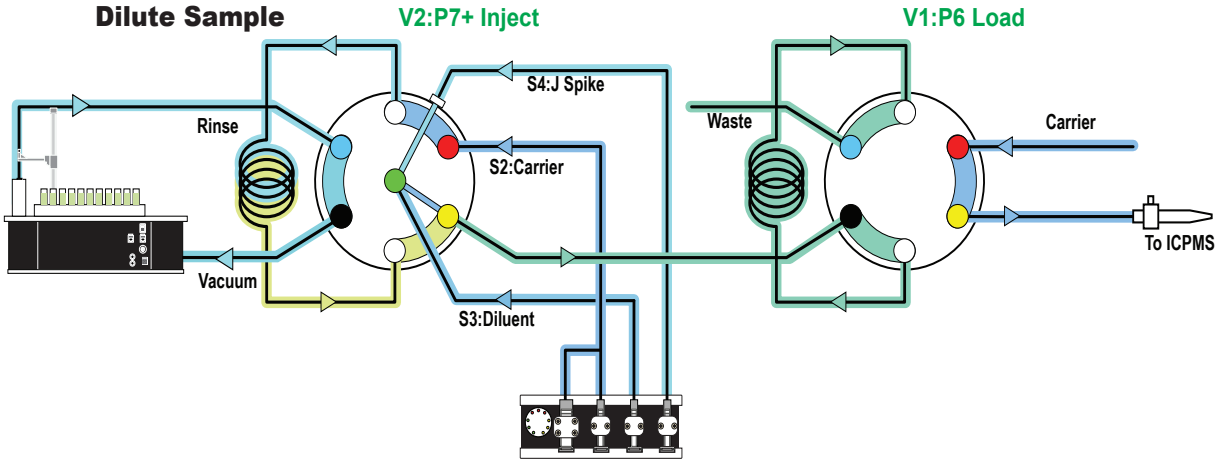
Automating USP <233>

prep*FAST*
The Next Stage of Automation

prep*FAST*: Preparing for USP <232> <233> Through Automation

The prep*FAST* inline autodilution system with ICP and ICP-MS, fully automates USP <233> methods. The prep*FAST* can 1) dilute a single stock standard to build linear calibration curves, 2) dilute samples to the appropriate TDS and 3) spikes samples at user defined J values.



Benefits of this approach for the demands of a high throughput pharmaceutical laboratory include:

- prep*FAST* – autocalibration: Single multi-element standard for all J values
- prep*FAST* – auto inline dilution: Eliminate final manual dilution step
- prep*FAST* – auto J spiking
- Run undiluted samples up to 1% TDS (ICP)
- Easy-to-use automated system for USP protocols
- Pre-developed fully automated methods
- Exceeds all USP validation criteria: Stability, Repeatability, Ruggedness, and Accuracy

Trace metal impurities in pharmaceutical products are either the direct result of catalysts added during drug formulation or contamination during production. An element's toxicity is a function of exposure (bioavailability) and route of administration.

Based on the toxicity of elemental impurities, the United States Pharmacopeia (USP) has set values for their Permissible Daily Exposure (PDE) based on route of administration (Table 1).

Table 1. Maximum permissable daily exposure – PDE

Element	Oral Daily Dose PDE (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalation Daily Dose PDE (µg/day)
Cadmium	5	2	2
Lead	5	5	5
Arsenic (Inorganic)	15	15	2
Mercury (Inorganic)	30	3	1
Iridium	100	10	1
Osmium	100	10	1
Palladium	100	10	1
Platinum	100	10	1
Rhodium	100	10	1
Ruthenium	100	10	1
Molybdenum	3000	1500	10
Nickel	200	20	5
Vanadium	100	10	1
Copper	3000	300	30
Chromium	11000	11000	3

The USP Chapter <232> defines a target (J) value as a function of PDE (µg/day) and a drug's daily dose (g/day), whereas Chapter <233> outlines specific protocols for the determination of toxic metals by ICP/ICP-MS.

To appropriately determine the J value for analysis, the final dilution factor must be taken into consideration. For simplicity and homogeneity purposes, the adjacent example uses a 1 g mass of drug and requires a final diluent volume of 500 mL (0.2% TDS). The formula illustrates the calculation of J for Cd (PDE = 5 µg/day; Oral) in a drug with a maximum daily dose of 1 g/day.

To maximize detection limits, optimize stability and unify sample preparation for all solid (tablets and powders) drugs, a target Total Dissolved Solids (TDS) for ICP and ICP-MS are 1% (100 fold dilution of solid) and 0.2% (500 fold dilution of solid), respectively. By setting the dilution factor constant, for optimal analytical performance, the J value varies inversely with respect to daily dose. Therefore, large daily dose drugs require a lower concentration spike and calibration standard.

USP <233> requires a calibration curve and a series of QC validation protocols including spike recovery, accuracy, precision and stability tests to be based on the target values (J).

USP <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.

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

$$J = \frac{25\ ug/day}{\frac{20g}{day}\ x\ 500x}$$

$$J = 2.5\ ug/L$$

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

The PDE values (µg/day) of oral drugs are used to calculate 0.5J and 2J values for drugs with hypothetical daily doses of 1, 5, 10 and 20 g/day.

Table 2. J Values for a range of daily doses

Isotope	PDE (µg/day)	J Values in final solution 0.2% TDS (µg/L)					
		1 g/day daily dose		5 g/day daily dose		20 g/day daily dose	
		0.5J	2J	0.5J	2J	0.5J	2J
Cd 111	5	5	20	1	4	0.25	1
Pb 208	5	5	20	1	4	0.25	1
As 75	15	15	60	3	12	0.75	3
Hg 202	30	30	120	6	24	1.5	6
Ir 193	100	100	400	20	80	5	20
Os 192	100	100	400	20	80	5	20
Pd 106	100	100	400	20	80	5	20
Pt 195	100	100	400	20	80	5	20
Rh 103	100	100	400	20	80	5	20
Ru 102	100	100	400	20	80	5	20
Mo 98	3000	3000	12000	600	2400	150	600
Ni 60	200	200	800	40	160	10	40
V 51	100	100	400	20	80	5	20
Cu 63	3000	3000	12000	600	2400	150	600

USP <233> offers four different approaches to sample preparation,

1) **Neat**, undiluted sample
2) **Direct aqueous solution**, dilute in aqueous solution or acid
3) **Direct organic solution**, dilute in appropriate organic solvent
4) **Indirect solution**, use closed vessel acid digestion for insoluble samples.
5) **Closed vessel digestion**, use strong acids in closed vessel, for insoluble samples

Drugs already in solution can be run neat or diluted, whereas drugs in solid form need to be solubilized and diluted. Regardless of form of drug delivery (solid/liquid), all final solutions need to be analyzed at appropriate TDS and the correct J based calibration. Given typical detection limits and TDS tolerance for ICP and ICP-MS instruments the PDEs and J formula above are used to develop appropriate prep*FAST* methods for drug types and daily doses.

Table 3.

Route of Administration	ICP	ICP-MS
Orals (> 1g/day)	-	dilute (0.2% TDS)
Orals (< 1g/day)	dilute (~1.0% TDS)	dilute (0.2% TDS)
Inhalation	undiluted (~1.0% TDS)	dilute (0.2% TDS)
LVP	undiluted (~1.0% TDS)	dilute (0.2% TDS)

The prep*FAST* system's inline mixing capabilities eliminates the need to prepare calibration standard solutions or manual sample dilutions. This stable platform easily surpasses the validation criteria of USP <233>, 1) stability, 2) repeatability, 3) ruggedness and 4) spike recovery. Automating the full process removes human error and reduces notebook entries simplifying compliance with FDA's 21 CFR Part 11 record integrity regulation.

References

1. United States Pharmacopeia General Chapter <232> *Elemental Impurities – Limits*: 2nd Supplement of USP 35-NF 30
2. United States Pharmacopeia General Chapter <233> *Elemental Impurities – Procedures*: 2nd Supplement of USP 35-NF 30

2DX prep*FAST*