples. Acceptance criteria for the repeatability and intermediate precision tests are less than 20 % and less than 25 % respectively.

The results of the sample analysis (Table 3) show all of the elements with the exception of As are below the component limit. The level of As is shown to exceed the component limit by 100 % and if the maximum daily dose of the product is taken then the PDE limit is exceeded by 300 %. A literature search revealed the level of As seen in the cold and flu relief product is not unexpected and was highlighted in the UK's national media around a decade ago. The method detection limits (MDL) obtained for the elements in the solid (based on predicted detections limits calculated by iTEVA Security Software) are all at least 10 times lower than the component limits. Instrument detection limit (IDL) data is also shown in Table 3 for reference.

	IDL	MDL	Sample	Sample 1	Sample 2	Mean 3	Component Limit	Daily dose	Permitted daily exposure
As 189.042 nm	0.0021	0.107	3.00	2.97	2.97	2.98	1.5	59.5	15
Cd 228.802 nm	0.0002	0.008	0.03	0.02	0.03	0.03	0.5	0.5	5
Cr 283.563 nm	0.0003	0.014	<0.014	<0.014	<0.014	-	25	-	250
Cu 324.754 nm	0.0002	0.009	1.17	0.24	0.14	0.51	250	10.3	2500
Hg 184.950 nm	0.0008	0.041	0.51	0.53	0.53	0.52	1.5	10.4	15
Ir 224.263 nm	0.0003	0.015	0.08	0.06	0.06	0.07			
Mn 257.610 nm	0.0001	0.003	0.06	0.05	0.05	0.05	250	1.1	2500
Mo 202.030 nm	0.0002	0.011	0.06	0.07	0.06	0.06	25	1.2	250
Ni 221.647 nm	0.0002	0.012	0.21	0.22	0.20	0.21	25	4.2	250
Os 225.585 nm	0.0006	0.029	0.08	0.10	0.08	0.08			
Pb 220.353 nm	0.0008	0.041	0.11	0.09	0.11	0.10	1	2.0	10
Pd 340.458 nm	0.0010	0.050	1.21	0.55	0.31	0.69	10	13.8	100
Pt 214.423 nm	0.0012	0.062	0.52	0.36	0.37	0.42	10	8.3	100
Rh 343.489 nm	0.0012	0.062	<0.062	<0.062	<0.062	-			
Ru 267.876 nm	0.0005	0.026	<0.026	<0.026	<0.026	-			
V 309.311 nm	0.0004	0.019	0.16	0.16	0.15	0.16	25	3.1	250
Sum of Os, Rh, Ru, Ir		-	0.16	0.15	0.14	0.15	10	3.0	100

Table 3: The results of the triplicate sample analysis, detection limits based on solid samples, the amount of the element consumed if the recommended daily dose is taken, and the component and permitted daily exposure limits (All units are µg/g).

As the result of the As was over the permissible limit in these analyses, the sub-array plots were further examined to ensure that no interference was present. Single element solutions of all of the elements that emit light in the same region (+/- 20 nm of the As wavelength) were prepared at 0.5 µg/g. These solutions where then analyzed – acquiring data for the As 189.042 nm wavelength and the resultant concentrations were found to be significantly lower than the instrument detection limits reported for this wavelength. Figure 4 shows the plots obtained for each of the elements measured at the As wavelength, confirming that there are no significant interferences contributing to false positive data.

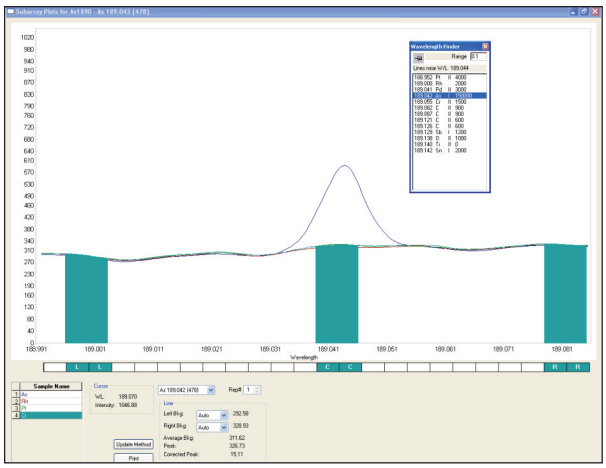

Figure 4: The sub-array of plot of As 189.042 nm with the plots of potential interferences overlaid.

Conclusions

The Thermo Scientific iCAP 6500 ICP-OES (Duo) is ideal for the analysis of trace elements in pharmaceutical products and for complying with the requirements of the proposed USP Chapters 232 and 233. The analyzed sample demonstrated an elevated level of As which, after a literature review, was not unexpected. However, prior introduction of these new proposed USP chapters would have prevented the drug from entering the market with its current trace element composition. The additional iTEVA Security Software and Thermo Scientific iCAP Validator Kit enable the iCAP 6500 ICP-OES (Duo) to be used in an FDA CFR 21 Part 11 compliant laboratory.

References:

1. <232> Elemental Impurities – Limits, Pharmacopeial Forum Vol.36(1) [Jan.-Feb.2010], United States Pharmacopeial Convention.
2. <233> Elemental Impurities – Procedures, Pharmacopeial Forum Vol.36(1) [Jan.-Feb.2010], United States Pharmacopeial Convention.

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