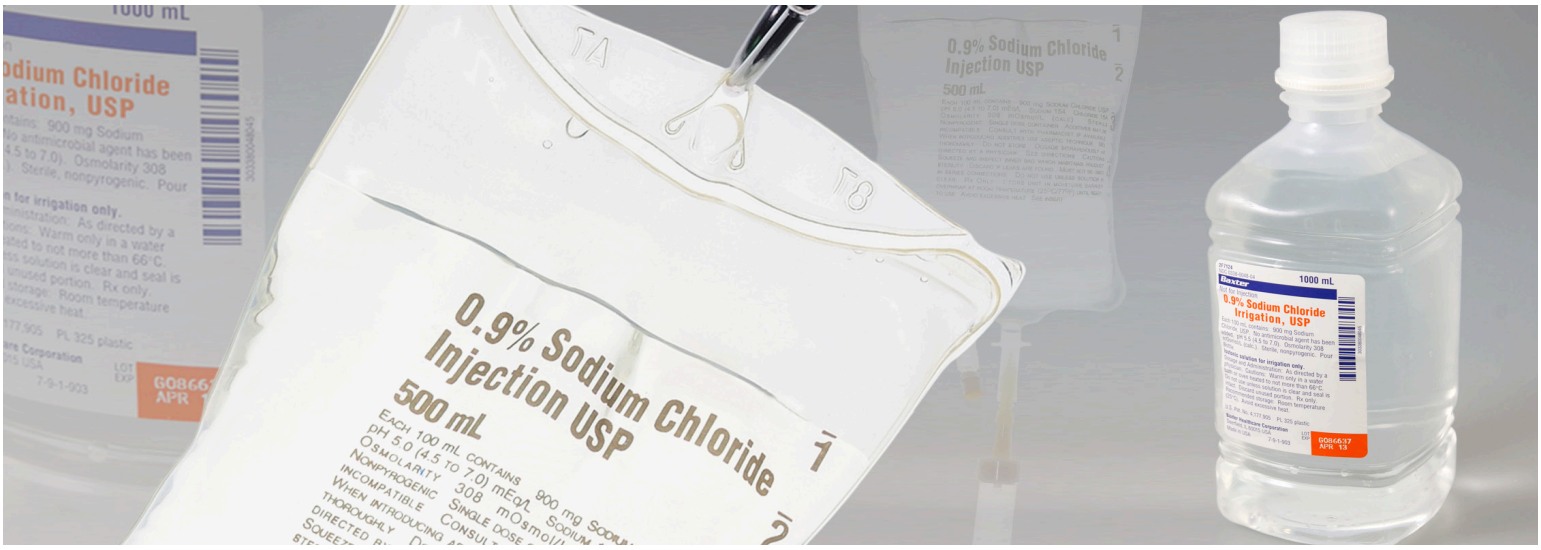
prepFAST ICP-OES: USP <232> <233> Parenteral Undiluted Automated Inline Calibration and Sample Spiking



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Brief

The prep*FAST* inline autodilution system with ICP-OES fully automates USP <233> J based calibrations protocols. The prep*FAST* provides 1) autocalibration, 2) autosample injection, and 3) autospike addition, eliminating manual sample preparation.

Features

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

Stability

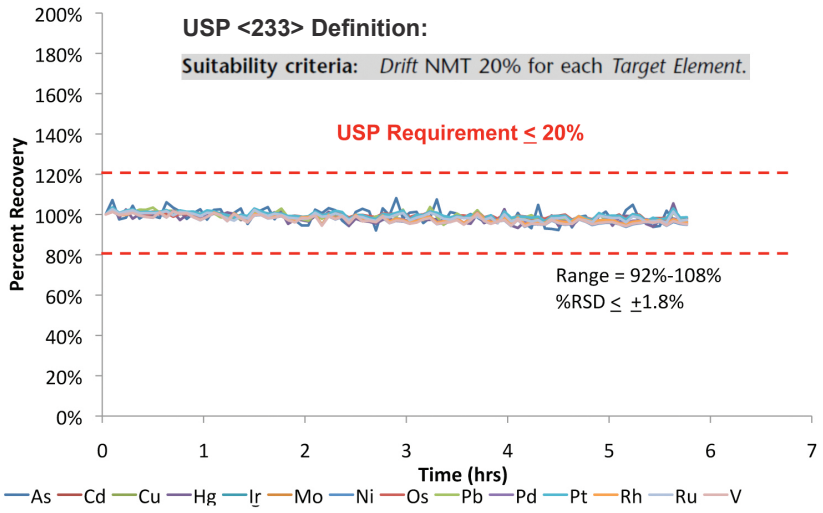

Figure 1. Stability is assessed (at 0.8J spike) throughout one analytical day. The long-term stability of the method is illustrated in a 6 hr run of 14 analytes from 120 analyses of saline solution. A drift of ± 2% RSD surpasses the USP acceptance criteria (± 20%) by a factor of 10.

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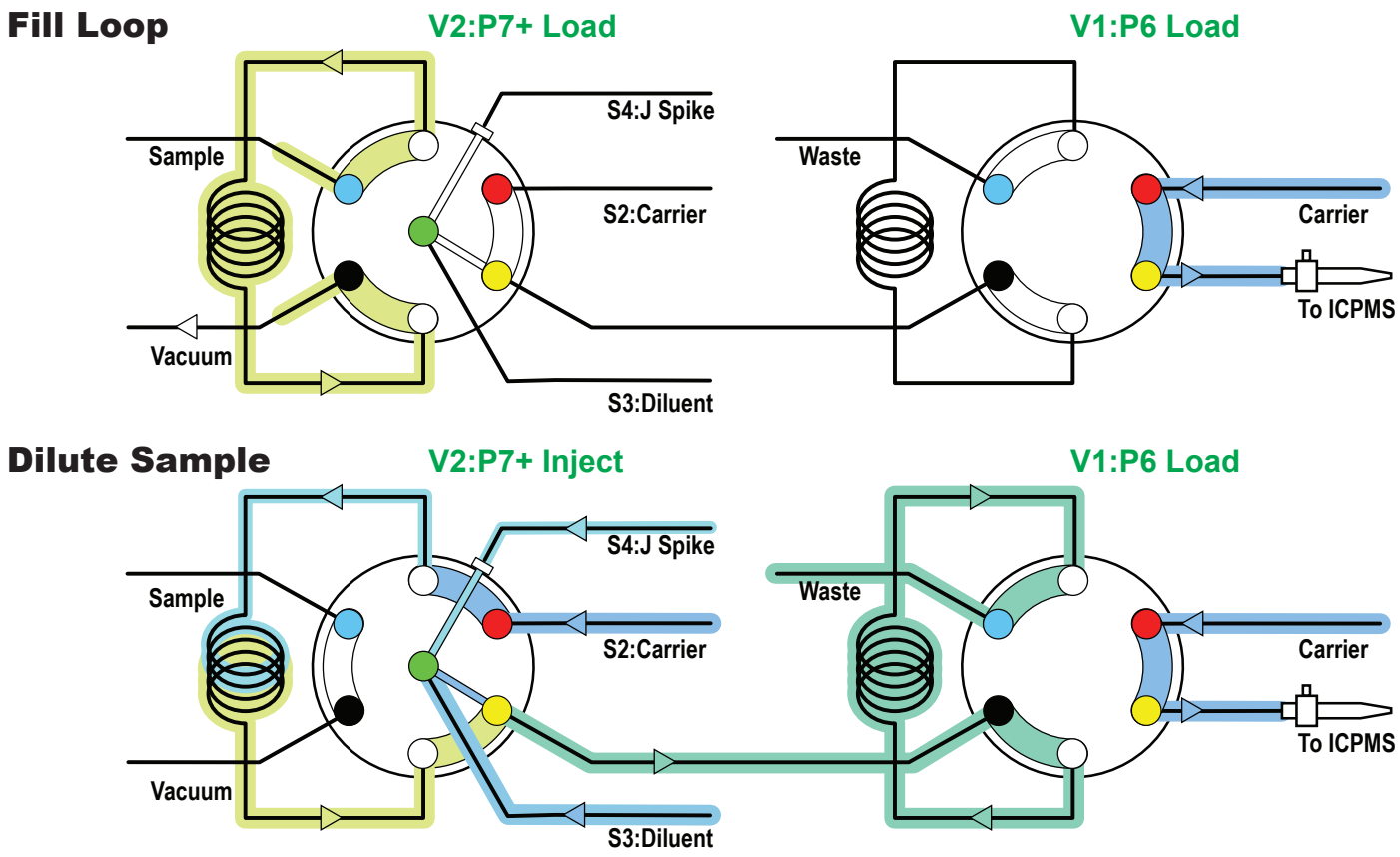

Figure 2. The prep*FAST* system schematic illustrating a two-step process of loading sample into a loop and injecting sample while performing inline dilution.

Abstract

Direct analysis of undiluted parenteral solutions by prep*FAST* ICP-OES delivers a fully automated USP <233> method. 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. The high Total Dissolved Solids (TDS) tolerance of ICP-OES eliminates the need for sample dilution, freeing one prep*FAST* syringe for the inline spike addition.

The prep*FAST* fully automates 1) J based calibration, 2) unspiked sample injection, and 3) sample spiking at any J level (USP <233> 0.8 and 1.0 for validation tests). This capability of the prep*FAST* ICP-OES requires only a blank solution and samples be placed in the autosampler. The seamlessly integrated prep*FAST* ICP-OES system easily surpasses USP <233> validation criteria of, 1) stability < ± 5% (USP limit ± 20%), 2) repeatability < ± 5% (USP limit ± 20%), 3) ruggedness < ± 5% (USP limit ± 25%) and 4) accuracy < ± 10% (USP limit ± 20%).

Automating the J based calibration and J spiking process removes human error and reduces notebook entries simplifying compliance with FDA's 21 CFR Part 11 record integrity regulation.

Introduction

The parenteral route of exposure includes both small (needle) and large volume (IV) solutions. USP <232> dictates that "When the daily dose of an injection is > 100 mL (large volume parenteral (LVP)), the amount of elemental impurities present in the drug product must be controlled through the individual components used to produce the drug product."

Lactated Ringer's solution, having similar osmotic pressure and viscosity as human blood, contains sodium, potassium and/or calcium chloride (~1%), lactose in the form of sodium lactate and a glucose solution. This common diluent for injected (IV) drugs has an acceptable level of Total Dissolved Solids (TDS) for direct (undiluted) analysis by ICP-OES. USP <233> outlines specific validation protocols that require standardization, precision and spike recovery to be based on a target (J) value. The prep*FAST* ICP-OES system calibrates, injects samples and spikes samples inline eliminating manual sample and standard preparation. The fully automated prep*FAST* ICP-OES surpasses all USP <233> acceptance criteria.

Table 1. The USP Chapter <232> defined PDE (µg/day) values for parenteral 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.

Maximum Permissible Daily Exposure - PDE

Element	Parental Daily Dose PDE (µg/day)	LVP Component Limit (µg/g)
Cd	2	0.2
Pb	5	0.5
As	15	1.5
Hg	3	0.3
Co	5	0.5
V	10	1
Ni	20	2
Tl	8	0.8
Au	100	10
Pd	10	1
Ir	10	1
Os	10	1
Rh	10	1
Ru	10	1
Se	80	8
Ag	10	1
Pt	10	1
Li	250	25
Sb	90	9
Ba	700	70
Mo	1500	150
Cu	3 00	30
Sn	600	60
Cr	1100	110

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. For example, if the target elements are

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

$$J = \frac{1.5ug/day}{0.010\frac{L}{day}\ x\ 1x}$$ ← undiluted

$$J = 150\ ug/L$$

Figure 3. USP <232><233> defined calculation of J for Hg in parenteral solution with 10mL/day daily dose and no dilution factor. NOTE: At 10mL daily dose, PDE is equivalent to LVP component limit (Table 1). Therefore, J for this data set is also appropriate for LVP component limits.

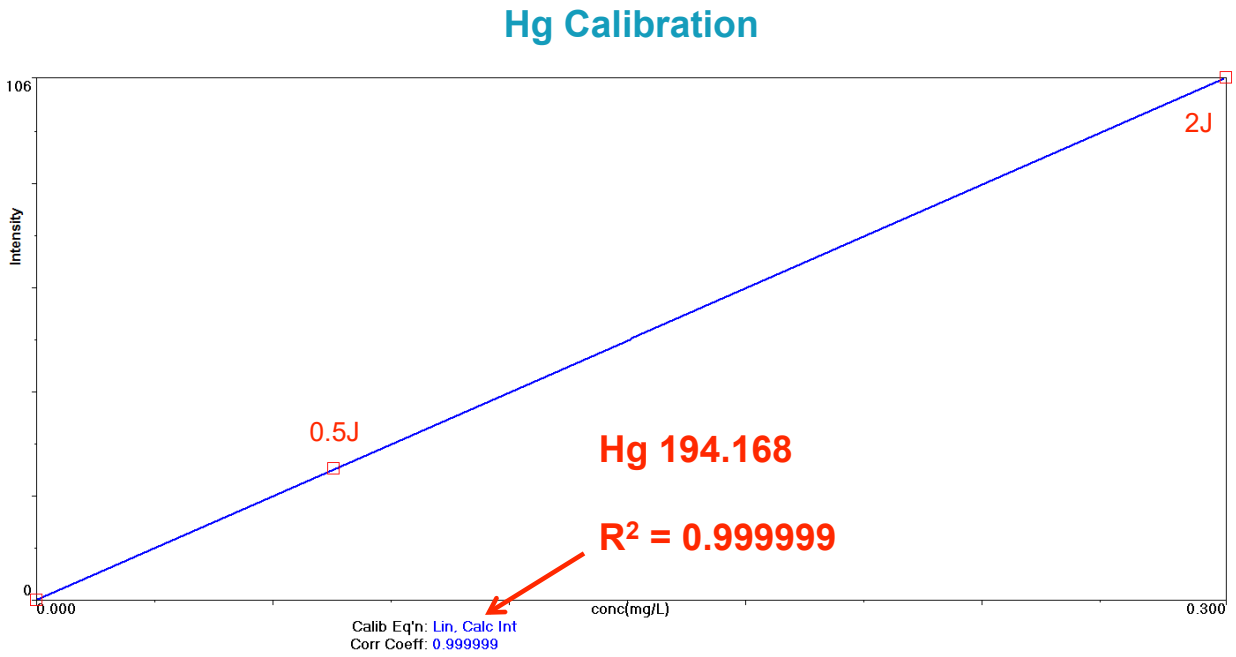

Figure 4. Autocalibration of Mercury at 0.5 and 2J using inline J spiking.

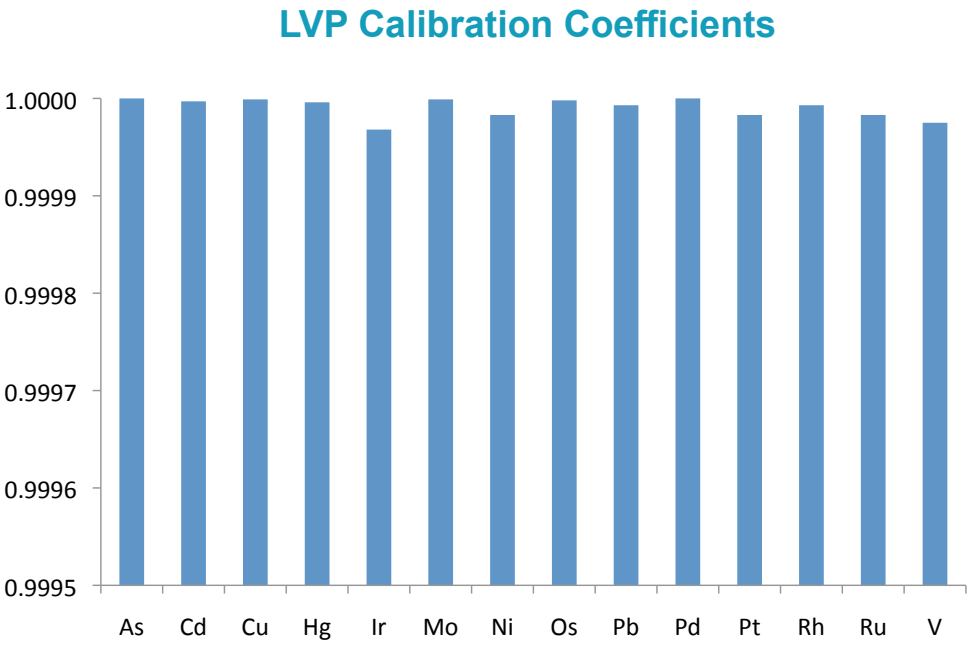

Figure 5. Fully automated inline dilutions from a single stock standard generate linear (> 0.9999) calibration curves for USP elements.

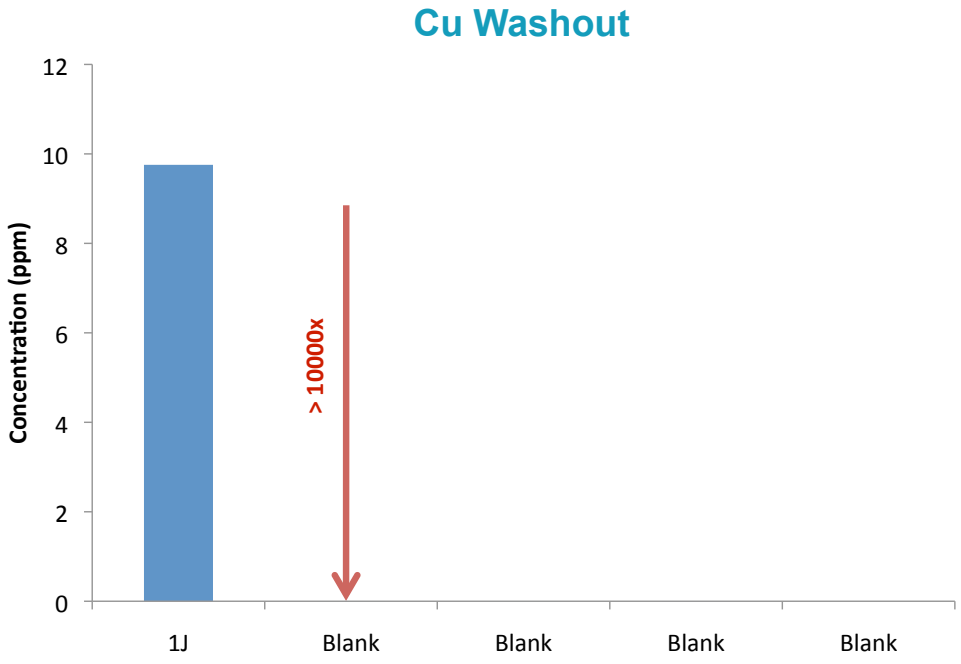

Figure 6. A blank solution analyzed immediately after a J spiked sample returns to baseline. prep*FAST*'s > 10,000 fold washout indicates no detectable carryover when performing inline spiking.

Repeatability

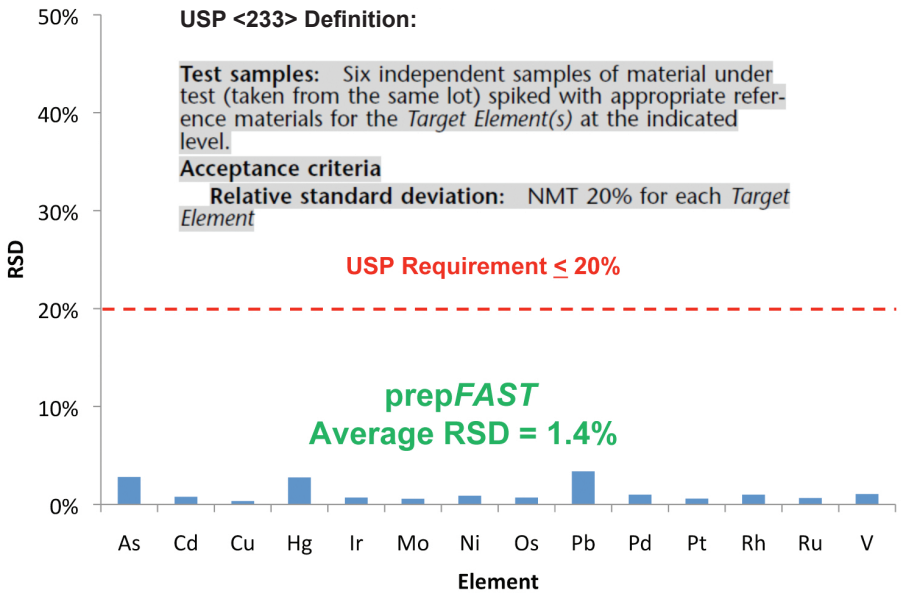

Figure 7. Repeatability for all analytes of interest of < ± 3% at 1J spike in 0.9% saline solution is significantly below the USP accepted criteria of < ± 20% RSD.

Ruggedness

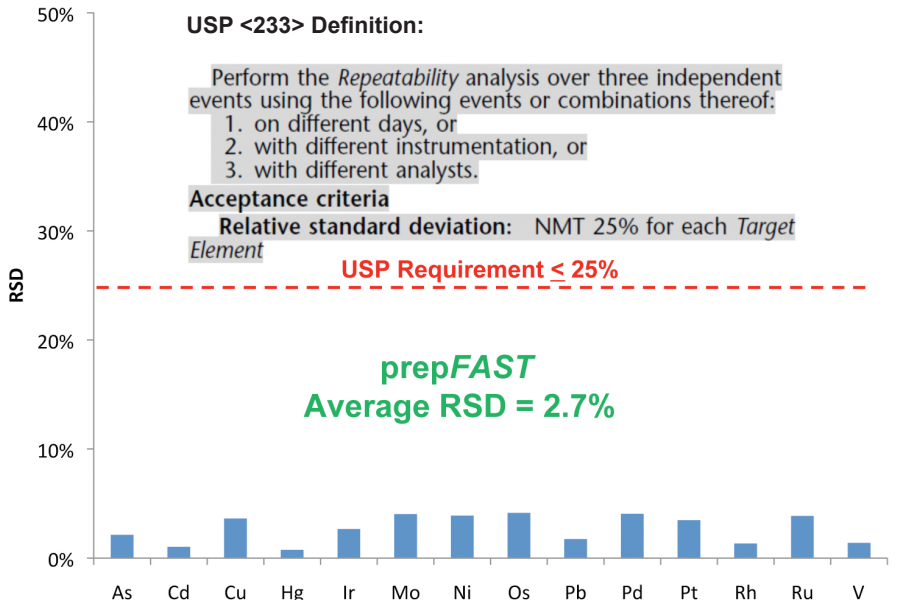

Figure 8. The ruggedness of the method demonstrated on 3 separate days yields accuracy (recoveries) of < ± 10% and reproducibility of < ± 4%. The USP acceptance criteria is defined as < ± 25% RSD for each target analyte.

Spike Recovery

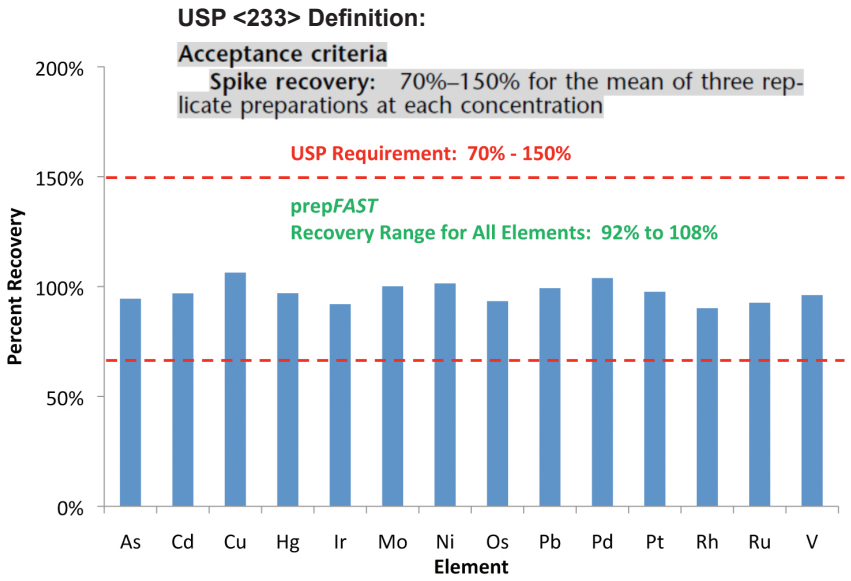

Figure 9. Excellent spike recovery (±10%) for 1J spike to Ringer's Solution indicates the method is accurate to levels that are significantly better than the USP threshold (70-150%).

Table 2. Concentrations determined in lactated Ringer's Solution are all significantly below USP <232> PDE limits.

Results		
Element	Determined LVP (µg/g)	PDE (µg/g)
Cd	-	2
Pb	-	5
As	-	15
Hg	-	3
Ir	0.030	10
Os	-	10
Pd	0.036	10
Pt	-	10
Rh	0.006	10
Ru	-	10
Mo	-	1500
Ni	0.025	20
V	0.007	10
Cu	0.051	300

Benefits

- prep*FAST*: autocalibration
  - Single multi-element standard for all J values
- prep*FAST*: auto inline J spiking
  - Eliminate final manual J spiking step
- Run undiluted samples up to 1% TDS
- 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

Figure 10. 2DX prep*FAST*