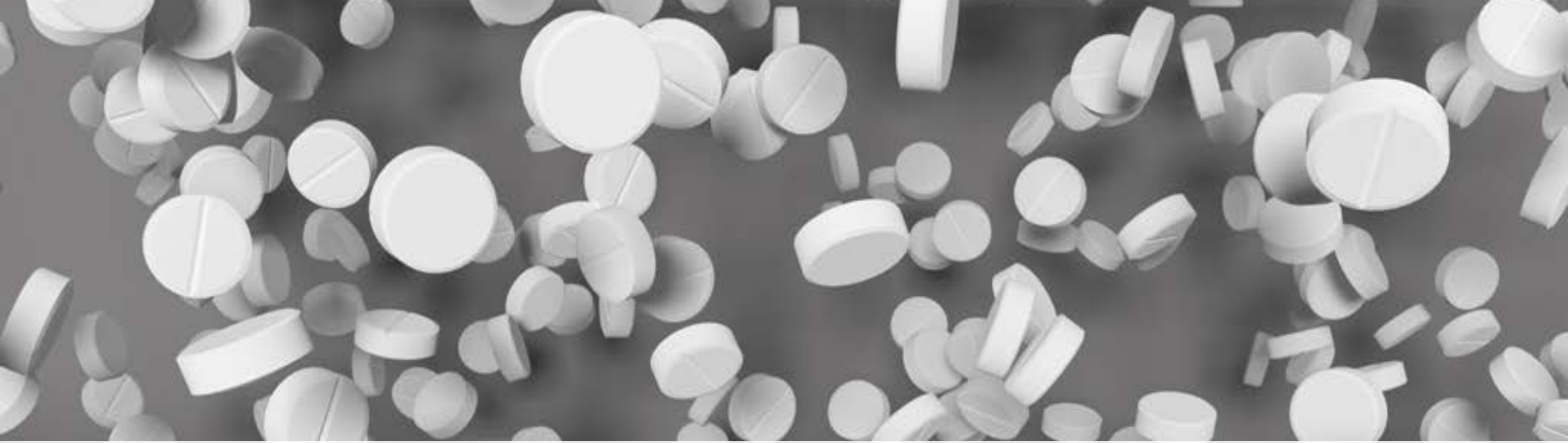

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USP <232>/<233>: Be Prepared for the Changes to Come

Accelerating Innovation Seminar Series - 2016

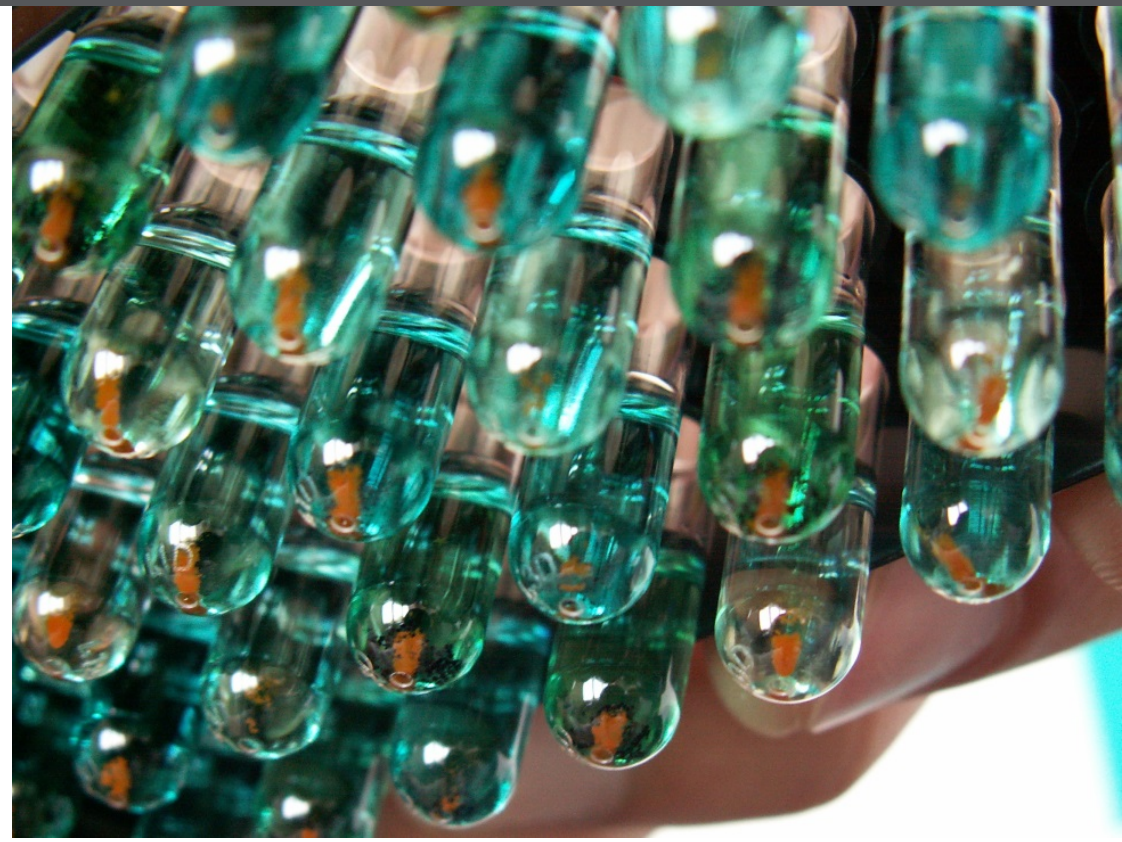
Elemental Impurities in Pharmaceutical Products

- Why Do We Test for Elemental Impurities?
  - Shelf Life Concerns
    - Shortened shelf life
    - Tainted flavor
  - Toxicity Concerns
    - Monitor for known toxic elements
  - Quality Assurance and Control
    - Ensure proper product labeling
    - Flag contaminated products before they are packaged and consumed

So, how do we do this testing?

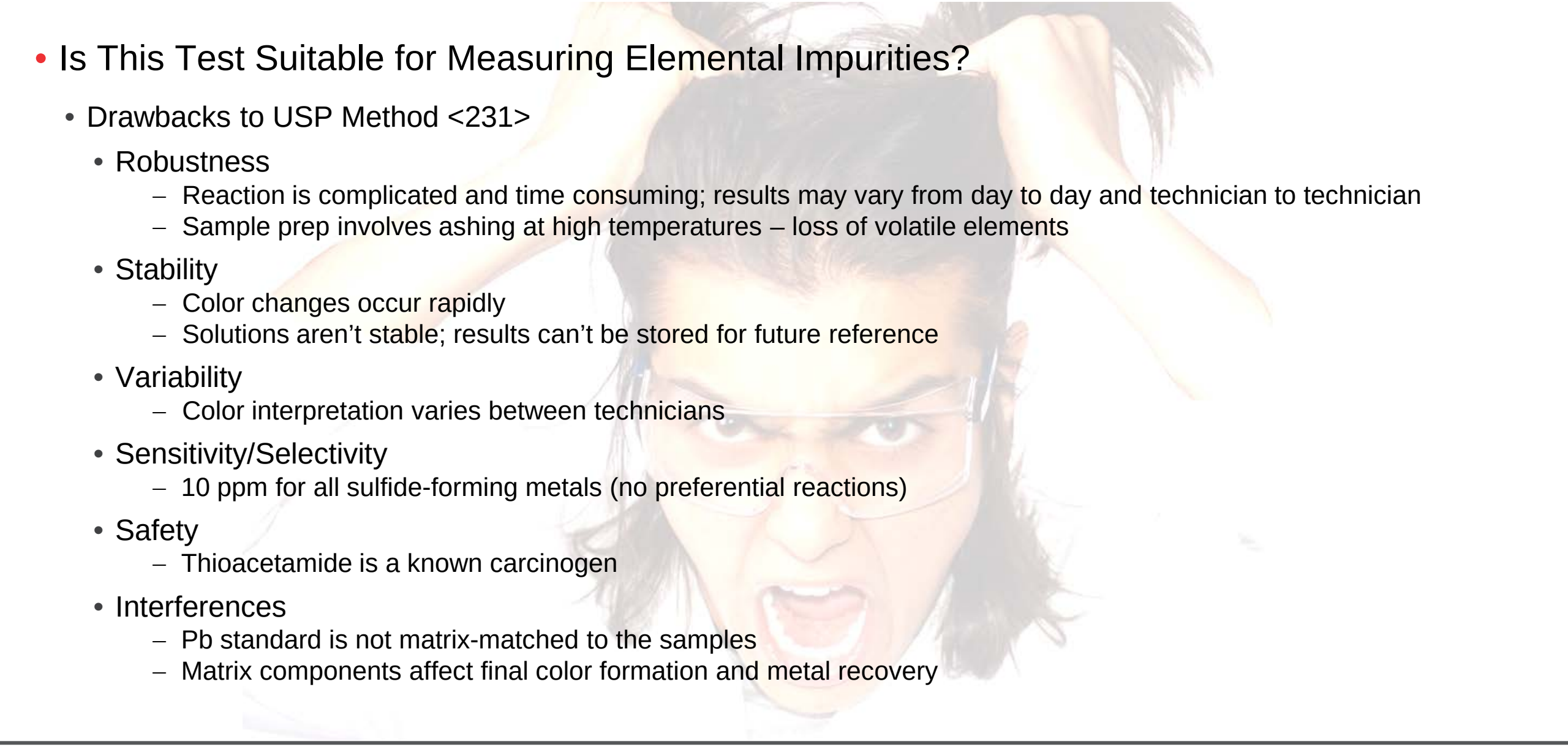
Overview of Current USP Guidelines

- How Do We Test for Elemental Impurities?
  - USP General Method for Heavy Metals <231>
    - Colorimetric reaction for heavy metals (Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu, Mo)
    - Reaction with thioacetamide at low pH
    - Reaction produces a colored solution and an insoluble metal sulfide
    - Colored solution visually compared to a standard solution containing 10 ppm Pb



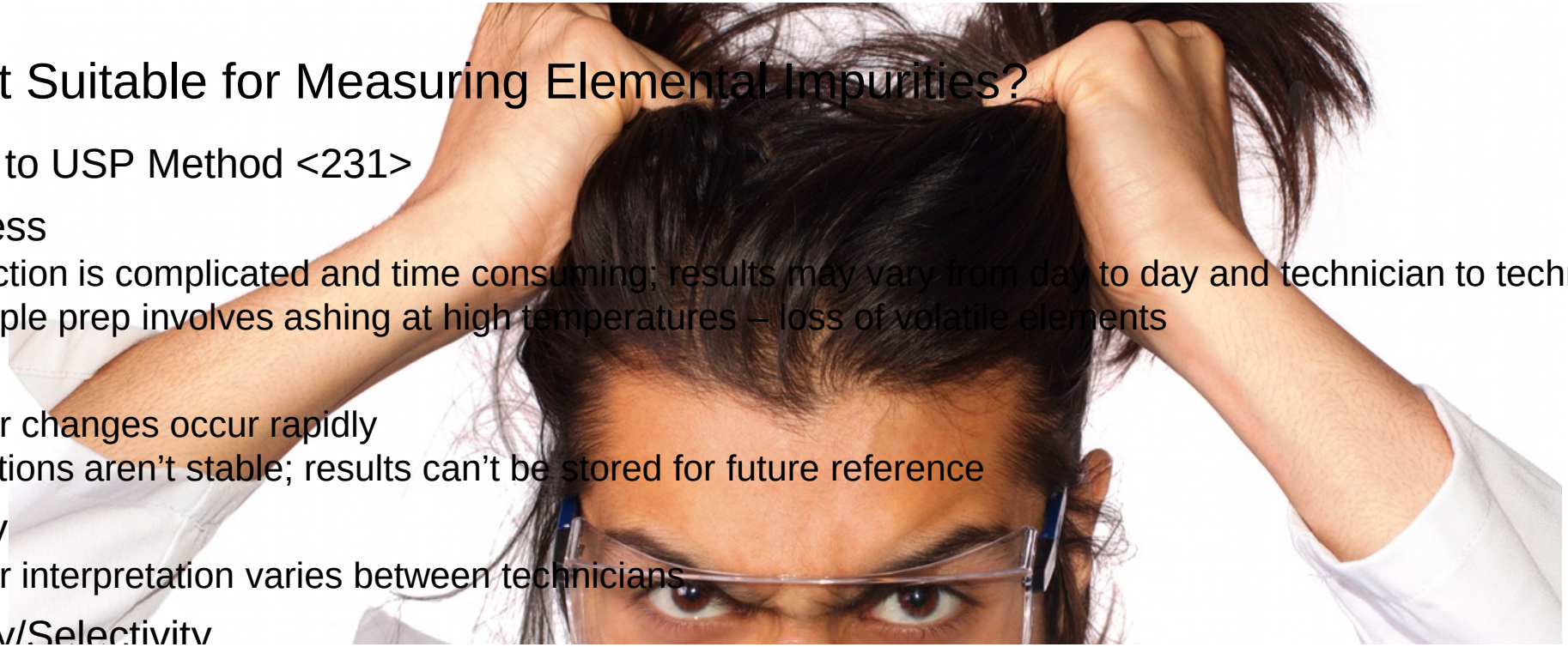
Is this test fit for purpose?

Overview of Current USP Guidelines



- Is This Test Suitable for Measuring Elemental Impurities?
  - Drawbacks to USP Method <231>
    - Robustness
      - Reaction is complicated and time consuming; results may vary from day to day and technician to technician
      - Sample prep involves ashing at high temperatures – loss of volatile elements
    - Stability
      - Color changes occur rapidly
      - Solutions aren't stable; results can't be stored for future reference
    - Variability
      - Color interpretation varies between technicians
    - Sensitivity/Selectivity
      - 10 ppm for all sulfide-forming metals (no preferential reactions)
    - Safety
      - Thioacetamide is a known carcinogen
    - Interferences
      - Pb standard is not matrix-matched to the samples
      - Matrix components affect final color formation and metal recovery

Overview of Current USP Guidelines



- Is This Test Suitable for Measuring Elemental Impurities?
  - Drawbacks to USP Method <231>
    - Robustness
      - Reaction is complicated and time consuming; results may vary from day to day and technician to technician
      - Sample prep involves ashing at high temperatures – loss of volatile elements
    - Stability
      - Color changes occur rapidly
      - Solutions aren't stable; results can't be stored for future reference
    - Variability
      - Color interpretation varies between technicians
    - Sensitivity/Selectivity

How do we test for metal impurities?

Overview of Upcoming USP Guidelines

- USP Chapters to Replace Chapter <231>
  - <232> Elemental Impurities – Limits
  - <233> Elemental Impurities – Procedure
  - <2232> Elemental Contaminants in Dietary Supplements
- Chapter <232>
  - Limits for 15 elements
  - “Big Four” – As, Cd, Hg, Pb (mandatory)
  - Remaining 11 elements (quantify if they might be present)
- Chapter <233>
  - Procedure 1 – ICP-OES
  - Procedure 2 – ICP-MS
  - Alternative procedure acceptance criteria
- Chapter <2232>
  - Information and guidance purposes
  - Limits for As, Cd, Hg, Pb
  - Impurity testing according to Chapter <233>

Status of Chapters <232> and <233>

- USP has...
  - Deferred introduction of both chapters in May 2013
  - Both chapters have undergone revision to be aligned with ICH Q3D
  - Both chapters became official in August 2015, and implemented (for new pharmaceutical products) in December 2015
  - Both chapters will be implemented for all existing pharmaceutical products on **January 1st, 2018** in alignment with ICH Q3D
- ICH Q3D...
  - Step 4 ICH guideline issued on December 16th, 2014
  - Final implementation (Step 5) set for January 1st 2018
- Other regulatory bodies like the European Medicines Agency (EMA)...
  - Delayed implementation dates for compliance for e.g. marketed products

USP <232> Elemental Impurities - Limits

Elements	Oral daily dose PDE (µg/day)	Parenteral daily dose PDE (µg/day)	Inhalation daily dose PDE (µg/day)	LVP Component Limit (µg/g)
Cadmium	5	2	2	0.2
Lead	5	5	5	0.5
Inorganic arsenic	15	15	2	1.5
Inorganic mercury	30	3	1	0.3
Iridium	100	10	1	1.0
Osmium	100	10	1	1.0
Palladium	100	10	1	1.0
Platinum	100	10	1	1.0
Rhodium	100	10	1	1.0
Ruthenium	100	10	1	1.0
Chromium	11000	1100	3	110
Molybdenum	3000	1500	10	150
Nickel	200	20	5	2.0
Vanadium	100	10	1	1.0
Copper	3000	300	30	30

PDE values based on an adult weighing 50 kg (110 lb)
*Not considered a safety concern

USP <233> Elemental Impurities – Procedure

Calibration Requirements

- Definition of J:
  - Concentration (w/w) of the Target (PDE) Limit, appropriately diluted to the working range of the instrument

- Calculate J Values for All Analytes of Interest

$$J = \frac{\text{PDE}}{\text{(Max. Daily Dose) X (Dil. Factor)}}$$

Assume the following:
Administration: Oral
Dose: 10g/day

	As	Cd	Hg	Pb
Target value [µg/day]	15	5	15	5
Target limit [µg/g]	1.5	0.5	1.5	0.5
Dilution factor for ICP-MS	1000	1000	1000	1000
J [ng/g]	1.5	0.5	1.5	0.5
0.5 J [ng/g]	0.75	0.25	0.75	0.25
1.5 J [ng/g]	2.25	0.75	2.25	0.75

- Calibrate the Instrument
  - Calibrate for each element at concentrations equal to 0.5*J* and 1.5*J*

USP <233> Elemental Impurities – Procedure

Validation Requirements – Detectability

- Preparation:
  - Prepare each sample in triplicate. Leave one preparation unspiked. Spike the remaining two preparations with the elements of interest at concentrations equal to *0.5J* and *1.5J*
- Analysis:
  - Analyze the unspiked solution against the spiked solutions to calculate a recovery for each element of interest
  - Analyze each solution with 3 replicates to calculate an average concentration for each element in each prepared solution
- Acceptance:
  - The concentrations in the *1.5J* solution must be within +/- 15% of the concentrations in the unspiked solution. The concentrations in the *0.5J* solution must be less than the concentrations in the unspiked solution.

USP <233> Elemental Impurities – Procedure

Validation Requirements – Accuracy

- Preparation:
  - **Standard Solutions** – prepare standards (not unknown samples) spiked with the elements of interest at concentrations equal to 0.5*J*, 1*J* and 1.5*J*, where *J* is the indicated limit. Prepare each solution in triplicate
  - **Test Solutions** – spike unknown samples such that they are spiked with the elements of interest at concentrations equal to 0.5*J*, 1*J* and 1.5*J*, where *J* is the indicated limit. Prepare the samples according to the established protocol (digestion, dilution, etc). Prepare each solution in triplicate
- Analysis:
  - Analyze each solution and report the concentration for each element as a spike recovery against the known (spiked) concentration
- Acceptance:
  - Results for the test samples described above must be within 70-150% of the spiked levels

USP <233> Elemental Impurities – Procedure

Validation Requirements – Precision

- Preparation:
  - Prepare six replicate preparations of the material under test, spiked with the elements of interest
- Short-term precision
  - Measure all six samples back-to-back (no recalibration or drift correction in between samples)
  - The relative standard deviation of the samples must be lower than 20%
- Intermediate precision
  - Repeat the short-term precision analysis on either a different instrument, a different day or by a different analyst
  - The combined relative standard deviation of these and short-term precision samples must be less than 25%

Sample Preparation

- A typical drug can be described as an API (active pharmaceutical ingredient) + an excipient.
- Common excipients are:
  - Binders e.g. xanthan gum
  - Glidants and lubricants e.g magnesium stearate
  - Disintegrants e.g. crospolividone (E1202)
  - Sweeteners e.g. sucrose
  - Flavourings e.g. fruit
  - Pigments e.g. titanium dioxide
  - Preservatives e.g. methylparaben
  - Coating e.g. shellac or gelatine

- For USP <233> three sample preparation options:

1. **Direct Aqueous**
   - Dissolution in an aqueous matrix
   - Not all excipients soluble e.g. TiO_2
2. **Direct Organic**
   - Dissolution in an organic matrix
   - Not all excipients soluble e.g. Magnesium stearate
   - Example with DMSO and ICP-OES
3. **Indirect Solution**
   - Closed vessel digestion
   - See ICP-MS section for an example
   - **Most universal method**

Pharmaceutical Analysis – the Scope of Thermo Scientific's Elemental Offering

Single-Element Techniques
Lower Sample Throughput

Trace Elemental Products

Multi-Element Techniques
Higher Sample Throughput

AA Flame | AA Furnace | ICP-OES | Q-ICP-MS | HR-ICP-MS

Analytical capabilities (detection limits, sensitivity, analysis speed)

Initial investment

Preferred Instrumentation for USP <233>

ICP-OES
Procedure 1

ICP-MS
Procedure 2

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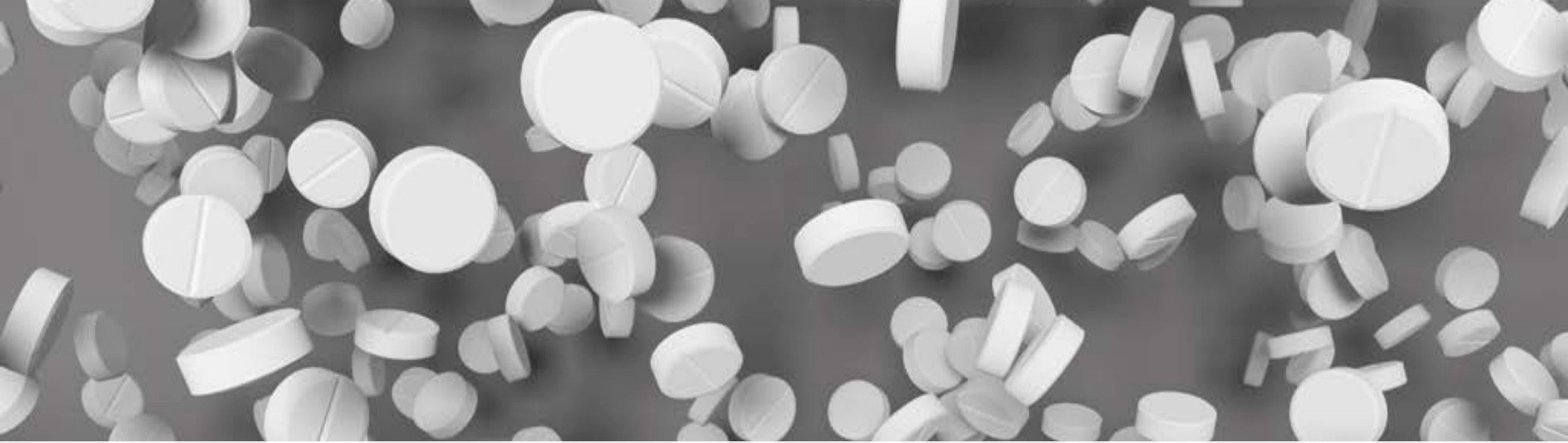

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Application Example: Over-the-Counter Medicine

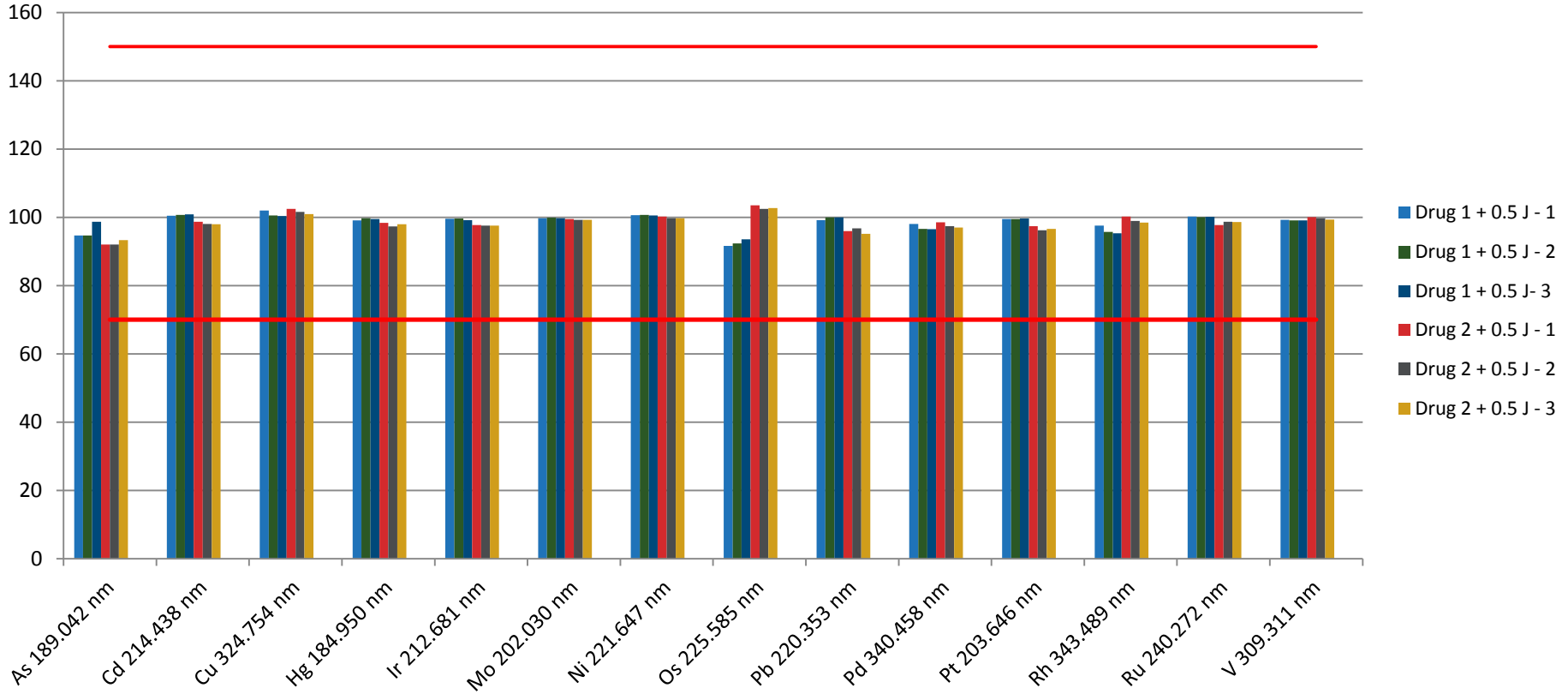
Analysis by ICP-OES

Samples: Anti-inflammatory and Antihistamine

- Preparing samples in DMSO
  - DMSO (dimethyl sulfoxide) is a very strong solvent
  - Less toxic than DMF (dimethylformamide)
  - High-boiling point
- Drawbacks of using DMSO
  - Require silicone pump tubing
  - O-rings on spray-chamber require changing more often
  - Will not dissolve all excipients
    - For example: silica, titanium dioxide

Sample Preparation and Analysis

- 0.5 g of dehydrated sample was dissolved in 25 g of DMSO
  - J defined as the w/w concentration of analyte at Target Limit <u>after</u> dilution
  - Target Limit > MDL; recoveries tested at the 0.5J and 1.5J

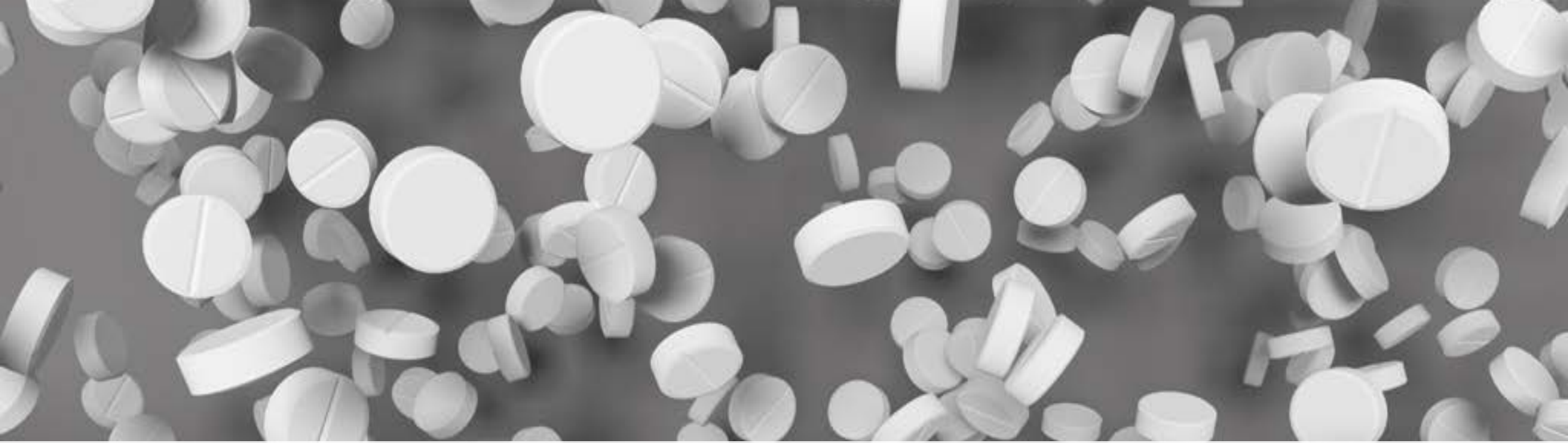


Elements	0.5 J (µg/kg)
Cadmium	25
Lead	25
Inorganic As	75
Inorganic Hg	75
Iridium	500
Osmium	500
Palladium	500
Platinum	500
Rhodium	500
Ruthenium	500
Molybdenum	900
Nickel	3000
Vanadium	600
Copper	6500

Sample Analysis and Spike Recovery Data

- Precision
  - Determined by analyzing six individual samples
  - Samples spiked at 1J
  - USP acceptance criteria < 20%

Elements	Measured Conc Results for Drug 1 (µg/L)						
	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	% RSD
Cd	232.4	232.7	234.7	239.1	235.6	229.9	1.4
Pb	45.9	45.2	44.6	47	46.6	43	3.2
As	12.1	12.7	12.8	14	12.9	11.4	6.9
Hg	130.7	130.8	132,5	136.5	131.8	127.4	2.3
Ir	944.5	941.3	948.2	963.7	950.9	924.5	1.4
Os	954.8	952.7	959	974.9	960.5	940	1.2
Pd	918.8	914.7	914.6	928.6	929.4	890.6	1.5
Pt	924.4	917.6	931.5	949.9	934.6	910.7	1.5
Rh	921.5	907.2	907.5	917.6	915.8	874.9	1.9
Ru	955.5	966.5	953.6	972.8	967.5	932.7	1.5
Mo	956.8	952	959.6	974	959.5	937.7	1.2
Ni	4669	4666	4706	4787	4718	4610	1.3
V	962.5	952.9	945.5	960.1	961.7	928.9	1.4
Cu	9680	9590	9522	9666	9668	9318	1.5



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Application Example: Over-the-Counter Medicine

Analysis by ICP-MS

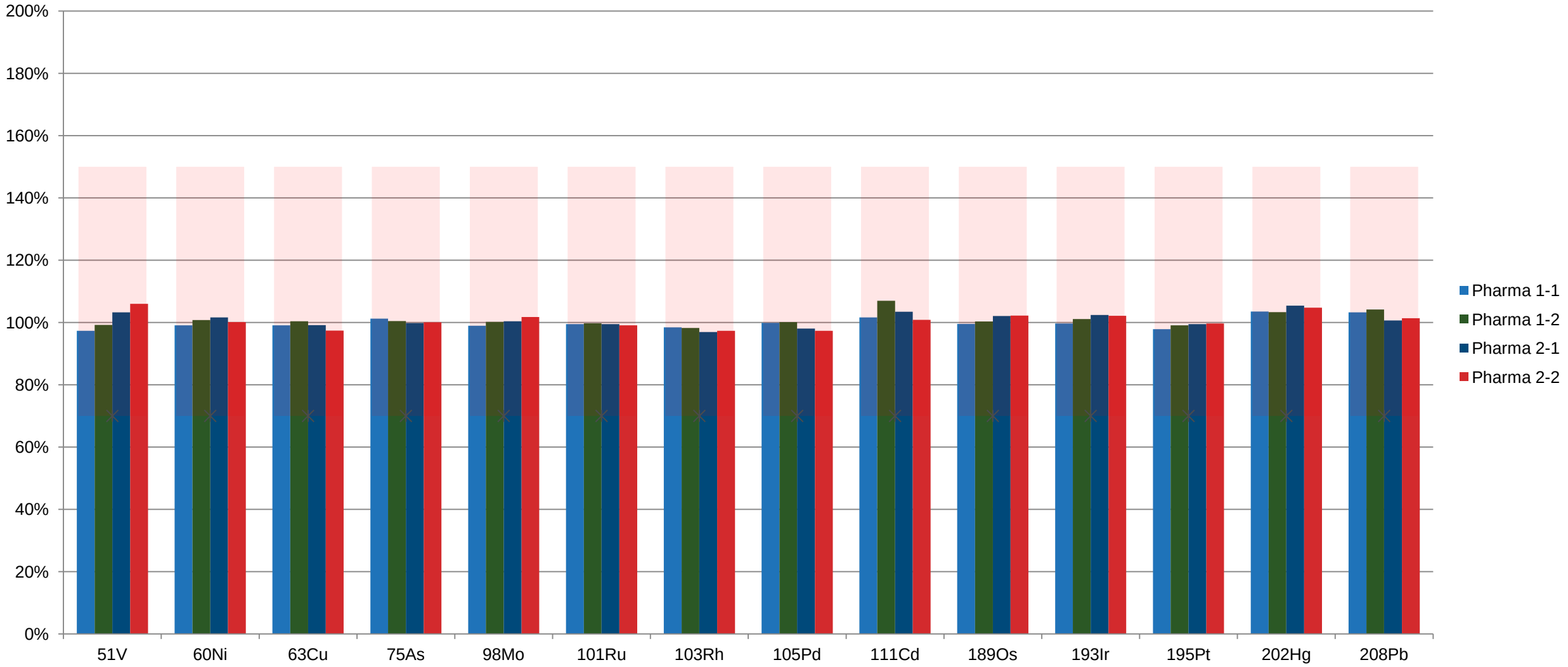
Analysis of Over-the-Counter Medicine

- Four over-the-counter products were locally sourced
- Two samples of each were weighed into 15 ml disposable glass vials
- 3 ml of conc. HNO_3 was added to each vial
- System was closed, and pressurized with N_2 at 40 bar
- Microwave digestion procedure:

Step	Time (min)	Temperature (˚C)	Power (kW)
1	15	200	1.5
2	10	200	1.5

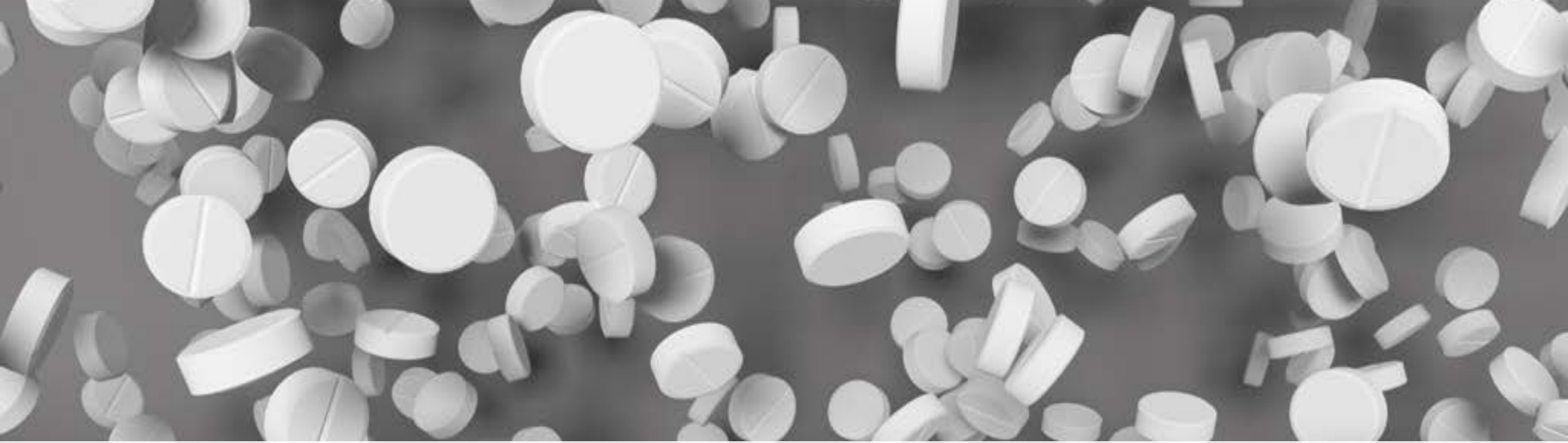
- When the solution was cooled to <60 ˚C, the digest was transferred to a polypropylene vial and made up to 50 ml with 1% HCl
- Samples were further diluted before analysis (with high purity 2% HNO_3) to give total dilution factors of between 100 and 1000

Results: Spike Recoveries at 0.5J



ICP-MS Detection Limits Compared to Daily Dose

Element	Instrument Detection Limit (ng/mL)	Method Detection Limit (µg/g)	Concentration Limit Max. Daily Dose of ≤10 g/day (µg/g)
Cd	0.0001	0.0001	0.5
Pb	0.0005	0.0005	0.5
As	0.0005	0.0005	1.5
Hg	0.003	0.003	1.5
Ir	0.002	0.002	10
Os	0.0006	0.0006	10
Pd	0.0008	0.0008	10
Pt	0.0005	0.0005	10
Rh	0.0007	0.0007	10
Ru	0.001	0.001	10
Mo	0.003	0.003	18
Ni	0.003	0.003	60
V	0.006	0.006	12
Cu	0.009	0.009	130



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Simplified Workflow and Reporting

A Simple Workflow to Quality Results

Thermo Scientific™ Qtegra™ Intelligent Scientific Data Solution™ Software

1. **Dashboard**
   "Get Ready"

2. **LabBook**
   "Create LabBook"

3. **LabBook**
   Results and report

Template
Experiment method and QA/QC protocol

Sample Details
Manual
LIMS
Bar / QR Code

LIMS

A Simple Workflow to Quality Results

- Seven pre-loaded report formats available, plus IQ/OQ
  1. Instrument precision
     - Avg, %RSD multiple replicates
  2. Standard stability
     - Precision of standard injections made over several days
  3. Accuracy
     - Avg, %RSD, %Range calculated for 5 spiked standards
  4. Repeatability
     - Avg, %RSD calculated for 6 sample spikes
  5. Intermediate Precision
     - Avg, %RSD (and pooled %RSD) for repeatability on different days/different chemists
  6. Quantitation Limit
     - Avg, %RSD, %Range calculated for 6 low level spiked samples
  7. Linearity
     - Linear correlation calculated for up to 6 calibration standards
- Calculations performed in 21 CFR Part 11 environment

Data Reporting – Example 1

USP Validation Precision Results

7/2/2014 12:18:41 PM

QTEGRA

Summary:

Labbookname	USP method 3.imexp	Computer name	MP14-PC
Acquired by	MP14	Labbook started	5/26/2014 4:34:00 PM

Instrument Information

Instrument iCAP Q Serial Undefined

Recovery results:

Index	Label	51V (KED)	60Ni (KED)	63Cu (KED)	75As (KED)	95Mo (KED)	101Ru (KED)	103Rh (KED)
6	QL-1	99.694 %	100.407 %	99.645 %	101.250 %	98.827 %	101.090 %	100.357 %
7	QL-2	100.427 %	102.909 %	102.164 %	101.526 %	101.349 %	104.287 %	103.111 %
8	QL-3	101.375 %	103.373 %	103.428 %	102.341 %	101.552 %	103.719 %	102.586 %
9	QL-4	99.907 %	101.901 %	101.484 %	100.474 %	101.157 %	102.563 %	101.723 %
10	QL-5	97.024 %	99.432 %	98.962 %	98.413 %	98.993 %	100.036 %	99.607 %
11	QL-6	102.300 %	104.298 %	104.575 %	103.628 %	104.133 %	104.982 %	104.088 %
	Average	100.1211 %	102.0534 %	101.7097 %	101.2722 %	101.0019 %	102.7795 %	101.9123 %
	RSD	1.7997 %	1.8131 %	2.1196 %	1.7423 %	1.9311 %	1.8682 %	1.6648 %

Index	Label	105Pd (KED)	111Cd (KED)	189Os (KED)	193Ir (KED)	195Pt (KED)	202Hg (KED)	208Pb (KED)
6	QL-1	101.843 %	101.189 %	100.801 %	102.608 %	102.424 %	103.669 %	103.967 %
7	QL-2	103.690 %	103.302 %	100.775 %	103.353 %	102.547 %	103.658 %	104.247 %
8	QL-3	104.340 %	102.683 %	101.614 %	103.150 %	102.839 %	103.922 %	104.056 %
9	QL-4	104.025 %	101.675 %	102.225 %	103.508 %	103.434 %	105.653 %	104.592 %
10	QL-5	100.373 %	99.471 %	99.138 %	100.760 %	100.596 %	102.439 %	100.711 %
11	QL-6	105.611 %	104.318 %	102.849 %	104.454 %	104.234 %	105.507 %	105.081 %
	Average	103.3138 %	102.1063 %	101.2338 %	102.9723 %	102.6789 %	104.1414 %	103.7756 %
	RSD	1.8256 %	1.6751 %	1.2899 %	1.2042 %	1.1877 %	1.1803 %	1.4990 %

LabBook information:
Created by, Acquired by, Last changed by,...

Customized table:
Direct overview on precision test for Sample XYZ, Average Recovery and RSD are automatically calculated

Data Reporting – Example 2

USP Validation Intermediate Precision Results

7/2/2014 12:40:55 PM

QTEGRA

Summary:

Labbookname	USP method 3 - second user.imexp	Computer name	MP14-PC
Acquired by	MP14 - second user	Labbook started	5/26/2014 5:20:22 PM
Labbookname	USP method 3.imexp	Computer name	MP14-PC
Acquired by	MP14	Labbook started	5/26/2014 4:34:00 PM

Instrument Information

Instrument	iCAP Q	Serial	Undefined
Instrument	iCAP Q	Serial	Undefined

Recovery results:

User name	Index	Label	51V (KED)	60Ni (KED)	63Cu (KED)	75As (KED)	95Mo (KED)
MP14-PC\MP14 - second user	6	QL-1	101.811 %	103.496 %	102.844 %	102.576 %	102.713 %
MP14-PC\MP14 - second user	7	QL-2	99.219 %	101.195 %	100.859 %	100.530 %	101.905 %
MP14-PC\MP14 - second user	8	QL-3	100.279 %	102.939 %	101.654 %	101.867 %	103.282 %
MP14-PC\MP14 - second user	9	QL-4	100.180 %	103.087 %	102.325 %	101.860 %	103.092 %
MP14-PC\MP14 - second user	10	QL-5	100.677 %	103.694 %	102.819 %	101.864 %	104.355 %
MP14-PC\MP14 - second user	11	QL-6	98.861 %	102.034 %	101.584 %	100.142 %	102.505 %
		Average	100.1712 %	102.7407 %	102.0141 %	101.4732 %	102.9753 %
		RSD	1.0544 %	0.9262 %	0.7698 %	0.9177 %	0.8064 %
MP14-PC\MP14	6	QL-1	99.694 %	100.407 %	99.645 %	101.250 %	98.827 %
MP14-PC\MP14	7	QL-2	100.427 %	102.909 %	102.164 %	101.526 %	101.349 %
MP14-PC\MP14	8	QL-3	101.375 %	103.373 %	103.428 %	102.341 %	101.552 %
MP14-PC\MP14	9	QL-4	99.907 %	101.901 %	101.484 %	100.474 %	101.157 %
MP14-PC\MP14	10	QL-5	97.024 %	99.432 %	98.962 %	98.413 %	98.993 %
MP14-PC\MP14	11	QL-6	102.300 %	104.298 %	104.575 %	103.628 %	104.133 %
		Average	100.1211 %	102.0534 %	101.7097 %	101.2722 %	101.0019 %
		RSD	1.7997 %	1.8131 %	2.1196 %	1.7423 %	1.9311 %
		Pooled Recovery	100.1461	102.3970	101.8619	101.3727	101.9886
		Pooled RSD	1.4064 %	1.4141 %	1.5266 %	1.3309 %	1.7277 %

User name	Index	Label	101Ru (KED)	103Rh (KED)	105Pd (KED)	111Cd (KED)	189Os (KED)
MP14-PC\MP14 - second user	6	QL-1	104.332 %	103.144 %	105.311 %	103.472 %	98.802 %
MP14-PC\MP14 - second user	7	QL-2	103.276 %	102.279 %	104.240 %	101.515 %	97.453 %
MP14-PC\MP14 - second user	8	QL-3	103.090 %	102.823 %	103.941 %	102.357 %	98.593 %
MP14-PC\MP14 - second user	9	QL-4	103.573 %	102.672 %	104.237 %	102.247 %	97.344 %
MP14-PC\MP14 - second user	10	QL-5	104.058 %	103.206 %	105.080 %	102.812 %	99.644 %
MP14-PC\MP14 - second user	11	QL-6	102.545 %	102.603 %	103.626 %	101.779 %	98.853 %
		Average	103.4787 %	102.7878 %	104.4058 %	102.3637 %	98.4484 %
		RSD	0.6317 %	0.3398 %	0.6287 %	0.6914 %	0.9029 %
MP14-PC\MP14	6	QL-1	101.090 %	100.357 %	101.843 %	101.189 %	100.801 %
MP14-PC\MP14	7	QL-2	104.287 %	103.111 %	103.690 %	103.302 %	100.775 %
MP14-PC\MP14	8	QL-3	103.719 %	102.586 %	104.340 %	102.683 %	101.614 %
MP14-PC\MP14	9	QL-4	102.563 %	101.723 %	104.025 %	101.675 %	102.225 %
MP14-PC\MP14	10	QL-5	100.036 %	99.607 %	100.373 %	99.471 %	99.138 %
MP14-PC\MP14	11	QL-6	104.982 %	104.088 %	105.611 %	104.318 %	102.849 %
		Average	102.7795 %	101.9123 %	103.3138 %	102.1063 %	101.2338 %
		RSD	1.8682 %	1.6648 %	1.8256 %	1.6751 %	1.2899 %
		Pooled Recovery	103.1291	102.3501	103.8598	102.2350	99.8411
		Pooled RSD	1.3725 %	1.2254 %	1.4078 %	1.2278 %	1.8057 %

Report Intermediate Precision Test:

- ✓Results obtained by two operators are summarized in one table
- ✓Average value and RSD are calculated
- ✓Every individual LabBook as datasource can be indentified and history can be displayed

Typical Instrument Implementation Process

Blog Site: analyteguru.com

- Educational

Trace Elemental Analysis: Which Instrument is Best for You?

September 14, 2015 by Dr. Maura Rury

Read

These are a Few of My Favorite (Chemistry) Things

December 8, 2014 by Bill Berry

Read

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November 11, 2015 by Paula De Oliveira

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June 15, 2016 by Paul Dewsbury

Read

Pittcon 2016 – Day 1 – Accelerating Innovation

March 7, 2016 by Charlie D. Chromeleon

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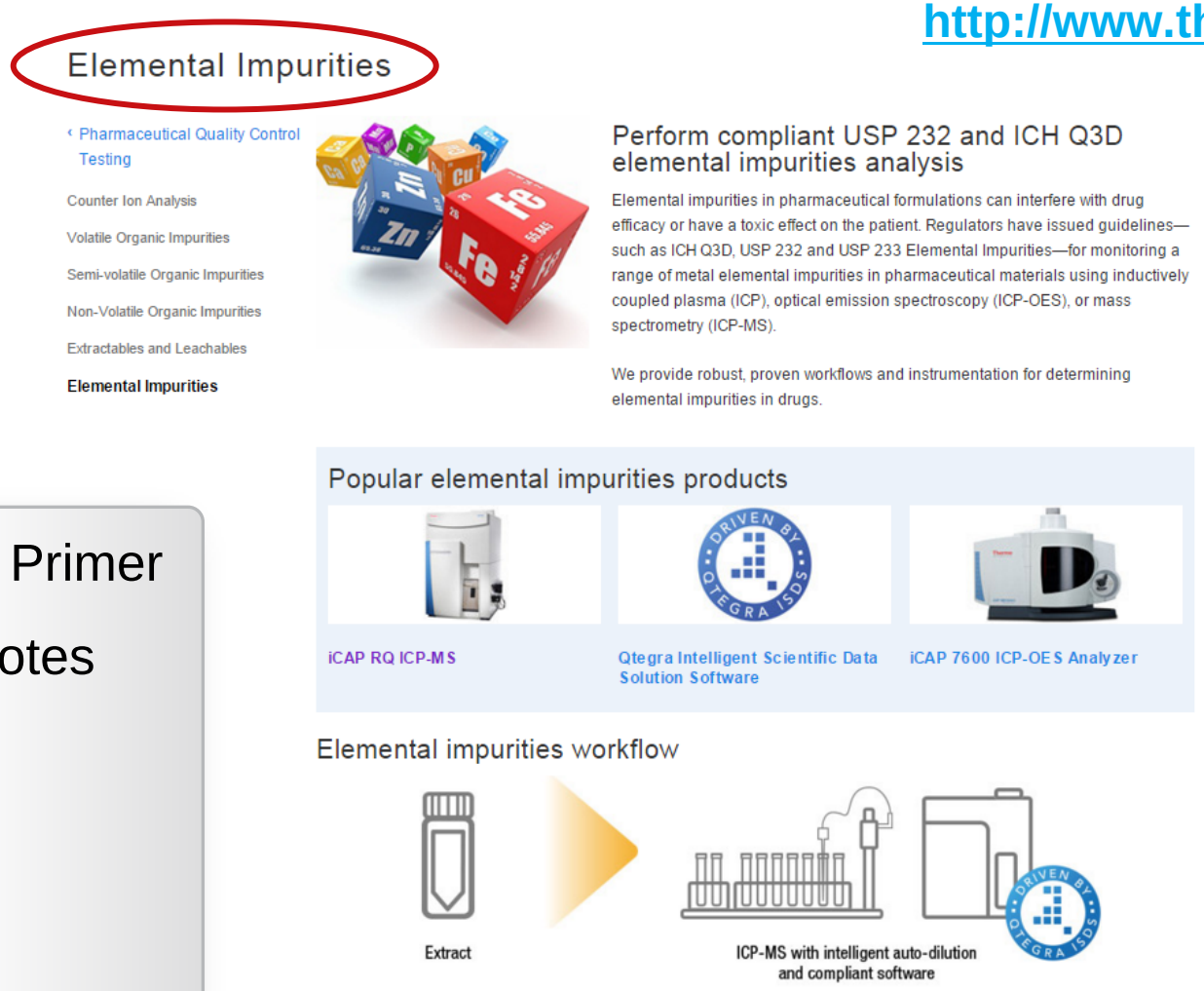
Pharma Resources

Check out our pharma-specific resources: http://www.thermofisher.com/usp232
http://www.thermofisher.com/ichq3d

- ebook – USP Primer
- Application Notes
- Podcasts
- Videos
- Webinars



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USP Resources

U.S. Pharmacopeial Convention

Additional Information:

- http://www.usp.org
- qualitymatters.usp.org

Quality Matters | USP U.S. Pharmacopeial Convention

Key Issue: Elemental Impurities

In the News: **Read about the impact of Elemental Impurities on drug quality at our *Quality Matters* blog.**

Original Posting: 20–Jul–2010; Last Update: 08–Feb–2016

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- **Media:** Theresa Laranang-Mutlu (trl@usp.org or 301-816-8167)

General Chapters and Related Information

- Publishing in Pharmacopeial Forum 42(2) [Mar.–Apr. 2016]
  - <232> Elemental Impurities—Limits
- Published in USP 39–NF 34, official May 1, 2016:
  - <232> Elemental Impurities—Limits -- *Incorporates correction to units in Table 2 in the Drug Substance and Excipients section, which was published as an Erratum on May 29, 2015. Otherwise unchanged from USP 38–NF 33, Second Supplement Revision* (posted 10–Dec–2015)
- Published in USP 38–NF 33, Second Supplement, official December 1, 2015:
  - <232> Elemental Impurities—Limits
  - <233> Elemental Impurities—Procedures
- Revision Bulletin, official February 1, 2013:
  - <232> Elemental Impurities—Limits
  - <233> Elemental Impurities—Procedures
- General Notices
- Standards-setting Record
- Revision Plan (updated March 27, 2015)

Frequently Asked Questions

- FAQs on the Implementation of USP General Chapters <232> Elemental Impurities—Limits <233> Elemental Impurities—Procedures, and <2232> Elemental Contaminants in Dietary Supplements (updated 27–Mar–2015)
- FAQs: Rationale for USP's Proposed Standards for Elemental Impurities (updated 14–Jan–2015)

Updates

June 1, 2015: USP posts Notice of Intent to Revise for multiple monographs and general chapters that were revised in the Second Supplement to USP 38–NF 33 to reinstate the references to General Chapter <231> Heavy Metals and specify that General Chapter <231> will remain in effect until January 1, 2018.

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