prepFAST ICP-MS: USP <232><233> Oral Drugs by Dilution
Automated Inline Calibration and Sample Dilution

Authors: Kyle Uhlmeyer and Paul Field (field@icpms.com)

Brief

The prep*FAST* inline autodilution system with ICP-MS fully automates USP <233> sample dilutions and J based calibrations. The prep*FAST* automatically 1) dilutes a single stock standard to build linear calibration curves surpassing all USP<233> validation criteria and 2) dilutes samples to the appropriate Total Dissolved Solids (TDS).

Features:

- Autocalibration from a single J stock standard
- Auto Sample Dilution
- Priority Sample Dilution
- Daily walk-up and analyze ICPMS instrument for USP
- Perfect for laboratories new to ICPMS
- Automate labor intensive steps to significantly reduce notebook entries

Stability

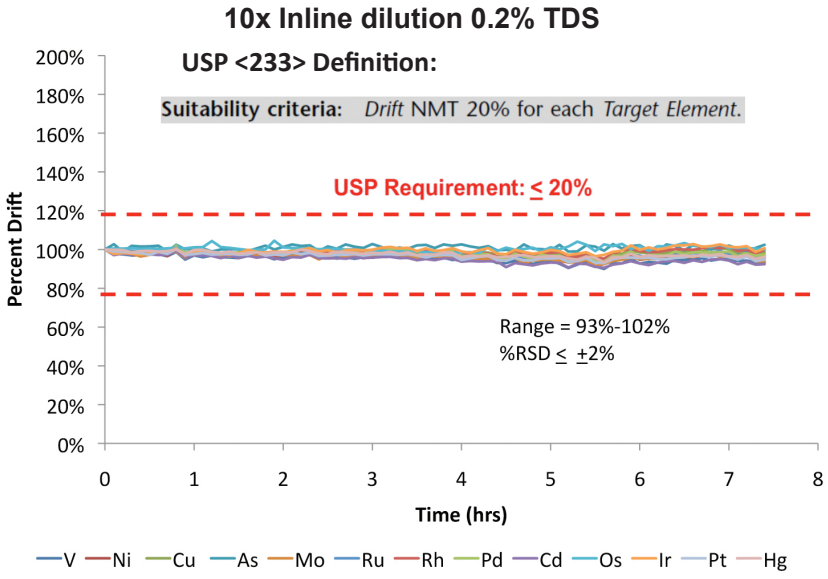

Figure 1. Stability is assessed (at 0.8J spike) throughout one analytical day. The long-term stability of the method is illustrated in a 7 1/2 hr run of 14 analytes from 150 analyses of oral medication. A drift of ± 2% RSD surpasses the USP acceptance criteria (± 20%) by a factor of 10.

Elemental Scientific

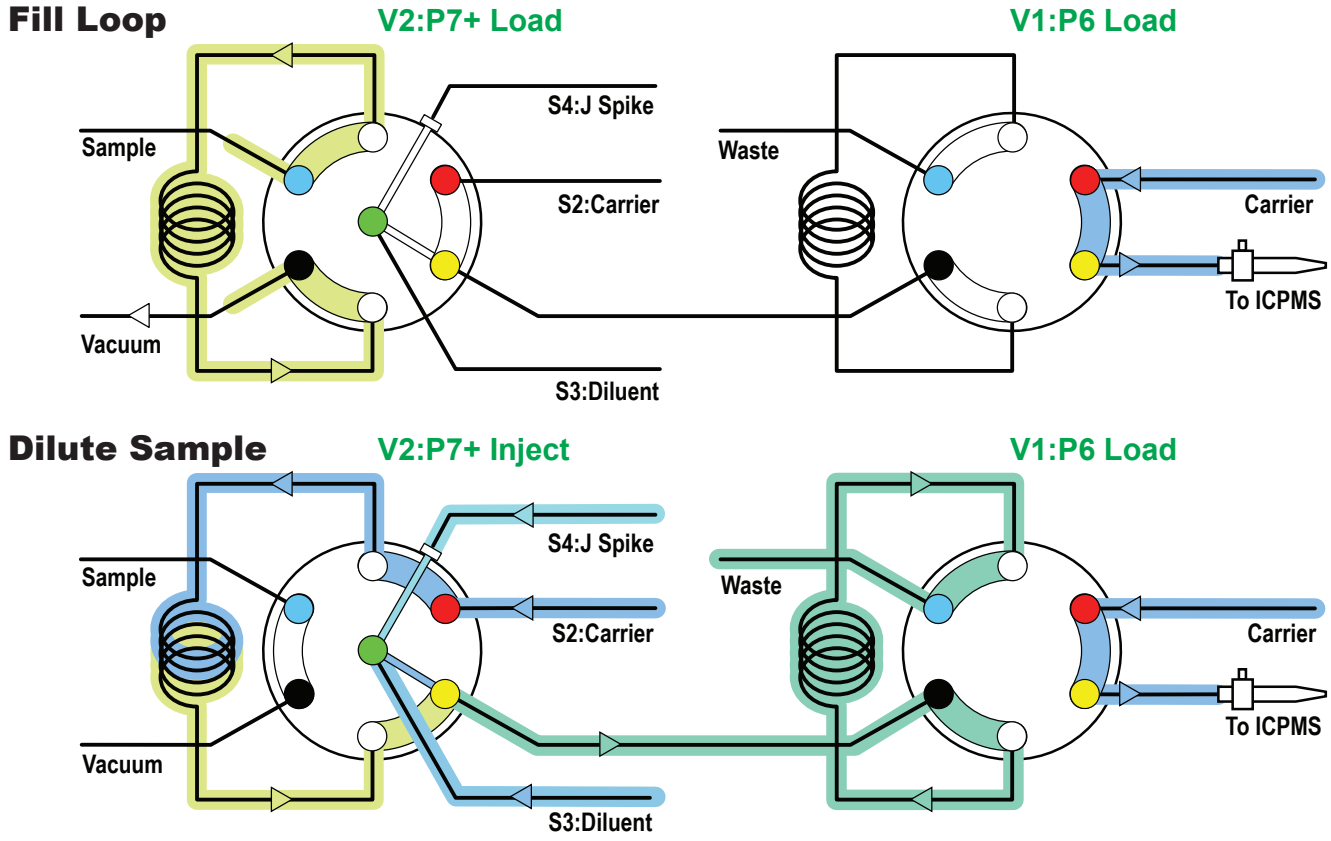

Figure 2. The prep*FAST* system schematic illustrating a two-step process of loading sample into a loop and injecting sample while performing inline dilution.

Abstract

The target value (J) for USP <233> defined calibration and validation is dependent on a drugs daily dose. Oral drugs have a wide range of daily doses that require drug specific J values and therefore drug specific calibrations. The prep*FAST* rapidly and automatically performs inline dilutions to build linear calibration curves from a single stock solution (r^2 > 0.999s) for any J value. Dilution factors entered into the ICP-MS software are used for precise and accurate inline dilution. Samples already in the solution phase are simply poured into a sample tube eliminating manual sample preparation. The seamlessly integrated prep*FAST* ICP-MS system easily surpasses USP <233> validation criteria of, 1) stability < ± 5% (USP limit ± 20%), 2) repeatability < ± 3% (USP limit ± 20%), 3) ruggedness < ± 4% (USP limit ± 25%) and 4) accuracy < ± 10% (USP limit ± 20%). Automating the full calibration and sample dilution process removes human error and reduces note book entries simplifying compliance with FDA's 21 CFR Part 11 record integrity regulation.

Introduction

All drugs absorbed through the digestive track and mucosal membranes are included in the oral category. The oral route has the greatest Permissible Daily Exposure (PDE) of all pathways outlined by USP <232>. Liquid oral drugs such as syrups and mucosal sprays can simply be diluted and analyzed by ICP-MS. USP <233> outlines specific validation protocols that require standardization, precision and spike recovery to be based on a target (J) value. J values vary as a function of PDE (µg/day), final dilution (dilution factor) and a drugs daily dose (g/day). This work will illustrate how the prep*FAST* ICP-MS system automatically calibrates and dilutes samples, easily exceeding all acceptance criteria outlined by USP <233>.

USP <232> <233> Definition:

J: The concentration (w/w) of the element(s) of interest at the *Target Limit*, appropriately diluted to the working range of the instrument.

$$J = \frac{PDE}{Maximum\ Daily\ Dose\ x\ Dilution\ Factor}$$

$$J = \frac{15\ \mu g/day}{\frac{20\ g}{day}\ x\ 500x}$$

$$J = 0.0015\ \mu g/g = 1.5\ \mu g/L$$

**Based on an assumed density of 1.00 g/mL*

Figure 3. USP <232><233> defined calculation of J using As as an example. PDE from Table 1 is combined with a hypothetical daily dose (20 g) and a dilution factor of 500. It is clear from this calculation that J value is inversely proportional to the daily dose.

Maximum Permissible Daily Exposure - PDE		
Element	**Oral Daily Dose PDE (µg/day)**	**LVP Component Limit (µg/g)**
Cd	5	0.5
Pb	5	0.5
As	15	1.5
Hg	30	3
Co	50	5
V	100	10
Ni	200	20
Tl	8	0.8
Au	100	10
Pd	100	10
Ir	100	10
Os	100	10
Rh	100	10
Ru	100	10
Se	150	15
Ag	150	15
Pt	100	10
Li	550	55
Sb	1200	120
Ba	1400	140
Mo	3000	300
Cu	3000	300
Sn	6000	600
Cr	11000	1100

Table 1. The USP Chapter <232> defined PDE (µg/day) values for Oral drugs are used (Figure 3) to calculate target values (J). USP <233> requires a calibration curve and a series of QC validation protocols including repeatability, ruggedness and spike recovery be based on the J value.

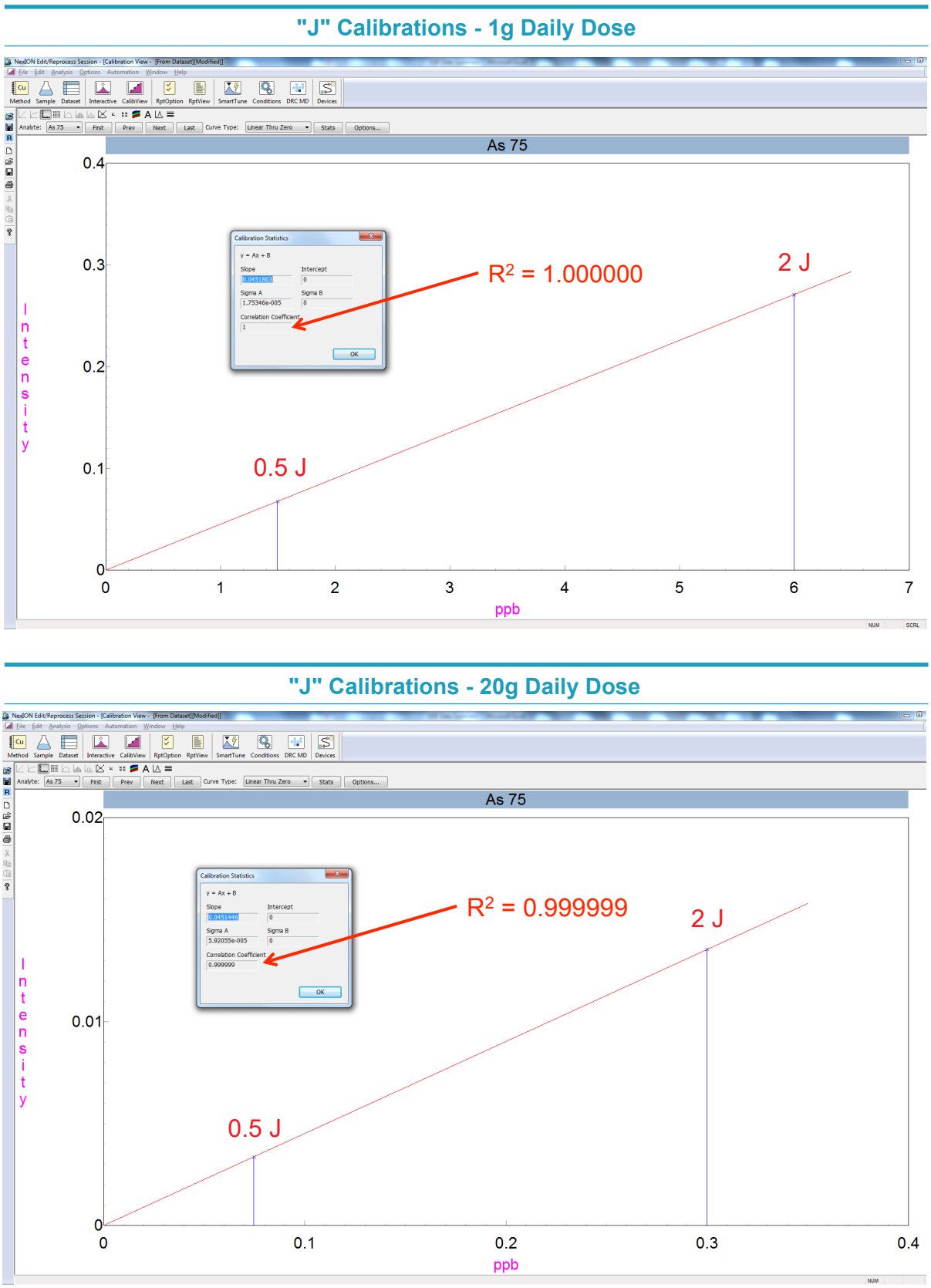

Figure 4. Fully automated inline dilutions of a single stock standard are used to generate linear calibration curves. The formula from Figure 3 is used to calculate J values for drugs with a wide range of daily doses (1 and 20 g/day are given as examples). Arsenic, the most challenging USP analyte with poor ionization efficiency, ArCl interference and the lowest PDE is easily autocalibrated with prep*FAST* for a wide range of J values.

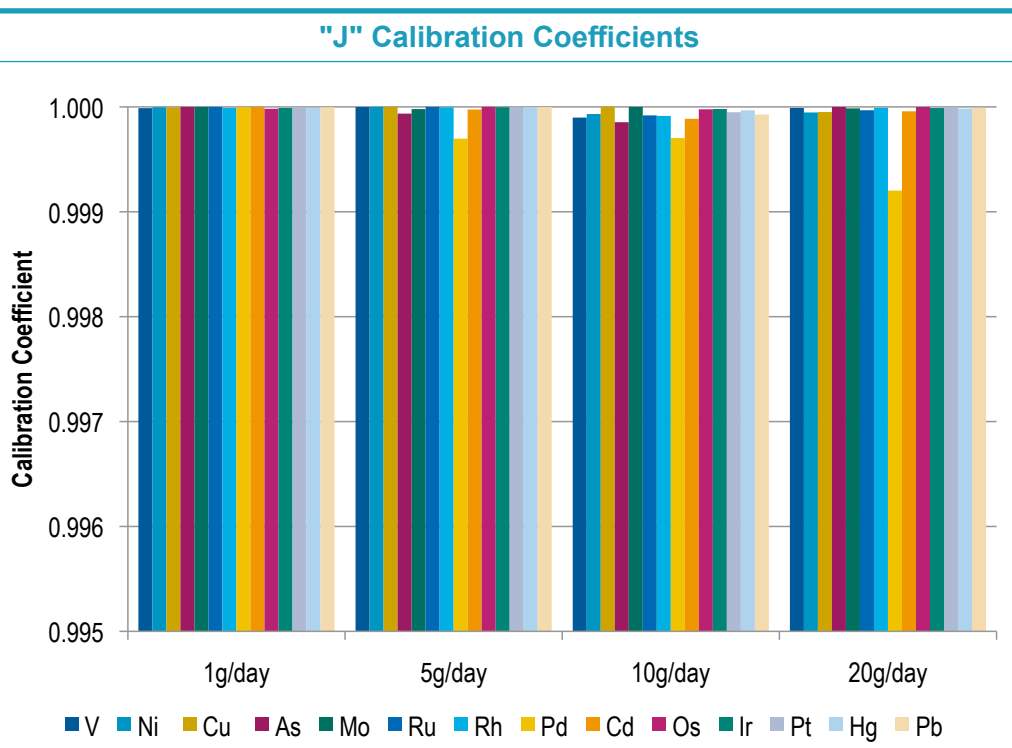

Figure 5. Fully automated inline dilutions from a single stock standard generates linear (>0.9999) calibration curves over a wide range of J values for all USP elements.

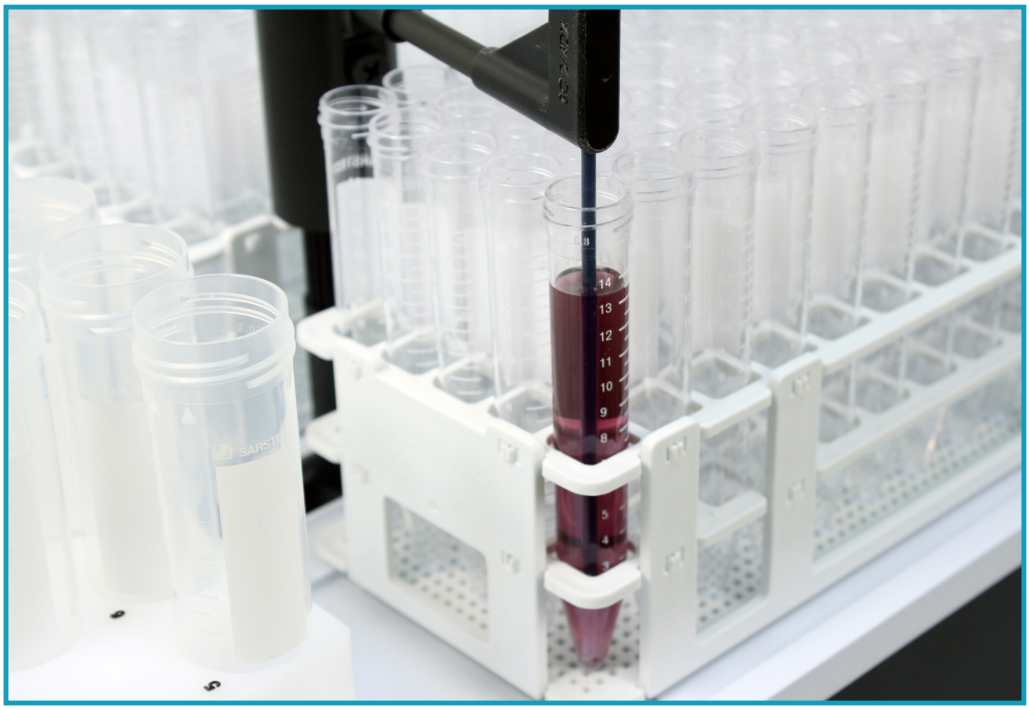

Figure 6. Simply pour solution (syrup) into tube and start analysis. Sample is autodiluted inline to appropriate TDS.

Repeatability

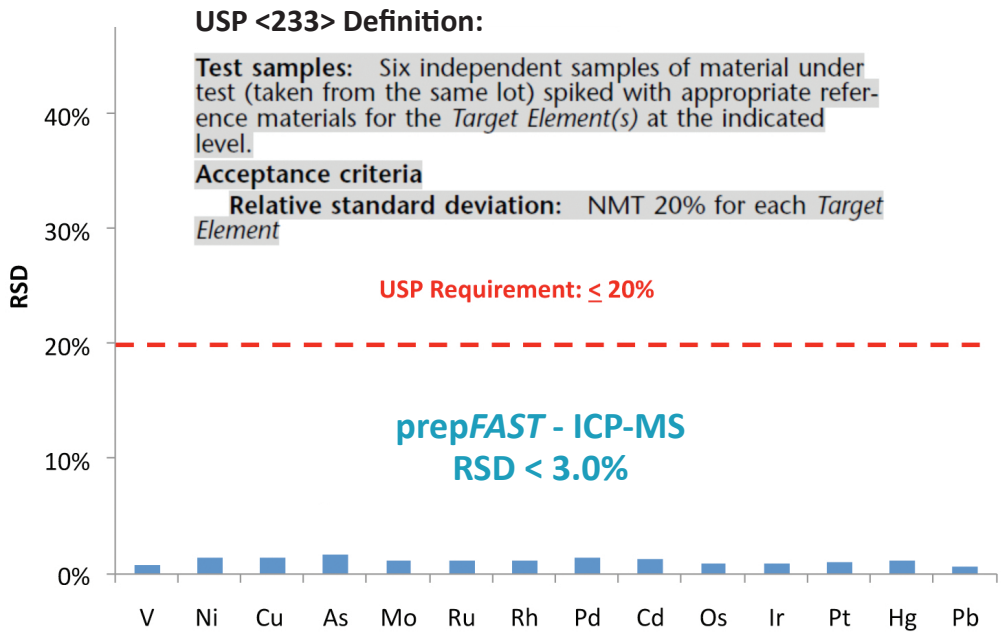

Figure 7. Repeatability for all analytes of interest of < ± 3% at 1J spike in over-the-counter flu remedy (liquid) is significantly below the USP accepted criteria of < ± 20% RSD.

Ruggedness

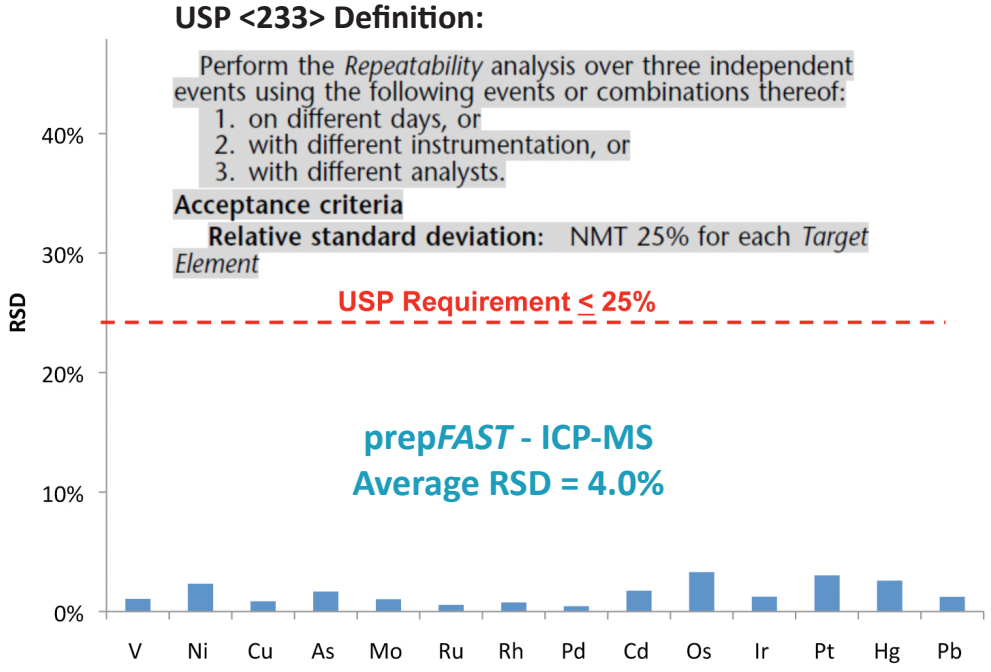

Figure 8. The ruggedness of the method demonstrated on 3 separate days yields accuracy (recoveries) of < ± 10% and reproducibility of < ± 4%. The USP acceptance criteria is defined as < ± 25% RSD for each target analyte.

Spike Recovery

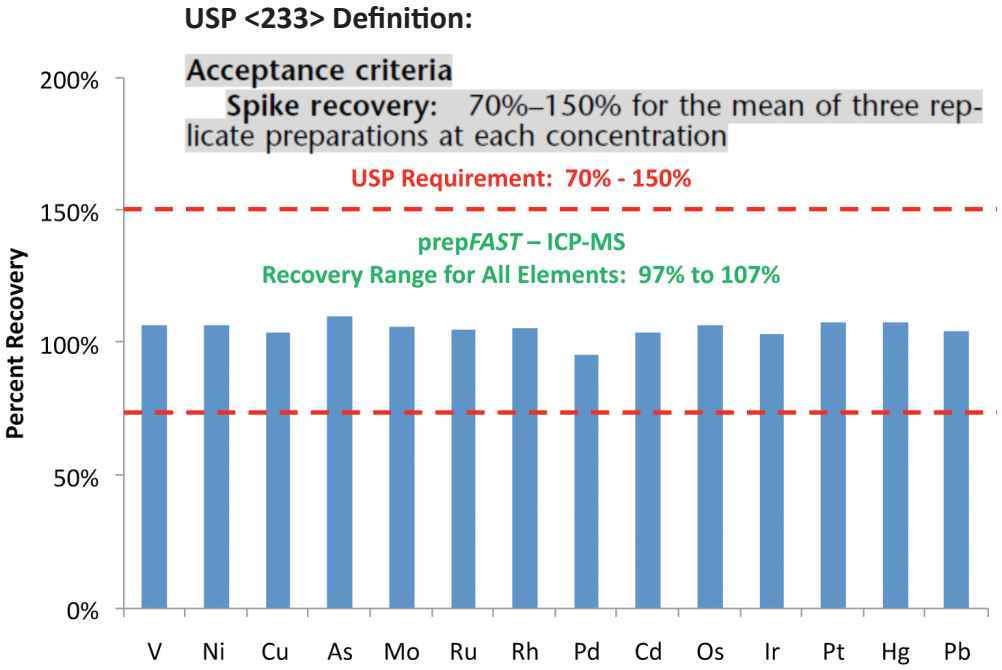

Figure 9. Excellent recovery for 1J spike in over-the-counter flu remedy (liquid) indicates the method is very robust constantly yielding spike recoveries (< ± 10%) that are significantly better than the USP threshold (70-150%).

Isotope	PDE (µg/day)	OTC Flu Remedy (Liquid) µg/day
V 51	100	1.08
Ni 60	500	-
Cu 63	1000	-
As 75	1.5	0.42
Mo 98	100	-
Ru 102	100	0.04
Rh 103	100	-
Pd 106	100	-
Cd 111	25	-
Os 192	100	-
Ir 193	100	-
Pt 195	100	-
Hg 202	15	-
Pb 208	5	-

Table 2. Results for OTC liquid flu remedy are significantly lower than USP <232> PDEs.

Benefits

- prep*FAST* autocalibration
  - Single multi-element standard for all J values
- prep*FAST* auto inline dilution
  - Eliminate final manual dilution step
- Brings samples to constant total dissolved solids (0.2%)
- Easy-to-use automated system for USP protocols
- Pre-developed fully automated methods
- Exceeds all USP validation criteria: Stability, Repeatability, Ruggedness, and Accuracy
- Well-suited to the demands of a high throughput pharmaceutical laboratory

2DX prep*FAST*

 | 7277 World Communications Drive | Omaha, NE 68122
Tel: 1-402-991-7800 | sales@icpms.com | www.icpms.com

14055-2