TELEDYNE CETAC TECHNOLOGIES
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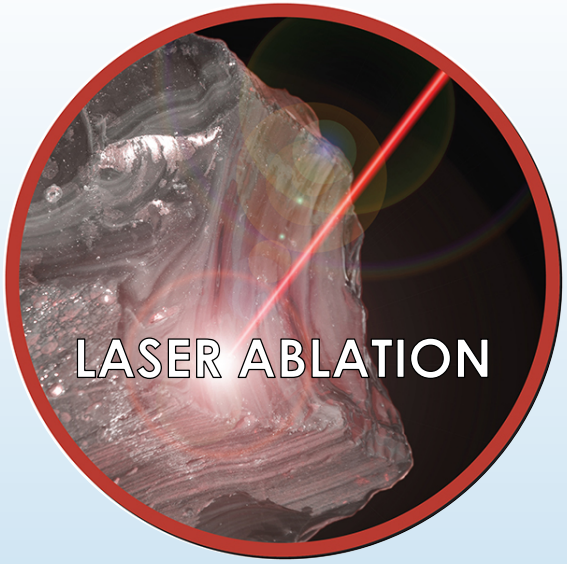
# Liquid Sample Introduction for ICP-AES

## *Measurement of Elemental Impurities in a Higher Daily Dose Drug Product by USP <232>/<233> using Ultrasonic Nebulization with ICP-AES Detection*


# USP <232>/<233>

On January 1, 2018 the U.S. Pharmacopeia (USP) enacted new criteria for element impurities in finished drug products. These criteria, detailed in USP <232>/<233>, recommend analysis of drug products for element impurities by either Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) or Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

Laboratories must measure impurities based on a J value for each drug product; drug products may be oral, parenteral (ex. intravenous, injection), or inhalation types. The J value of the drug is calculated based on an established permissible daily exposure (PDE), maximum daily dose (MDD) of the drug, and the dilution factor used in the sample preparation method. As a result of the J value calculation, drugs with a larger MDD require lower element impurity detection limits.

# Liquid Sample Introduction for ICP-AES
## Ultrasonic Nebulization

**An ultrasonic nebulizer is an accessory for ICP-AES that enables higher sample transport efficiency (versus a standard pneumatic nebulizer) to the ICP-AES plasma. This benefit can be helpful for detection of more difficult elements such as As, Cd, Pb, Hg, and Tl.**

**This work describes the use of ultrasonic nebulization for ICP-AES detection of element impurities in aspirin, a drug with a higher daily dose than a low dose drug (ex. 1 tablet per day) such as an allergy or sleep aid medicine.**

# Liquid Sample Introduction
## Ultrasonic Nebulization

**In place of a regulated gas flow for generation of a liquid sample aerosol (pneumatic nebulization), liquid sample is pumped across a quartz plate with an underlying oscillating (piezoelectric) crystal.**

**The oscillations of the crystal will break up the liquid flow and cause formation of a sample aerosol. Ultrasonic nebulization is typically up to 10x more efficient (versus a conventional pneumatic nebulizer) for conversion of liquid sample into a useable aerosol.**

# U5000AT+ Ultrasonic Nebulizer

## Dimensions and Weight


**Width:** 35.6 cm (14.0 in)
**Depth:** 34.9 cm (13.7 in)
**Height:** 25.4 cm (10.0 in)

**Weight:** 12.3 kg (27 lbs)

# Teledyne CETAC U5000AT+ Ultrasonic Nebulizer
## Front View

# Teledyne CETAC U5000AT+ Ultrasonic Nebulizer

## Back View

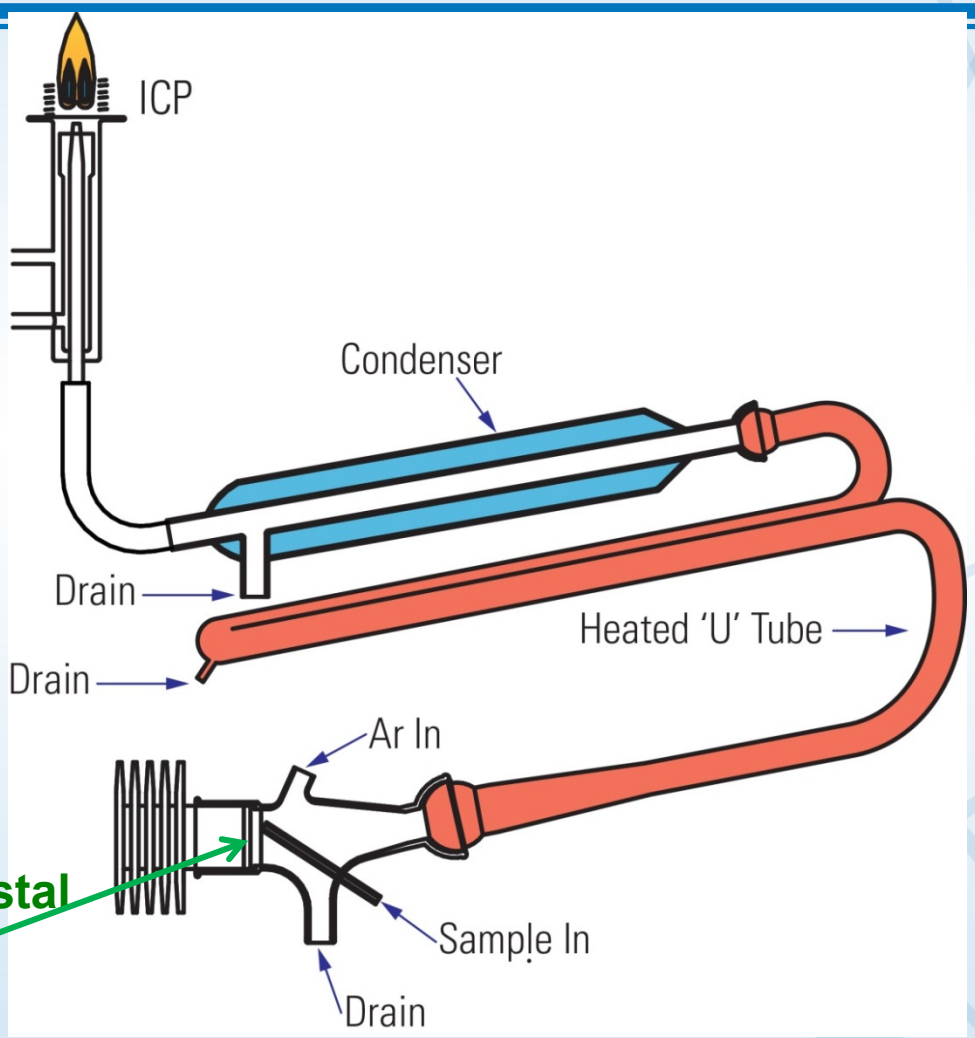

Sample Out

Argon In

Power Input

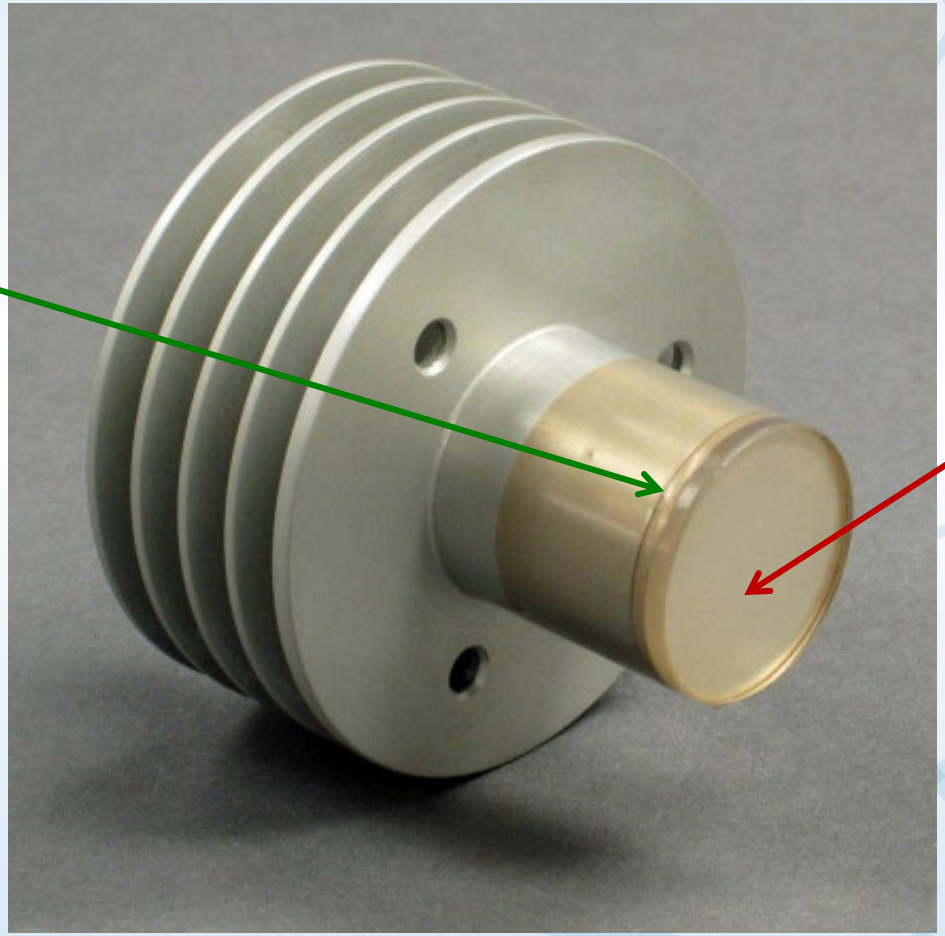
Drain Pump

# Teledyne CETAC U5000AT+ Schematic

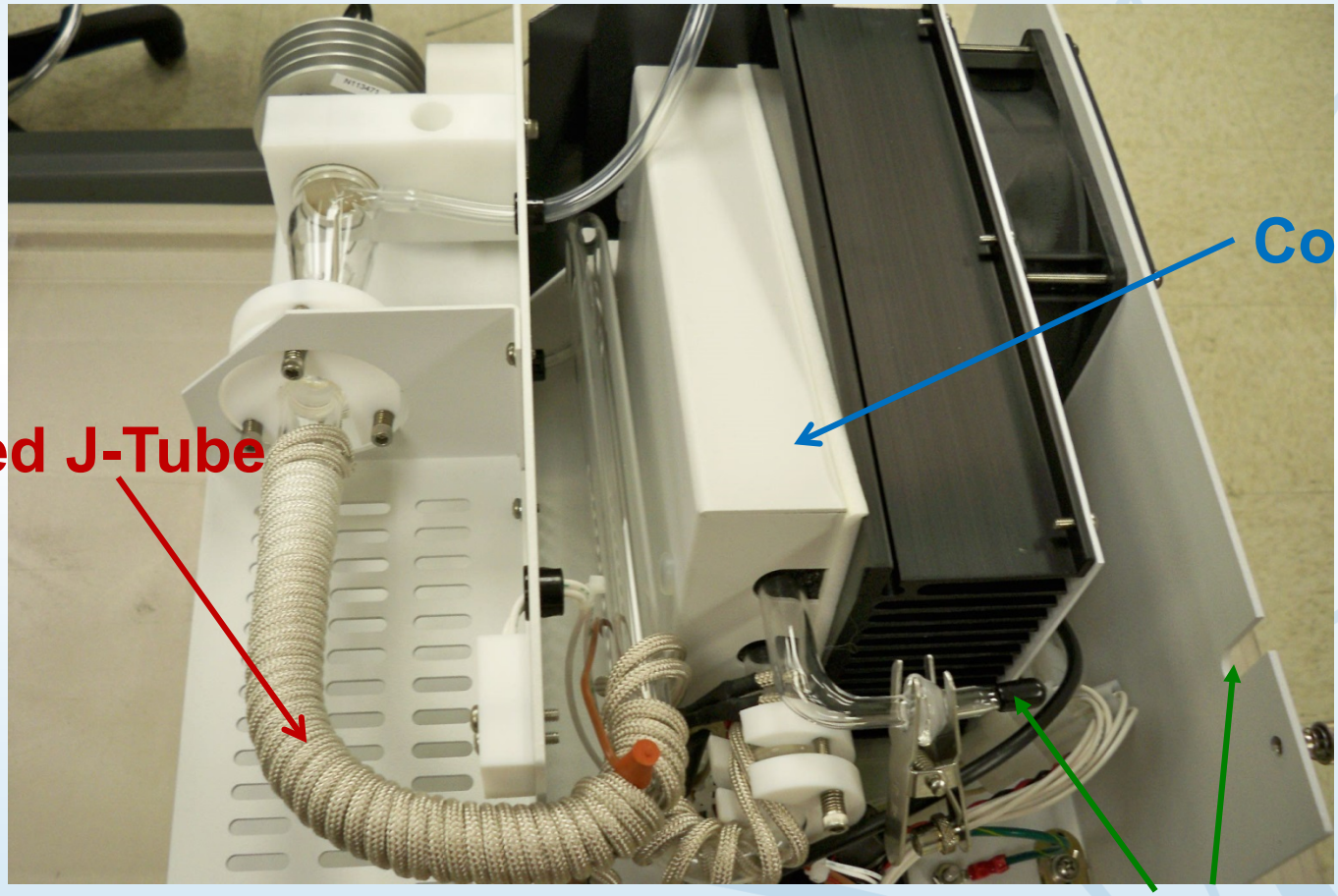



**Piezoelectric Crystal (Transducer)**

# U5000AT+ Transducer Assembly

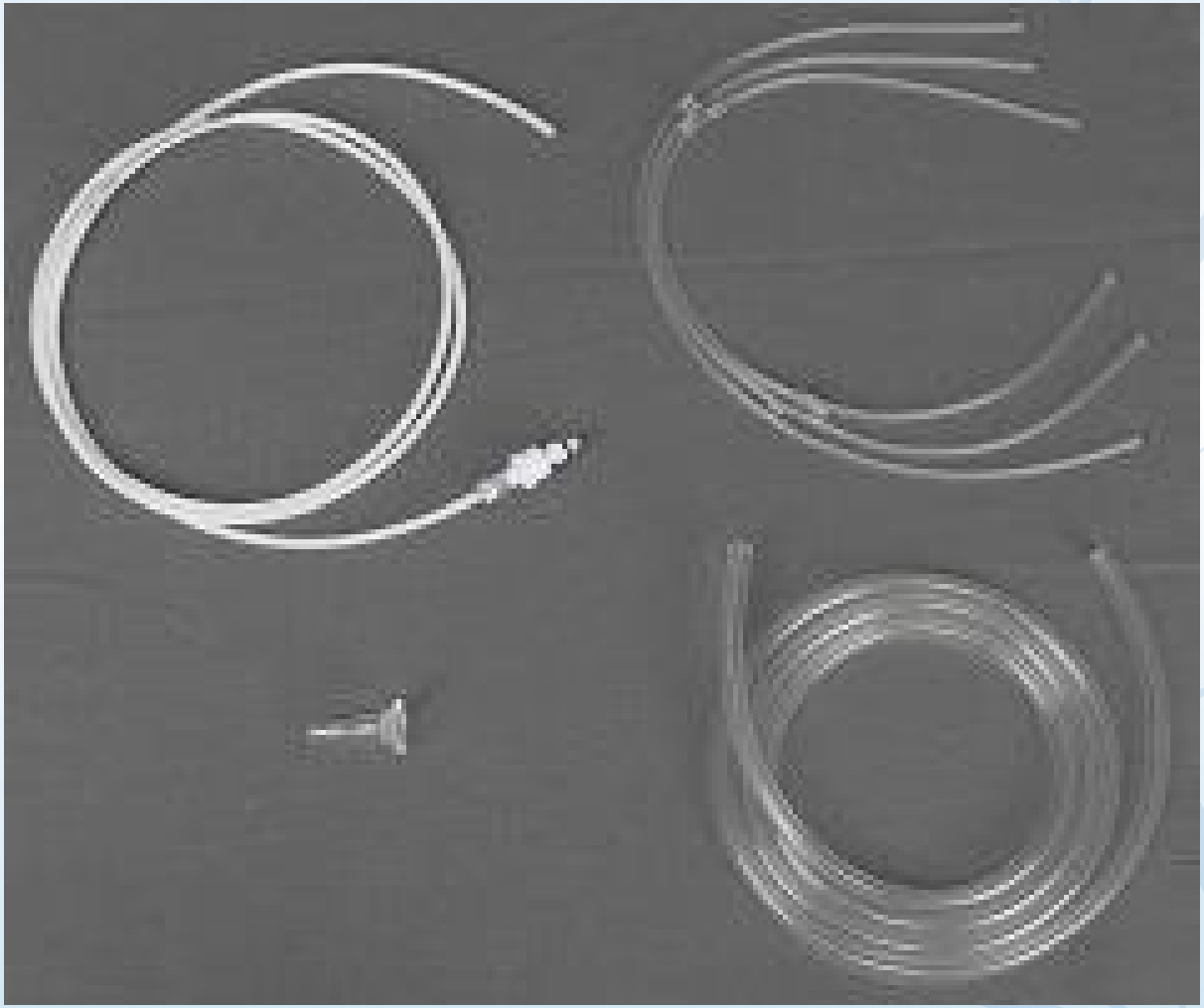


# U5000AT+ Ultrasonic Nebulizer
## Desolvation System



# U5000AT+ Ultrasonic Nebulizer

## Example Interface Kit



# U5000AT+ Ultrasonic Nebulizer
## Installation Steps

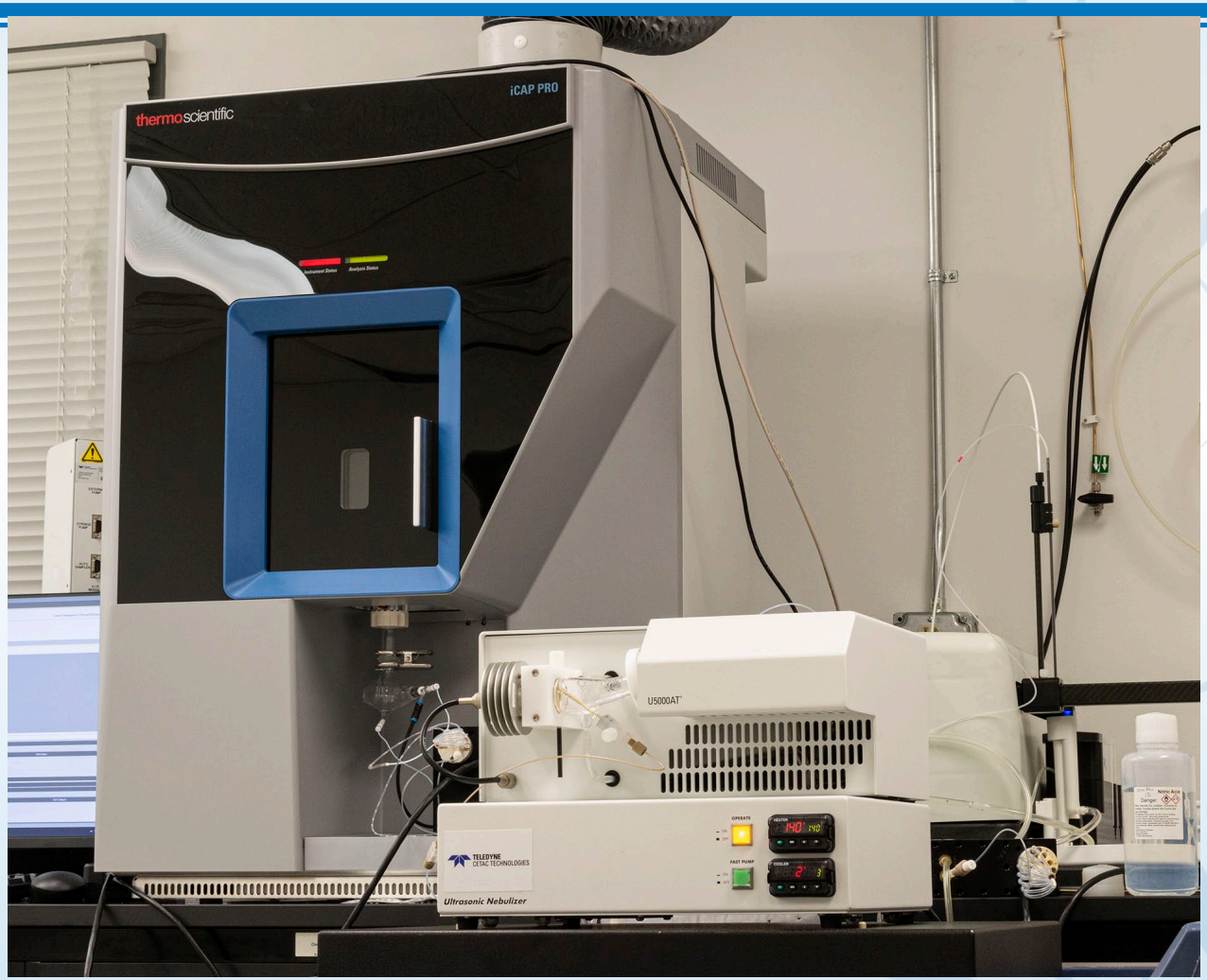
1. Remove standard nebulizer and spray chamber from the ICP-AES.
2. Connect nebulizer gas inlet line from ICP-AES to the USN.
3. Connect sample out line from USN to ICP torch.
4. Connect sample line from autosampler to USN inlet line.
5. Connect power cord to USN and turn on. Wait 10 minutes for heater and cooler to stabilize. Start ICP, introduce tune solution, press one button (Operate) to begin nebulizing samples.

***Overall setup takes about 15 minutes.***
***No computer control, no software installation needed.***

# ICP-AES w. Ultrasonic Nebulization


**Agilent 5100 ICP-AES & U5000AT+ USN**

# ICP-AES w. Ultrasonic Nebulization



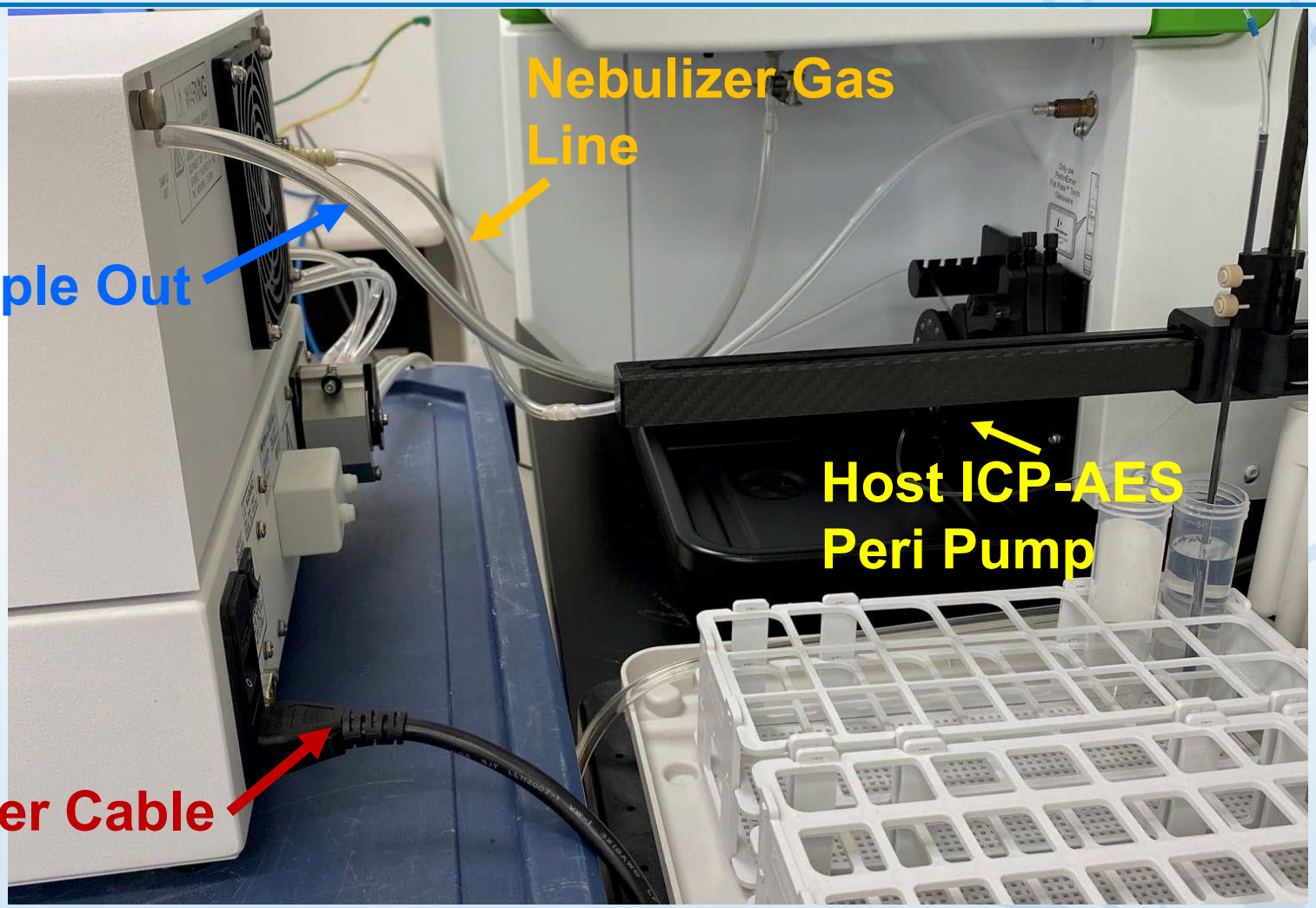



Thermo iCAP PRO & U5000AT+ USN

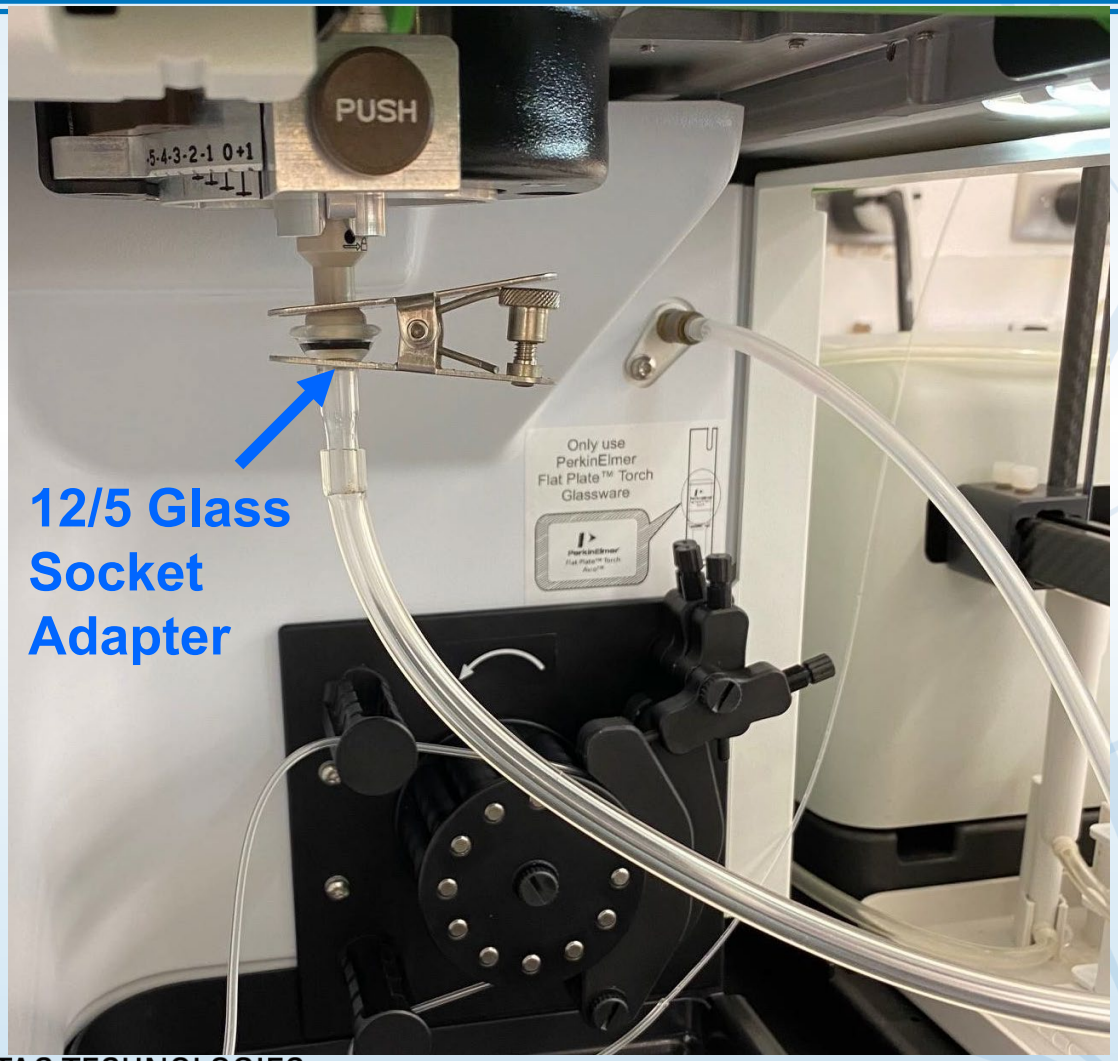
# ICP-AES w. Ultrasonic Nebulization


**PerkinElmer Avio 500 ICP-AES, U5000AT+ USN & ASX-280 Autosampler**

# Connections Between Host ICP-AES and U5000AT+ Ultrasonic Nebulizer



# Example Torch Adapter Connection



# Instrumentation

**ICP-AES: PerkinElmer Avio 500**

**Ultrasonic Nebulizer (USN): Teledyne CETAC U5000AT+**

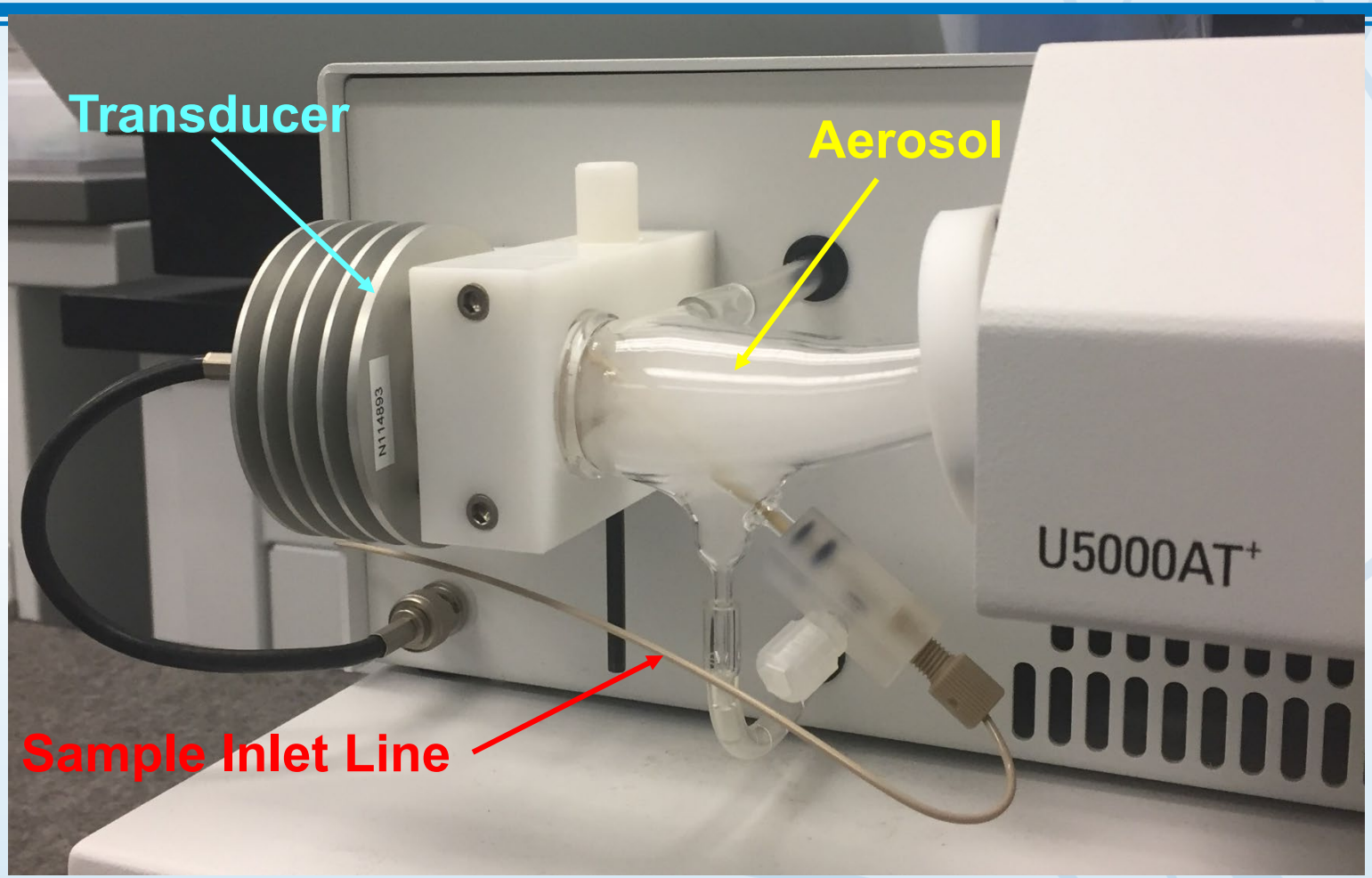
**Microwave Digestion System: CEM Mars 6**

# U5000AT+ Ultrasonic Nebulizer

## Aerosol Generation

# Ultrasonic Nebulizer Aerosol

## Close-Up View



# USP <232> Elements Class Grouping

- **Class 1 and 2A elements must be measured; Class 1 elements are most toxic (Cd, Pb, As, Hg).**
- **Class 2B elements must be measured if added to the drug product generation process.**
- **Class 3 elements are of lower toxicity via oral administration, but require measurement if drug product given by inhalation or parenteral routes.**

# Maximum Oral Daily Exposures for Elements Defined in USP <232> - I

| Element | Class | Max. Oral Daily Exposure (µg/day) |
|---|---|---|
| Cd | 1 | 5 |
| Pb | 1 | 5 |
| As | 1 | 15 |
| Hg | 1 | 30 |
| Co | 2A | 50 |
| V | 2A | 100 |
| Ni | 2A | 200 |
| Tl | 2B | 8 |
| Au | 2B | 100 |
| Pd | 2B | 100 |
| Ir | 2B | 100 |
| Rh | 2B | 100 |



* inorganic

# Maximum Oral Daily Exposures for Elements Defined in USP <232> - II

| Element | Class | Max. Oral Daily Exposure (µg/day) |
|---|---|---|
| Ru | 2B | 100 |
| Se | 2B | 150 |
| Ag | 2B | 150 |
| Pt | 2B | 100 |
| Li | 3 | 550 |
| Sb | 3 | 1200 |
| Ba | 3 | 1400 |
| Mo | 3 | 3000 |
| Cu | 3 | 3000 |
| Sn | 3 | 6000 |
| Cr | 3 | 11000 |



* inorganic

# Sample Preparation

A 0.5 g aspirin sample with multielement spike was added to each digestion vessel followed by 5 mL of reagent grade $HNO_3$ and 1 mL of reagent grade HCl. The vessels were left uncapped for 10 minutes in a fume hood to allow any initial gases to vent prior to sealing the vessels. Spiked and un-spiked samples were digested using a closed vessel microwave digestion program as specified by USP <233>.

| Stage | Power(W) | Ramp | Hold | Temp (°C) |
|---|---|---|---|---|
| 1 | 1050 | 15 min | 15 min | 200 |

# Sample Dilution and J Values

The final dilution for each sample after digestion was 100x with deionized water. With that dilution factor and a maximum daily dose of 4.32 g (one aspirin tablet is 0.36g, maximum dose is 12 tablets per day), the calculated J values (rounded down) are listed in the next two slides in mg/L. Following USP <233> protocol, a reagent blank, 0.5 J standard, and 1.5 J standard were used for calibration.

# Analytical Concentrations at Different J Values - I

| Element | J-value (mg/L) | 0.5 J | 1.5 J |
|---|---|---|---|
| Cd | 0.01 | 0.005 | 0.015 |
| Pb | 0.01 | 0.005 | 0.015 |
| As* | 0.03 | 0.015 | 0.06 |
| Hg* | 0.06 | 0.03 | 0.09 |
| Co | 0.10 | 0.05 | 0.15 |
| V | 0.20 | 0.10 | 0.30 |
| Ni | 0.40 | 0.20 | 0.60 |
| Tl | 0.016 | 0.008 | 0.024 |
| Au | 0.20 | 0.10 | 0.30 |
| Pd | 0.20 | 0.10 | 0.30 |
| Ir | 0.20 | 0.10 | 0.30 |
| Rh | 0.20 | 0.10 | 0.30 |



* inorganic

# Analytical Concentrations at Different J Values - II

| Element | J-value (mg/L) | 0.5 J | 1.5 J |
|---|---|---|---|
| Ru | 0.20 | 0.10 | 0.30 |
| Se | 0.30 | 0.15 | 0.45 |
| Ag | 0.30 | 0.15 | 0.45 |
| Pt | 0.20 | 0.10 | 0.30 |
| Li | 1.1 | 0.55 | 1.65 |
| Sb | 2.4 | 1.2 | 3.6 |
| Ba | 2.8 | 1.4 | 4.2 |
| Mo | 6 | 3 | 9 |
| Cu | 6 | 3 | 9 |
| Sn | 12 | 6 | 18 |
| Cr | 22 | 11 | 33 |

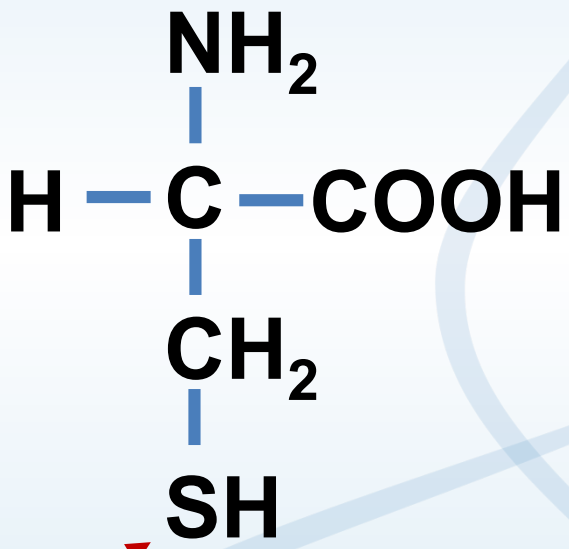
# Calibration & Reagent Addition

The ICP-AES was calibrated using standards that were matrix matched to the acid concentrations of the digested samples. An internal standard solution of 50 µg/L Y was added to all samples and standards using a mixing tee.

Samples for the Class 1 elements (includes Hg), 2A elements, and thallium were digested and analyzed separately from the Class 2B and Class 3 elements. For these elements, the reagent **L-cysteine, a thiol-containing amino acid**, was added to digested samples to assist element transport of Hg through the ultrasonic nebulizer.

L-cysteine was added to the 50 µg/L Y internal standard solution so the final concentration after sample mixing was 3 mg/ml. As nitric acid rapidly oxidizes L-cysteine, the internal standard solution was prepared in 0.07M HCl.

# L-Cysteine ($C_3H_7NO_2S$) Structure



# Aspirin Tablets: Notes

- Aspirin tablets did not contain $SiO_2$ or $TiO_2$, so hydrofluoric acid (HF) not needed for digestion
- If HF was required for digestion, then a neutralization of residual HF would be needed (ex. boric acid) before introduction to any glass components

# Emission Line Selection

- All elements required by USP <232> and other elements potentially in the aspirin sample (ex. Ca, Na, Si, Mg) were run individually to check for spectral interferences.
- When possible emission lines free of interferences were selected; otherwise multicomponent spectral fitting (MSF) or interelement correction factors (IECs) were used.
- An interference check solution was measured during the sample run to verify that spectral correction techniques were working properly.

# Operating Conditions

## ICP-AES with Standard Nebulizer and U5000AT+ USN

| Parameter | Std Nebulizer | U5000AT+ USN |
|---|---|---|
| ICP Power | 1500 W | 1500 W |
| Plasma Gas | 8.0 L/min | 8.0 L/min |
| Auxiliary Gas | 0.2 L/min | 0.2 L/min |
| Nebulizer Gas | 0.70 L/min | 0.62 L/min |
| Torch Injector | 2 mm | 2 mm |
| Uptake Rate | 1.5 mL/min | 1.0 mL/min |
| Cassette Position | -3.0 | -5.0 |
| Resolution | Normal | Normal |
| Nebulizer Type | Meinhard K | Piezoelectric |
| Spray Chamber | Baffled cyclonic | Conical |
| Heater Temp | N/A | 120°C |
| Cooler Temp | N/A | 5°C |
| Integration Time | 2 s min, 10 s max | 2 s min, 10 s max |
| Peak Area | 3 pts/peak | 3 pts/peak |
| Replicates | 3 | 3 |

# Elements, Wavelengths, Plasma View - I

| Element | Wavelength (nm) | Plasma View |
|---|---|---|
| Cd | 228.802 | Axial |
| Pb | 220.353 | Axial |
| As | 188.979 | Axial |
| Hg | 253.652 | Axial |
| Co | 228.616 | Axial |
| V | 292.402 | Axial |
| Ni | 231.604 | Axial |
| Tl | 190.801 | Axial |
| Au | 242.795 | Axial |
| Pd | 340.458 | Radial |
| Ir | 208.882 | Axial |
| Rh | 343.489 | Radial |

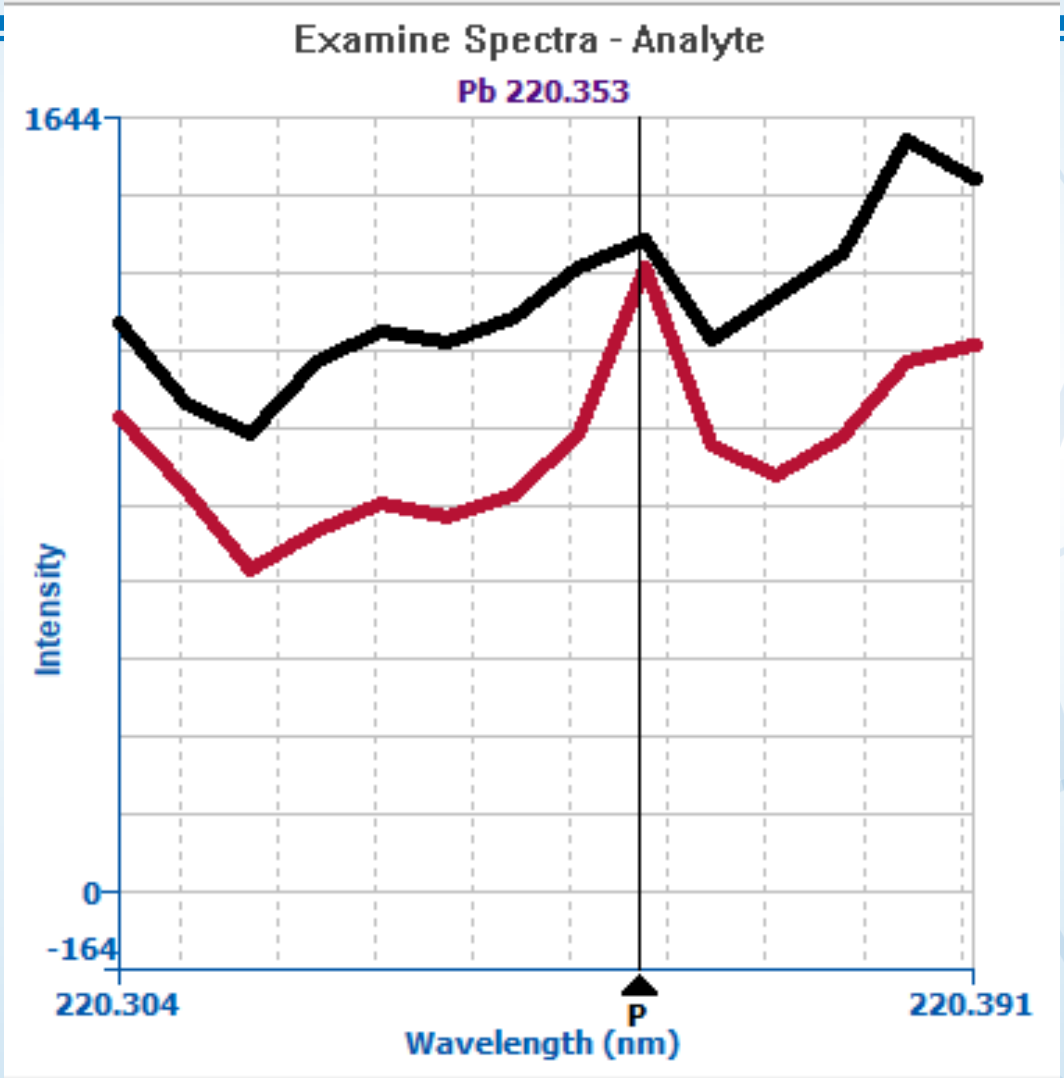


* inorganic

# Elements, Wavelengths, Plasma View - II

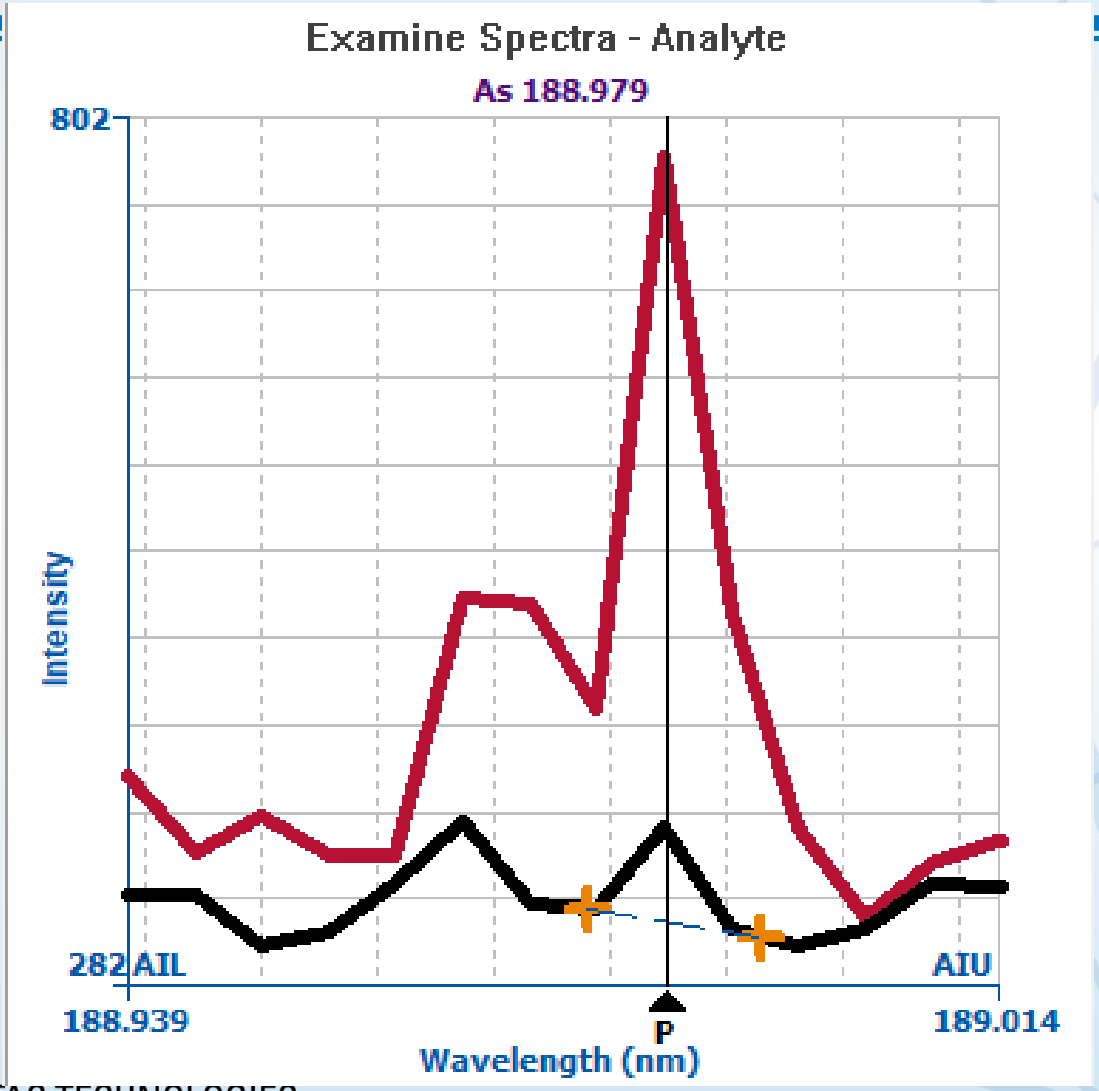
| Element | Wavelength (nm) | Plasma View |
|---|---|---|
| Ru | 349.894 | Radial |
| Se | 196.026 | Axial |
| Ag | 338.289 | Axial |
| Pt | 265.945 | Axial |
| Li | 670.784 | Radial |
| Sb | 231.146 | Radial |
| Ba | 493.408 | Radial |
| Mo | 202.030 | Axial |
| Cu | 324.752 | Radial |
| Sn | 189.927 | Axial |
| Cr | 267.716 | Radial |

# Pb (220.353 nm) Spectra at 0.01 mg/L Pb (Class 1)



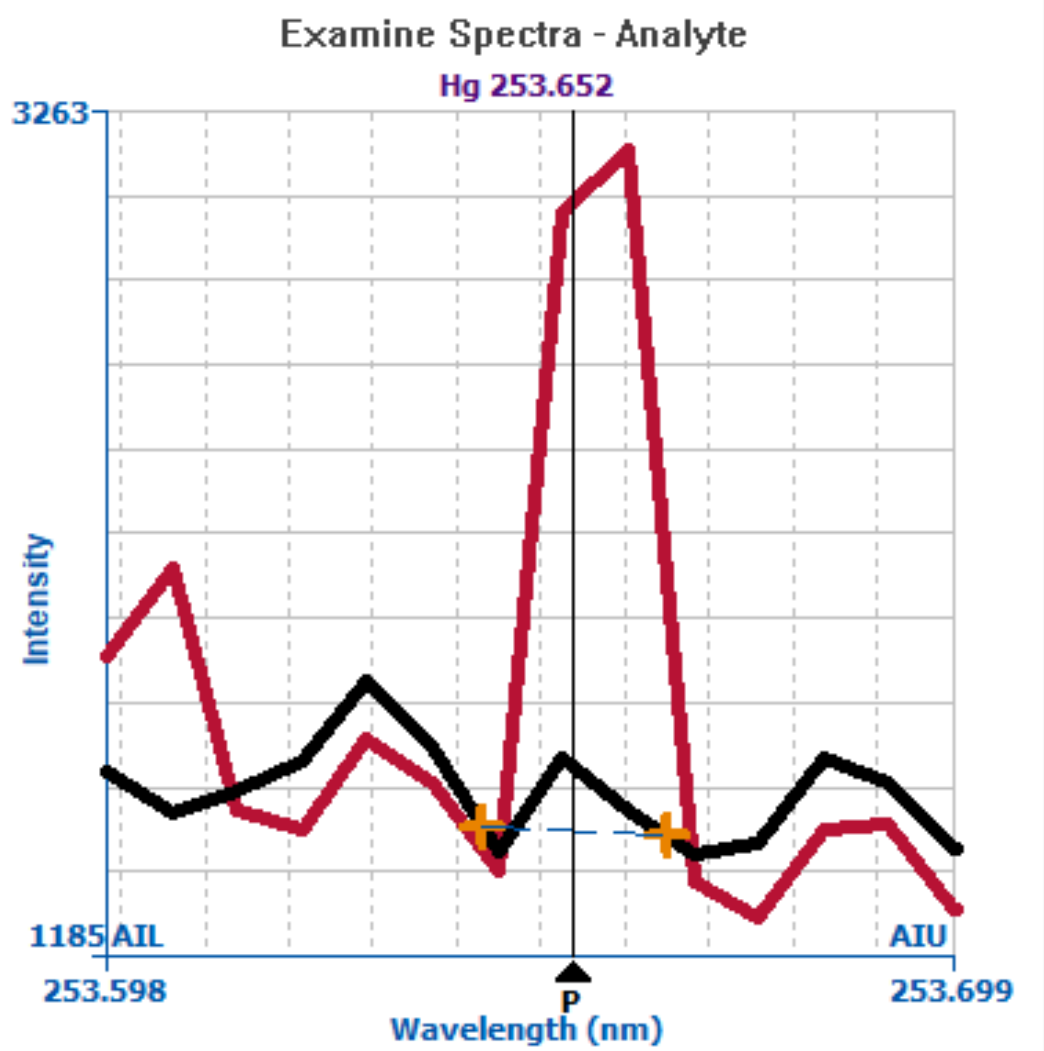

--- USN
--- Std Neb

# As (188.979 nm) Spectra at 0.03 mg/L As (Class 1)



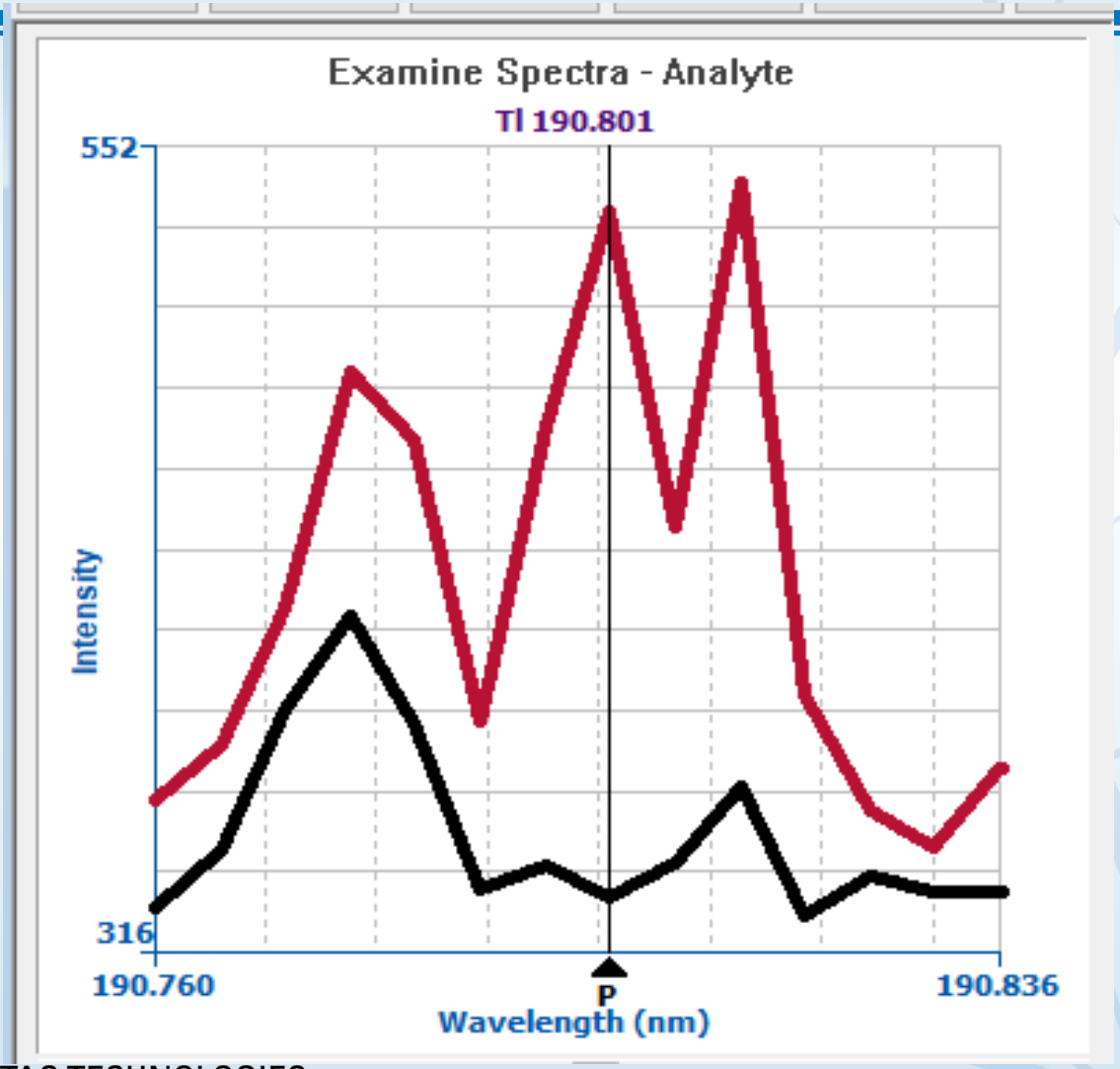

--- USN
--- Std Neb

# Hg ( 253.652 nm) Spectra at 0.06 mg/L Hg (Class 1)




--- USN
--- Std Neb

# Tl (190.801 nm) Spectra at 0.016 mg/L Tl (Class 2B)



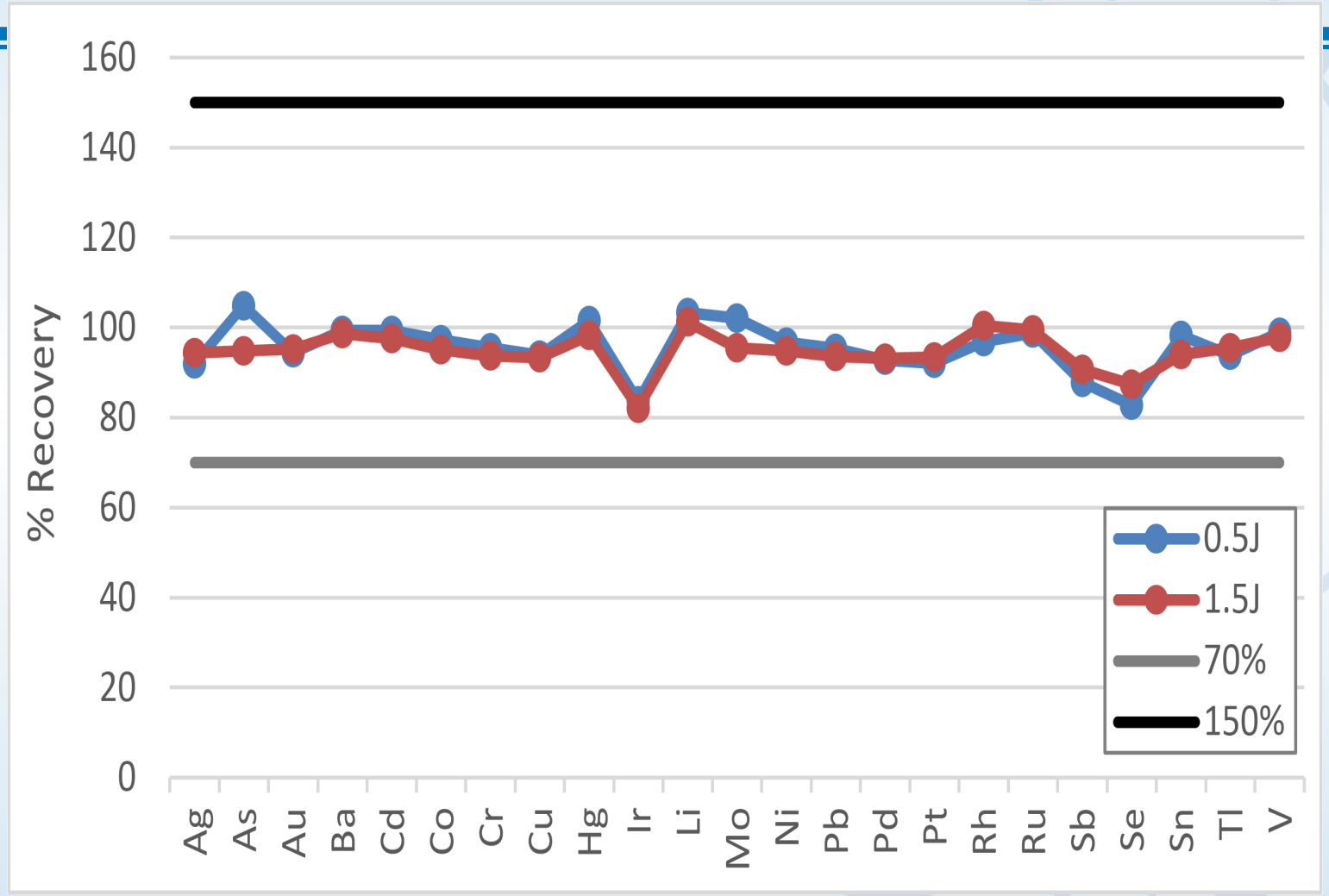

--- USN
--- Std Neb

# 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% |

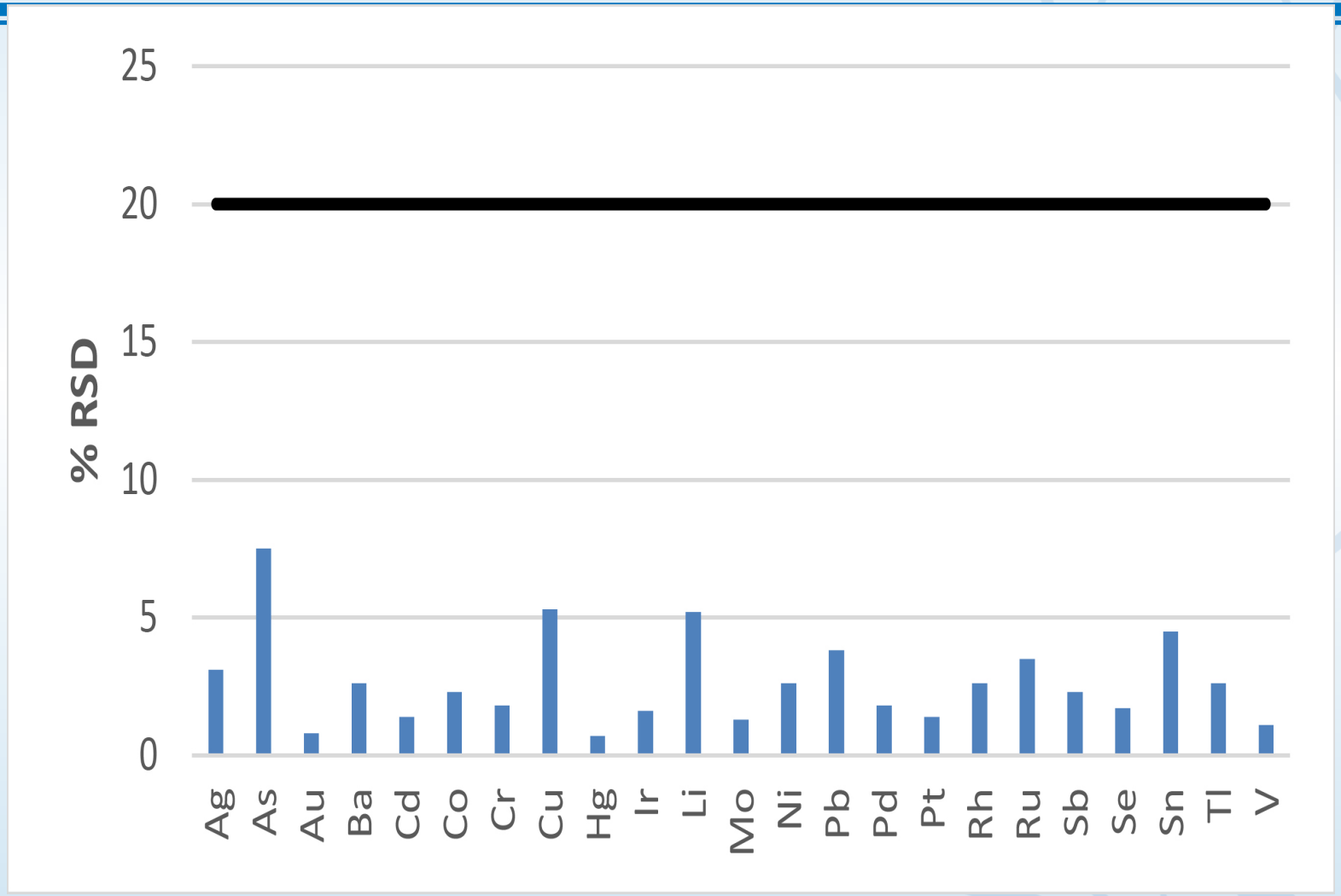
# Accuracy: 0.5J and 1.5J Spike Recoveries in Aspirin

## Black (top) and Gray (bottom) Lines Show USP <233> Limits




***Spike recoveries must be between 70% and 150%***

# Repeatability: %RSDs of Six Independent Samples Spiked at 1J

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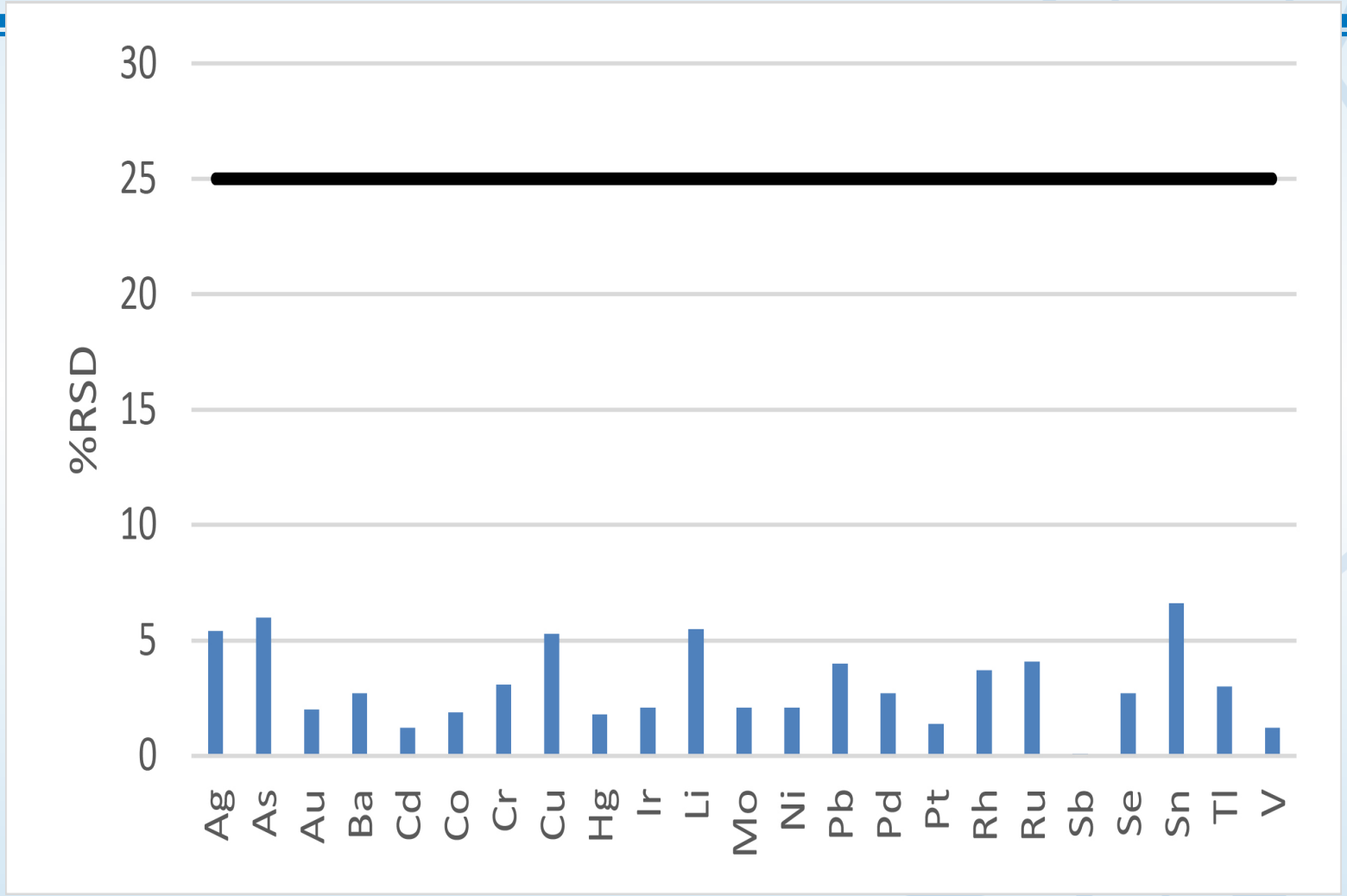
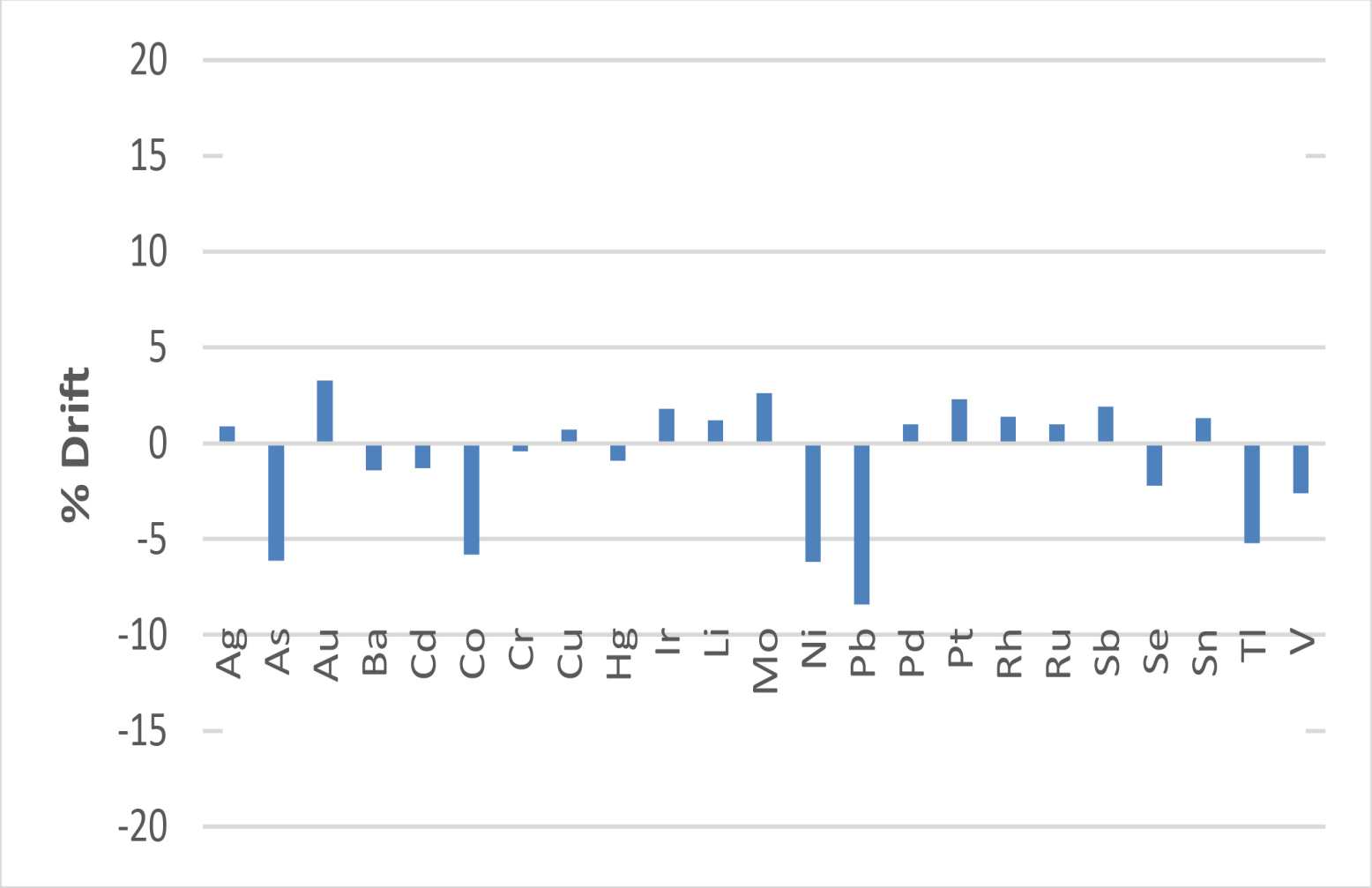
***%RSDs must be < 20%***

# Ruggedness: %RSDs of 6 Independent Samples Analyzed Over 2 Days (12 Measurements)




***%RSDs must be < 25%***

# System Suitability: Analysis of 1.5J at the Beginning and End of Analytical Run




***Difference in the results must be < 20%.***

# Summary

**All criteria required by USP <233> were met using the U5000AT+ Ultrasonic Nebulizer with ICP-AES detection of trace elements in aspirin. The U5000AT+ enables enhanced analyte sensitivity and lower background emission, improving ICP-AES measurement of more difficult elements in this example of a higher daily dose drug product.**

# U5000AT+ USN: Benefits & Advantages

- Enhanced detection of difficult Class 1 elements such as Pb, As, Hg and Class 2B element Tl
- Lower background emission due to less injected water vapor
- Fast and easy setup of the U5000AT+
- Convenient placement on laboratory cart or benchtop
- One button operation
- No computer control required
- Simple connection to autosampler (ex. ASX-280/560) for automated sample introduction

# Ultrasonic Nebulizers for ICP-AES
## Top Level Part Numbers

- **U5000AT+ Ultrasonic Nebulizer**
  - **U51-99-0001A+ (115 V)**
  - **U51-99-0001B+ (220 V)**

# U5000AT+ Interface Kits for ICP-AES

## U5000AT+ Compatibility

- All ICP-AES Models
  - Examples with Interface Kit SP Numbers ( )
    - Agilent (SP5155Y)
    - Analytik Jena (SP5155Y)
    - PerkinElmer (SP5155L)
    - Shimadzu (SP5155Z)
    - Spectro (SP5155P)
    - Teledyne Leeman (SP5155I)
    - Thermo Fisher (SP5155CC)

**One interface kit provided at no charge with each U5000AT+**

# Acknowledgement


- **Special thanks to Mary Jo Menke-Wright for her work in sample preparation, method development, data collection, and outline text for this important application.**

# Where to go for more information

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  - http://www.teledynecetac.com/resourceSite/Application%20Notes/AP-U5000-003.pdf