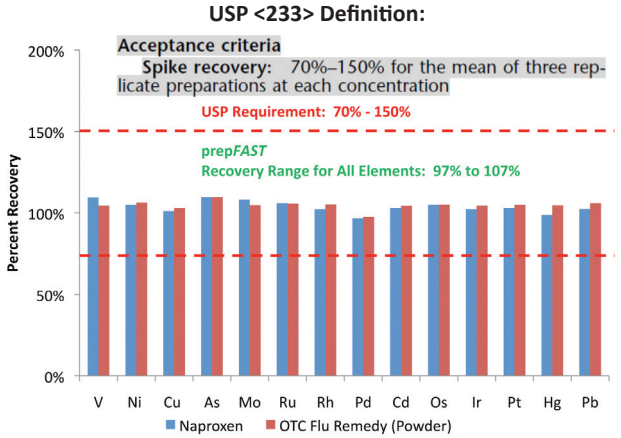
prepFAST ICP-MS: USP <232><233> Oral Drugs by Dissolution Automated Inline Calibration and Sample Dilution

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 and 2) dilutes samples to the appropriate Total Dissolved Solids (TDS) surpassing all USP <233> validation criteria.

Spike Recovery



Features:

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

Figure 1. Excellent recovery for 1J spike to Naproxen and OTC flu remedy indicates the method is very robust, constantly yielding spike recoveries (< ± 10%) that are significantly better than the USP threshold (70-150%).

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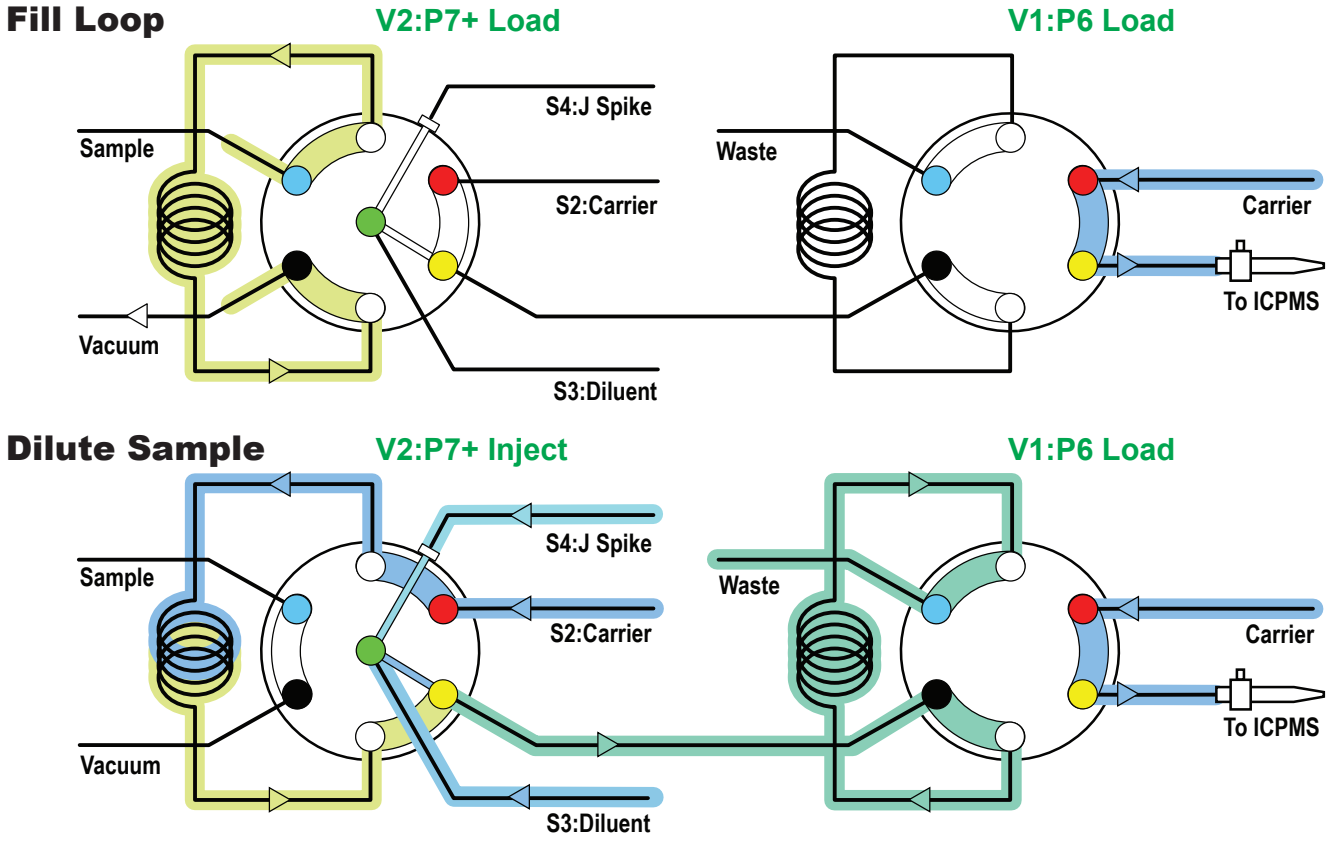


Figure 2. The prep*FAST* system schematic illustrating a two-step process of loading sample into a loop and injecting sample while performing inline dilution.

Abstract

USP <233> outlines specific protocols for the dissolution and analysis of metal impurities in solid samples. Calibration and validation protocols are based on a target (J) value that is a function of PDE (µg/day), final dilution (0.2% = 500x) and a drugs daily dose (g/day). The prep*FAST* automatically dilutes a single stock standard to build linear calibration (r^2 > 0.999s) for any J value. A 500 fold final dilution factor equates to an appropriate Total Dissolved Solids (TDS) for ICP-MS. Solid samples (1 g) initially digested in 50 mL of acid are automatically diluted inline 10x by prep*FAST* to obtain a final TDS of 0.2%, eliminating a second manual dilution step. 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 notebook entries simplifying compliance with FDA's 21 CFR Part 11 record integrity regulation.

Introduction

The oral route has the highest Permissible Daily Exposure (PDE) of all pathways. Oral drugs in the solid phase must first be digested and diluted to an appropriate Total Dissolved Solid (TDS) concentration (0.2%) for ICP-MS analysis. USP <233> outlines protocols for the dissolution of solid drugs. In this study, Over-the-Counter (OTC) flu remedy powder and Naproxen tablets are digested in an open vessel (warm 50 mL 2% HNO_3 / 0.5% HCl) mixture and closed vessel microwave system (50 mL 10% HNO_3 / 2.5% HCl / 2% H_2O_2) mixture, respectively. This equates to a 500 fold dilution of the solid and would either require large volumes of diluent (e.g. 0.2 g in 100 mL - 1g in 500 mL) or a second manual 10 fold dilution step to reach 0.2% TDS. Dilution factors entered into the ICP-MS software are used by prep*FAST* for precise and accurate inline dilutions, thereby eliminating the second manual dilution step. 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-MS system calibrates and dilutes samples easily fulfilling 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.

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

$$J = \frac{5\ \mu g/day}{\frac{1\ g}{day}\ x\ 500x}$$

$$J = 0.01\ \mu g/g = 10\ \mu g/L$$

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

Figure 3. USP <232><233> defined calculation of J using Cd as an example. PDE from Table 1 is combined with a hypothetical daily dose (1 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.

OTC Flu Remedy: Closed vessel digested (2% HNO_3, 0.5% HCl)

USP <232> <233> Definition:

Indirect Solution: Used when a material is not directly soluble in aqueous or organic solvents. Digest the sample using a closed-vessel digestion procedure, similar to the procedure provided below. The sample preparation scheme should yield sufficient sample to allow quantification of each element at the limit specified in the corresponding monograph or chapter.

Naproxen: Microwave digested (10% HNO_3, 2.5% HCl, 2% H_2O_2)

USP <232> <233> Definition:

Closed Vessel Digestion: This sample-preparation procedure is designed for samples that must be digested in a *Concentrated Acid* using a closed-vessel digestion apparatus. Closed-vessel digestion minimizes the loss of volatile impurities. The choice of a *Concentrated Acid* depends on the sample matrix. The use of any of the *Concentrated Acids* may be appropriate, but each introduces inherent safety risks. Therefore, appropriate safety precautions should be used at all times. [NOTE—Weights and volumes provided may be ad-

USP <233> Definition:

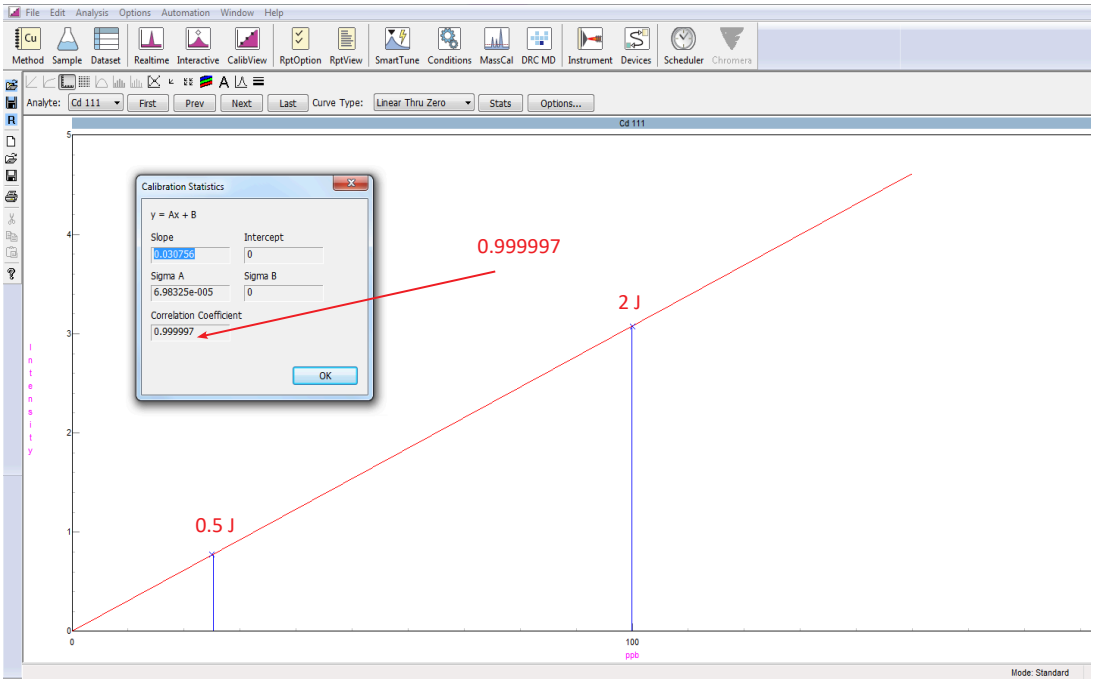
Standardization solution 1: *2J of the Target Element(s)* in a *Matched Matrix*

Standardization solution 2: *0.5J of the Target Element(s)*

		J Values in final solution 0.2% TDS (µg/L)					
		1g/day daily dose		5g/day daily dose		20g/day daily dose	
Isotope	PDE (µg/day)	0.5J	2J	0.5J	2J	0.5J	2J
Cd 111	5	5	20	1	4[5]	0.25	20[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	0.15	0.6
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	400	600	2400	600	2400
Ni 60	200	200	800	40	160	40	160
V 51	100	100	400	20	80	20	20
Cu 63	3000	3000	12000	600	2400	600	2400

Table 2. Calculated 0.5 and 2J values for a range of daily doses using formula in Figure 3.

"J" Calibrations - 1g Daily Dose



"J" Calibrations - 20g Daily Dose

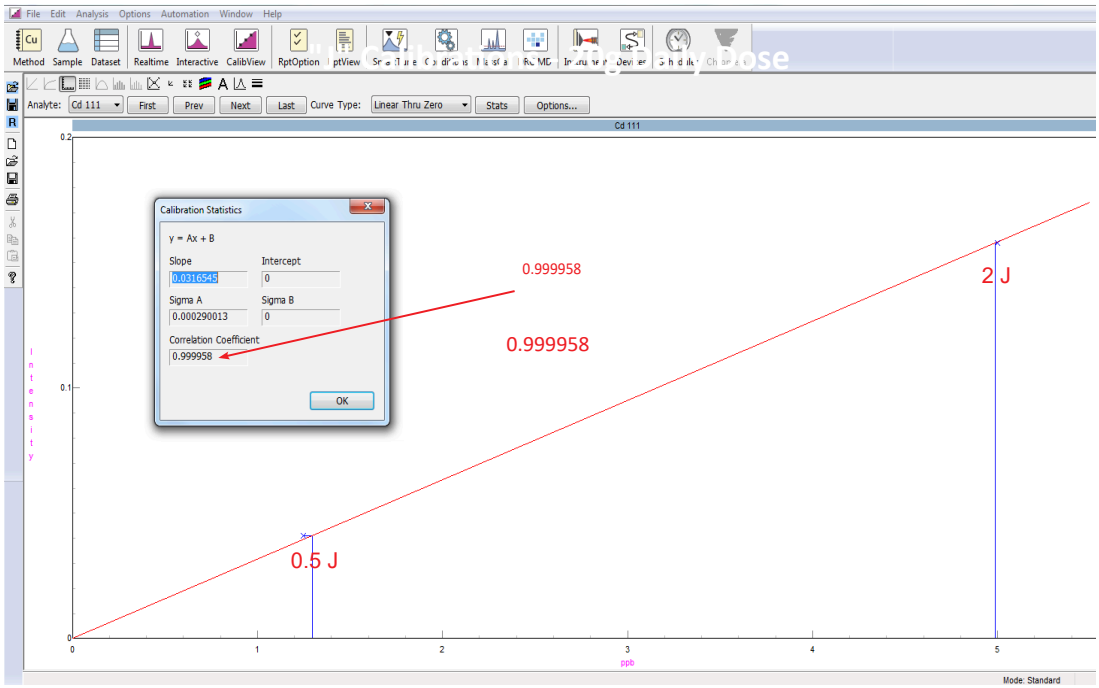


Figure 4. Fully automated inline dilutions of a single stock standard are used to generate linear calibration curves. The formula from figure 3 is used to calculate J values for drugs with a wide range of daily doses (1 and 20 g/day are given as examples).

"J" Calibrations Coefficients

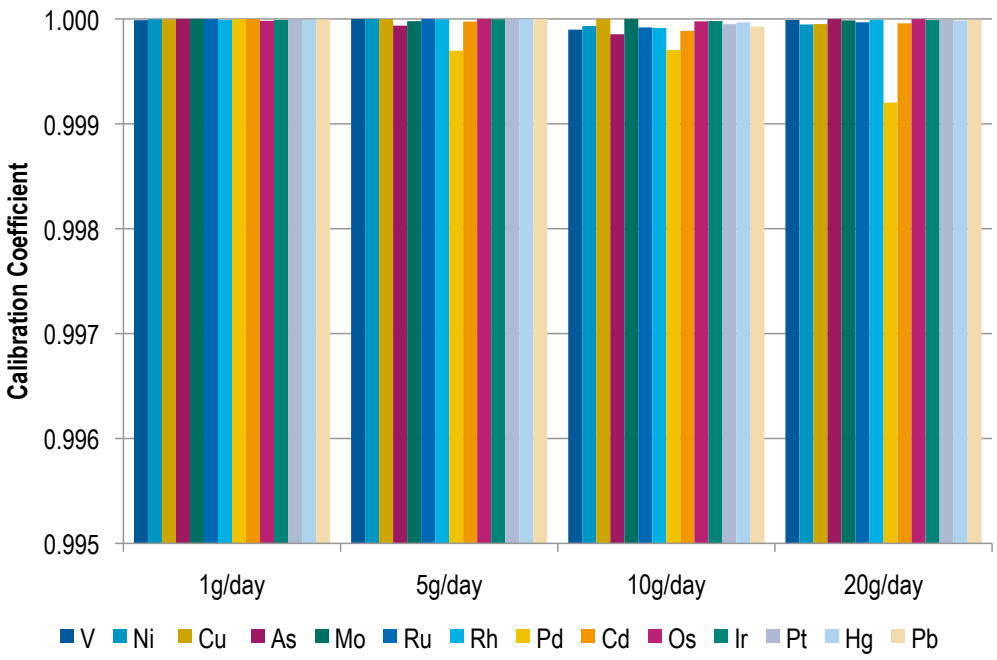


Figure 5. Fully automated inline dilutions from a single stock standard generates linear (>0.9999) calibration curves over a wide range of J values for all USP elements.

Repeatability

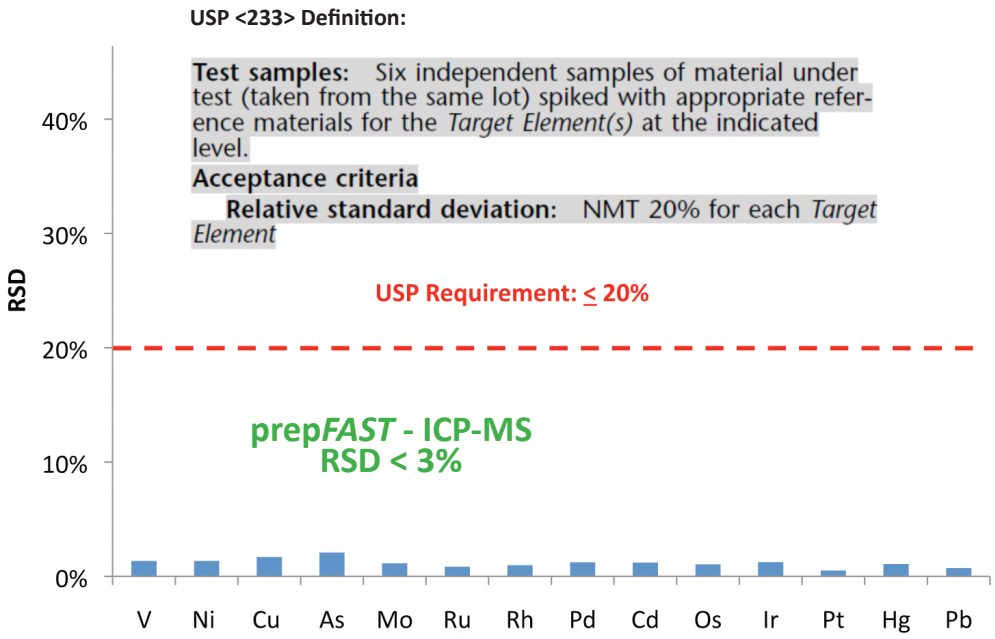


Figure 6. Repeatability for all analytes of interest of < ± 3% at 1J spike in over the counter flu remedy liquid is significantly below the USP accepted criteria of < ± 20% RSD.

Ruggedness

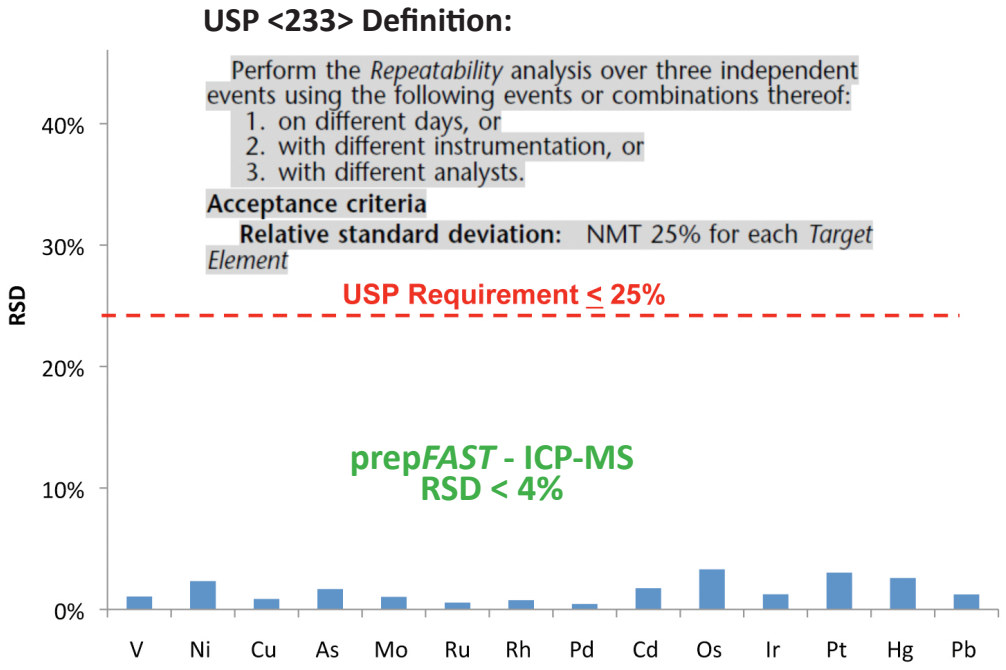


Figure 7. The ruggedness of the method demonstrated on 3 separate days yields accuracy (recoveries) of < ± 10% and reproducibility of < ± 4%. The USP acceptance criteria is defined as < ± 25% RSD for each target analyte.

Isotope	PDE (µg/day)	Naproxen µg/day	OTC Flu Remedy (Powder) µg/day
V 51	100	0.102	1.08
Ni 60	200	0.141	-
Cu 63	3000	0.011	-
As 75	15	-	0.12
Mo 98	3000	-	-
Ru 102	100	0.006	0.04
Rh 103	100	-	-
Pd 106	100	-	-
Cd 111	5	-	-
Os 192	100	-	-
Ir 193	100	0.031	-
Pt 195	100	-	-
Hg 202	30	-	-
Pb 208	5	0.016	0.06

Table 3. Results for OTC flu remedy and naproxen are significantly lower than USP 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*

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