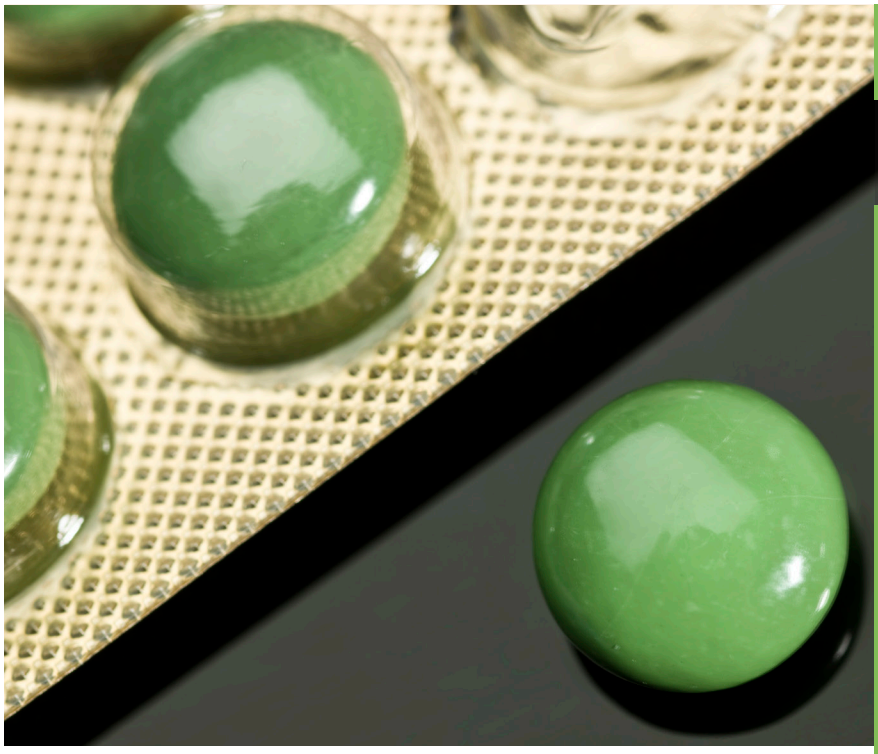

APPLICATION NOTE

ICP-Optical Emission Spectroscopy

Authors:

Ken Neubauer

Aaron Hineman

PerkinElmer, Inc.
Shelton, CT

Analysis of Allergy Medications Using ICP-OES Following USP 232/233 Guidelines with Software Designed to Aid in 21 CFR Part 11 Compliance

Introduction

With the implementation of USP <232>/<233> for the analysis of elemental impurities in finished drug products,[1,2] it is important for manufacturers to monitor the metal content of the final products to be in compliance. A detailed description of the requirements of USP <232>/<233> is available,[3] so only a brief description is given here. The maximum permitted daily exposure (PDE) of different target elements is defined in USP <232> and is based on the route of administration of the medications, as shown in Table 1 for oral, parenteral, and inhalation administration. Since parenteral and inhaled medications enter the blood stream faster than oral medications, their daily maxima are lower.

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Table 1. Maximum Oral and Inhalation Daily Exposures for Elements Defined in USP <232>.

Element	Class	Oral Daily Dose PDE* (µg/day)	Parenteral Daily Dose PDE* (µg/day)	Inhalation Daily Dose PDE* (µg/day)
Cd	1	5	2	2
Pb	1	5	5	5
As (inorganic)	1	15	15	2
Hg (inorganic)	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Ir	2B	100	10	1
Pd	2B	100	10	1
Pt	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Ag	2B	150	10	7
Se	2B	150	80	130
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

* PDE = permissible daily exposure based on a 50 kg person.

USP <233> defines the analytical requirements, which are all based on the J values for each element. The J values are a function of the PDE, maximum daily dose of the medication, and the dilution factor used in sample preparation. Because of the importance of the J value and the fact that it can vary by element and medication, a J-Value Calculator is available from PerkinElmer. The four analytical criteria specified in the validation of the quantitative procedures for USP <233> are accuracy, repeatability, ruggedness, and system suitability, with the requirements of each being summarized in Table 2.

It is important when analyzing pharmaceutical materials to maintain compliance with 21 CFR Part 11, which is mandatory for companies and their suppliers that operate in regulated environments to sell products into the United States. This regulation puts forward the criteria for electronic records, electronic signatures, and audit trails to ensure data integrity and reliability during the analytical testing. Syngistix™ for ICP Enhanced Security™ software version 4.0 was developed to help companies comply with regulations and sustain best practices delineated in 21 CFR Part 11.

Table 2. Analytical Criteria Defined in USP <233> for Quantitative Procedures.

Criteria	Description
Accuracy	Spike recoveries at 0.5J, J, and 1.5J must be between 70-150%
Repeatability	The RSDs of measurements of six independent samples spiked at J must be less than 20%
Ruggedness	Six solutions must be analyzed on different days, with different instruments, or with different analysts. The RSDs over the 12 measurements must be less than 25%
System Suitability	The difference in the results of the high calibration standard (1.5J) measured at the beginning and end of a batch must be < 20%

This work focuses on the analysis of allergy tablets with the PerkinElmer Avio® 500 ICP-OES and Syngistix for ICP Enhanced Security software version 4.0 to aid compliance with 21 CFR Part 11 regulations, following the criteria defined in USP <232>/<233>.

Experimental

Samples and Sample Preparation

Three different brands of allergy medications were purchased locally; each have loratadine at 10 mg as the active ingredient. All tablets weighed 0.10 g and had a daily dose of one tablet.

Sample preparation was accomplished with the Titan MPS™ Microwave Sample Preparation System (PerkinElmer, Shelton, Connecticut, USA) using the samples and reagents in Table 3. The goal was to minimize the amount of acid needed for sample preparation while maintaining analyte stability in solution to aid in reducing cost and waste. Nitric acid (HNO_3) is used to maintain most elements in solution, while hydrochloric acid (HCl) was necessary to stabilize mercury (Hg) and the platinum group elements (PGEs). The presence of HCl could potentially cause issues for Ag, which precipitates in the presence of low levels of HCl. However, Ag is stable in the presence of excess HCl. Therefore, a balance had to found between minimum acid content to accomplish digestion and using enough HCl to stabilize both Ag and the PGEs. It was found that 3% HNO_3 + 3% HCl (v/v) resulted in complete digestions and all elements being stable in solution. Lower HCl concentrations caused issues with Ag and/or the PGEs.

Each sample was added to a digestion vessel, followed by HNO_3, HCl, and deionized water. Any pre-digestion spikes were then added. The vessels were allowed to sit uncapped for 10 minutes before sealing and placing in the microwave for digestion to allow for gases produced during initial reactions to vent safely.

The Titan MPS digestion program used is shown in Table 4. The digestion itself is accomplished in the first two steps, with Step 3 being incorporated to rapidly cool the vessels for safe handling. If this step were eliminated, the vessels would require a significantly longer cooling time.

It should be noted that none of the allergy tablets contained silica dioxide (SiO_2) as an inactive ingredient, although it is commonly used as an excipient in medications. Tablets containing SiO_2 can be digested following a similar scheme, but with the addition of 0.5 mL hydrofluoric acid (HF). The digestion and analysis of SiO_2-containing tablets is covered in another application note.[4]

Table 3. Sample Amounts and Acids Used per Digestion Vessel.

Sample	Amount Per Digestion Vessel	HNO_3 70% (mL)	HCl 35% (mL)	Water (mL)
Tablet	1 Tablet = 0.10 g	1.5	1.5	7

Table 4. Titan MPS Digestion Program.

Step	Temperature (°C)	Pressure (Bar)	Ramp (Min)	Hold (Min)	Power (%)
1	160	35	5	1	90
2	190	35	5	5	100
3*	50	35	1	15	0

*Cooling step

Following the USP <233> protocol, calibration standards were prepared at the 0.5J and 1.5J levels in 3% HNO_3 + 3% HCl (v/v); the blank contained just the acid. All measurements were made against external calibration curves. To evaluate potential interferences, single-element standards of each analyte were prepared at the J value, analyzed individually, and the spectra observed. Table 5 shows the concentrations of the analytes at the various J values used in this work.

Table 5. Analyte Concentrations at Different J Values.

Element	0.5J (mg/L)	1J (mg/L)	1.5J (mg/L)
Cd	0.05	0.1	0.15
Pb	0.05	0.1	0.15
As	0.15	0.3	0.45
Hg	0.3	0.6	0.9
Co	0.5	1	1.5
V	1	2	3
Ni	2	4	6
Tl	0.08	0.16	0.24
Au	1	2	3
Ir	1	2	3
Pd	1	2	3
Pt	1	2	3
Rh	1	2	3
Ru	1	2	3
Ag	1.5	3	4.5
Se	1.5	3	4.5
Li	5.5	11	16.5
Sb	12	24	36
Ba	14	28	42
Mo	30	60	90
Cu	30	60	90
Sn	60	120	180
Cr	110	220	330

Instrumental Conditions

All analyses were performed on an Avio 500 ICP-OES system (PerkinElmer) using the conditions and parameters in Table 6, along with the analytical wavelengths and view modes listed in Table 7. Standard sample introduction components and conditions were used, including a total plasma argon flow of 9 L/min. All measurements were made against external calibration curves prepared in 3% HNO_3 +3% HCl (v/v). Yttrium (Y) and scandium (Sc) were added to all blanks, standards, and samples as internal standards.

Table 6. Avio 500 ICP-OES Instrumental Conditions.

Parameter	Value
Nebulizer	MEINHARD® Type K
Spray Chamber	Baffled glass cyclonic
Sample Uptake Rate	1.0 mL/min
RF Power	1500 W
Injector	2.0 mm id Alumina
Nebulizer Gas Flow	0.70 mL/min
Auxiliary Gas Flow	0.2 L/min
Plasma Gas Flow	8 L/min
Torch Position	-3
High Purge	Off
Read Time Range	1-5 seconds
Replicates	3

Table 7. Elements, Wavelengths, and Plasma View Modes.

Element	Wavelength (nm)	Plasma View
Ag	338.289	Axial
As	193.696	Axial
Au	242.795	Axial
Ba	233.527	Radial
Cd	214.440	Axial
Co	238.892	Axial
Cr	267.716	Axial
Cu	327.393	Axial
Hg	194.168	Axial
Ir	208.882	Axial
Li	670.784	Radial
Mo	202.031	Axial
Ni	231.604	Axial
Pb	220.353	Axial
Pd	340.458	Axial
Pt	214.423	Axial
Rh	343.489	Axial
Ru	240.272	Axial
Sb	217.582	Axial
Se	196.026	Axial
Sn	189.927	Axial
Tl	190.801	Axial
V	309.801	Axial
Sc (int std)	361.383	Radial
Y (int std)	371.029	Axial

To satisfy the data integrity requirements of the pharmaceutical industry, Syngistix for ICP Enhanced Security software version 4.0 was used. This software features all of the power of Syngistix for ICP-OES, with the added features required for 21 CFR Part 11 compliance for the regulated industry, including electronic signatures, electronic data review, the ability to set up different users and groups with different permissions, audit trail, version tracking, and much more.[5] Figures 1-3 show examples of electronic signatures, electronic data review, and showing differences between versions of the same method, respectively.

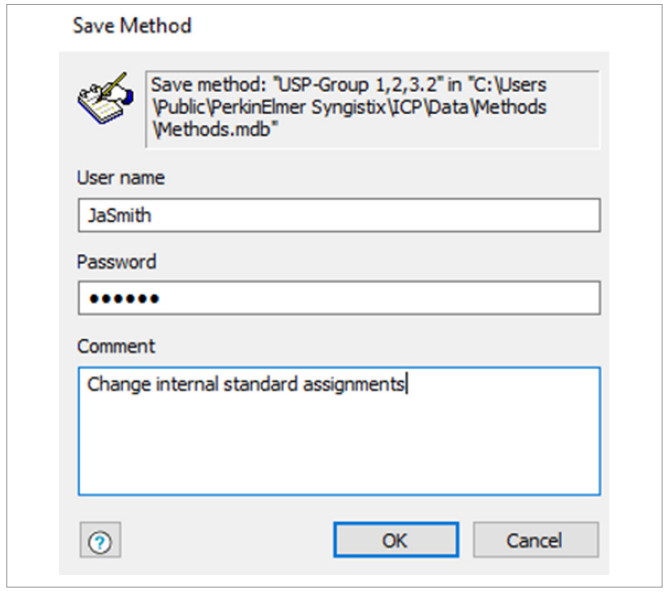

Figure 1. Example of electronic signatures in Syngistix for ICP Enhanced Security software version 4.0. Electronic signatures require the User Name and Password before proceeding. Comments can also be added, if desired. The Administrator can set the criteria for when an electronic signature is required.

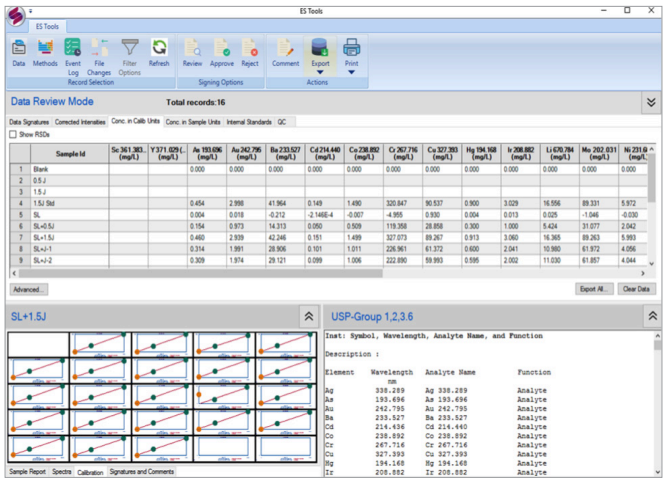

Figure 2. Example of electronic data review in Syngistix for ICP Enhanced Security software version 4.0. In Data Mode, it is possible to compare side-by-side the results, spectra, and calibrations, as well as review and add signatures and comments in customizable windows. This is an easy and quick way to view data. Those with appropriate permissions can approve or reject data.

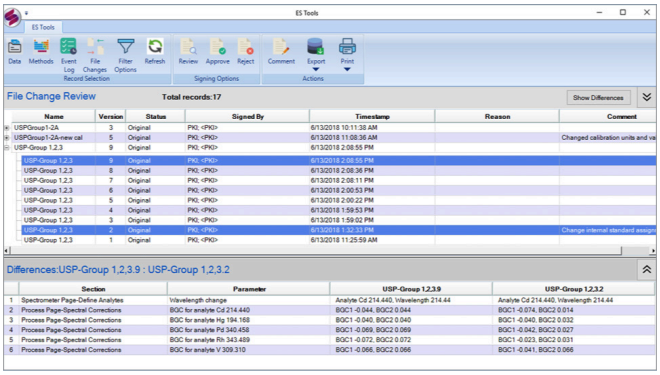

Figure 3. In Syngistix for ICP Enhanced Security software version 4.0, File Changes quickly and easily shows the differences between different versions of the same method or the differences between two different methods. In File Change Mode, simply select two methods or two versions of the same method and hit the Show Differences button. A list of differences between the methods appears, making approving or rejecting methods much easier.

Results and Discussion

Evaluation of Interferences

To evaluate the potential for interferences, all analytes were measured as single-element standards, and the spectra compared. This study showed that several of the analytes also interfere with other analytes, creating a bias in the results and causing inaccuracies. The analyst must be cautious as it is possible to successfully pass the USP <233> criteria even though interferences are being measured. For most analytes, it is possible to select wavelengths which do not suffer interferences; the exceptions are arsenic (As), rhodium (Rh), and thallium (Tl). Figure 4 shows a spectrum of As 193.696 nm, along with spectral interferences from platinum (Pt) and chromium (Cr), with each element at its 1.5J concentration. It is evident that the peaks from Cr and Pt overlap the As peak.

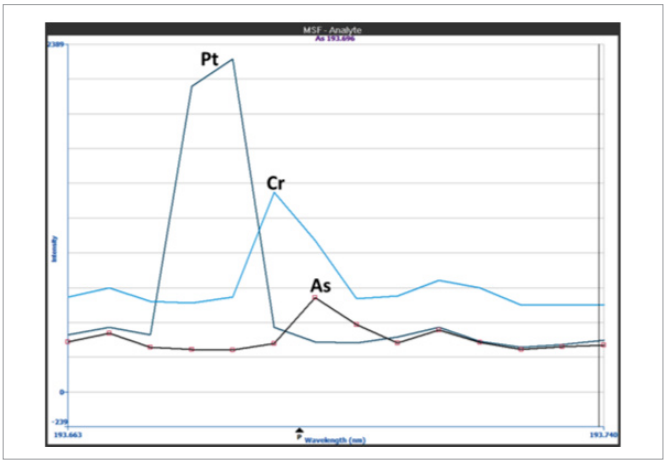

Figure 4. Spectrum of As 193.696 nm along with spectra of Pt and Cr. All single-element standards at their 1.5J concentration levels.

These interferences are easily resolved using Multicomponent Spectral Fitting (MSF), an algorithm included in Syngistix software to remove the effects of spectral interferences.[6,7] Figure 5 shows the resulting As spectrum after MSF has been applied, which is free of spectral overlaps, allowing for interference-free analysis of As.

Although not shown, MSF was also applied to Rh and Tl, both of which had molybdenum (Mo) spectral interferences. MSF can aid in removing interferences and improving detection limits when correctly applied.

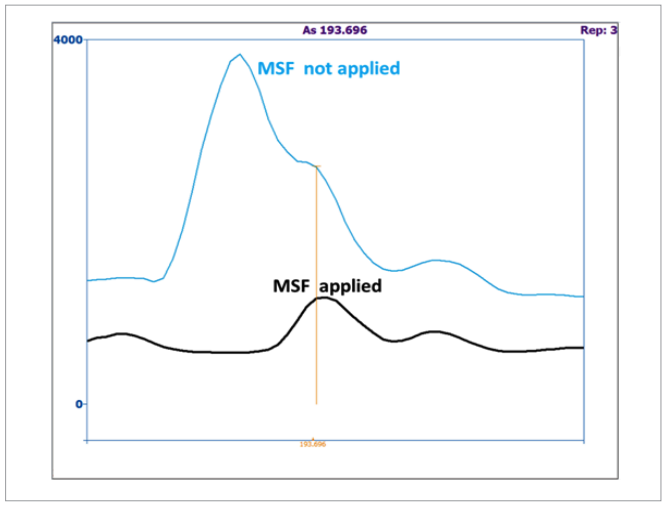

Figure 5. Spectra of As 193.696 nm in an allergy tablet with 1.5J analyte spike before (blue) and after (black) applying MSF.

Sample Analysis

The concentrations for all elements in all samples analyzed were less than 0.3J, a common actionable threshold which is more than three times lower than the PDE.

Meeting the USP <233> Criteria

To meet the criteria outlined in Table 2, one brand of allergy tablets was chosen to run through the full validation requirements.

First, the system suitability was determined by measuring the 1.5J standard at the beginning (after the calibration) and end of a batch analysis. With a drift of less than 4% (Figure 6), the methodology surpasses the acceptance limit of 20%.

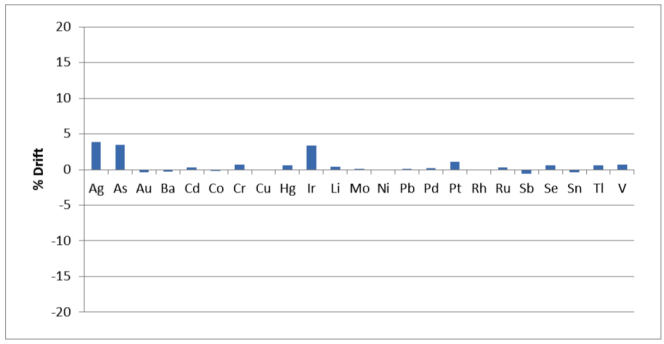

Figure 6. System suitability: drift over a batch analysis from 1.5J standards measured at the beginning and end of the batch analyses.

With the suitability of the system established, the accuracy of the methodology was evaluated. To meet the accuracy criteria, pre-digestion spikes of 0.5J, 1J, and 1.5J were added to the samples. Adding the spikes to the microwave vessels and carrying them through the complete sample preparation and analysis proves that analyte is not lost. Figure 7 shows that all recoveries are within 10%, easily meeting the method criteria of 70-150%.

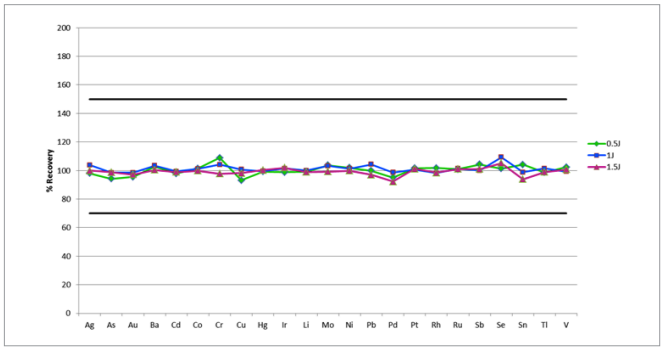

Figure 7. 0.5J, 1J, and 1.5J spike recoveries in allergy tablets. Black lines show USP <233> limits.

With the accuracy of methodology proven, the repeatability of the measurements was evaluated next by spiking six samples at the elemental impurity limits (J values) prior to digestion. These samples were then analyzed and showed RSDs less than 6% (as shown in Figure 8), easily meeting the method criteria of not more than (NMT) 20%.

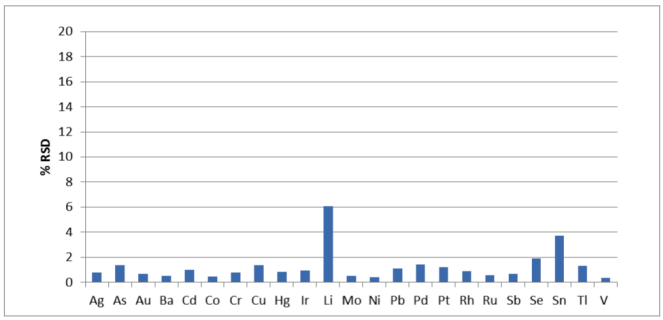

Figure 8. RSDs of six pre-digestion spikes of individual tablets.

Finally, the ruggedness of the methodology was determined by analyzing the same six solutions used for the repeatability test on two different days. With RSDs of the 12 measurements being much less than the method criterion of 25% (Figure 9), the requirement is easily met.

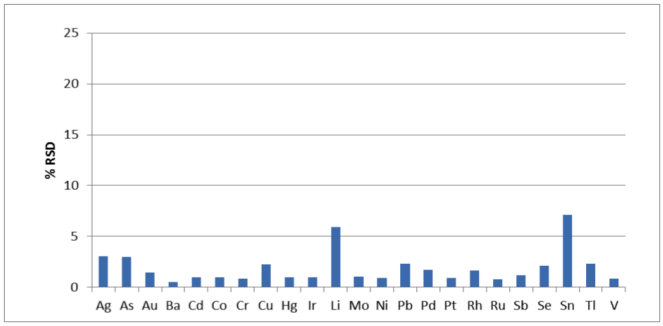

Figure 9. RSDs of six pre-digestion spikes of individual tablets analyzed over two days (12 total measurements).

Conclusion

This work demonstrates the ability of the Avio 500 ICP-OES to meet the USP <232>/<233> criteria for the analysis of orally-administered allergy tablets using Syngistix for ICP Enhanced Security software version 4.0, which provides the tools to help laboratories meet 21 CFR Part 11 compliance. Closed-vessel microwave digestion with the Titan MPS prevented analyte loss and resulted in rapid, complete digestions, with the minimal use of acids. Spectral interferences were avoided by choosing alternate analytical wavelengths when possible and employing MSF for those analytes which did not have interference-free wavelengths.

21 CFR Part 11 compliance is mandatory for pharmaceutical companies and their suppliers to sell products into the United States. Syngistix for ICP Enhanced Security software version 4.0 provides the features necessary that are outlined in 21 CFR Part 11, such as data integrity, electronic signatures and records, and secure audit trails, to keep regulated laboratories' data secure and traceable. The developed methodology using the Avio 500 ICP-OES with Syngistix for ICP Enhanced Security software version 4.0 easily meets the USP <233> criteria for system suitability, accuracy, repeatability, and ruggedness.

References

1. General Chapter <232> Elemental Impurities – Limits: 2nd Supplement of USP 35-NF 30.
2. General Chapter <233> Elemental Impurities – Procedures: 2nd Supplement of USP 35-NF 30.
3. "Implementation of USP New Chapters <232> and <233> of Elemental Impurities in Pharmaceutical Products", white paper, PerkinElmer, 2013.
4. "Analysis of SiO_2- and TiO_2-Containing Medications Using ICP-OES Following USP 232/233 Guidelines with Software Designed to Aid in 21 CFR Part 11 Compliance", application note, PerkinElmer, 2018.
5. "Syngistix for ICP Enhanced Security Software for 21 CFR Part 11 Compliance", product note, PerkinElmer 2018.
6. "Multicomponent Spectral Fitting", technical note, PerkinElmer, 2017.
7. "Using Multicomponent Spectral Fitting to Resolve Difficult Interferences in Metallurgical Samples with the Avio 500 ICP-OES", application note, PerkinElmer, 2017.

Consumables Used

Component	Part Number
Sample Uptake Tubing, Black/Black (0.76 mm id), PVC	N0777043 (flared) 09908587 (non-flared)
Drain Tubing, Red/Red (1.14 mm id)	09908585 (PVC) N077319 (Santoprene)
Autosampler Tubes	B0193233 (15 mL)B0193234 (50 mL)

PerkinElmer, Inc.
940 Winter Street
Waltham, MA 02451 USA
P: (800) 762-4000 or
(+1) 203-925-4602
www.perkinelmer.com

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