Current Status of the New USP Chapters on Elemental Impurities in Pharmaceutical Products and Dietary Supplements

Robert Thomas,
Principal Consultant
Scientific Solutions
Gaithersburg, MD

Why is USP Introducing These New Chapters?

- USP undergoes regular re–evaluation and revision of all its standards to update their scientific and public health relevance
- USP scientific experts felt that the elemental impurity standards should be updated to incorporate modern methods and health information.
- The current test methodology for heavy metals in the USP–NF Book of Compendial Methods is Chapter <231>, which was first introduced more than 100 years ago
- Chapter <231> is a heavy metals test based on precipitation of the metal sulfide in a sample, and comparing the color intensity to a lead standard
- Even though this test has been used for over a hundred years, it is well-accepted that it is prone to error and requires a skilled analyst to interpret the color correctly
- The Proposal is to replace Chapter 231 with three new Chapters, Chapter <232>, <233> and Chapter <2232>

Chapter <231>

- For more than 100 years, the standard method for measuring elemental impurities in pharmaceutical products sold in the United States for has been the “Heavy Metals Test”, described in Chapter 231
- This test is based on a sulfide precipitation of the analyte elements with a thioacetamide solution, and assumes that all analytes behave in a similar manner to a lead standard (10 ppm) with which samples are compared
- It was initially intended to detect a larger group of elements like Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu, Mo, and Se, but there was no clear definition of which individual elements the method was expected to detect
- Many limitations including low recoveries, inconsistent results and interpretation of color varied with experience of the analyst

Three New Chapters are <232>, <2232> and <233>

- **Chapter <232> Elemental Impurities - Limits** specifies the list of 15 elemental impurities (Cd, Pb, As, Hg, In, Os, Pd, Pt, Rh, Ru, Cr, Mo, Ni, V, Cu) and their toxicity limits in pharmaceutical products, defined as permitted daily exposure (PDE) levels of the four different drug administration categories - oral, parenteral (intravenous injection), inhalation and large volume parenteral
- **Chapter <2232> Elemental Contaminants in Dietary Supplements** specifies the list of 4 elements (Pb, As, Cd, Hg) and their toxicity limits, defined as permitted daily exposure (PDE) levels. This chapter refers to Chapter <233> for the analytical procedure to determine the elemental contaminants
- **Chapter <233> Elemental Impurities - Procedures** deals with the sample preparation, analytical procedure and QC validation protocols for measuring the elements, using ICP-AES or ICP-MS or any alternative technique that meets the validation requirements

USP Chapter <232> Permitted Daily Exposure (PDE)Levels

Element	Oral Daily Dose PDE (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalation Daily Dose PDE (µg/day)	LVP Component Limit (µg/g)
Cadmium	5.0	2.5	3.4	0.25
Lead	5.0	5.0	5.0	0.5
Arsenic (Inorganic)	15	15	1.9	1.5
Mercury (Inorganic)	15	1.5	1.2	0.15
Iridium	100	10	1.5	1.0
Osmium	100	10	1.5	1.0
Palladium	100	10	1.0	1.0
Platinum	100	10	1.5	1.0
Rhodium	100	10	1.5	1.0
Ruthenium	100	10	1.5	1.0
Chromium	*	*	2.9	*
Molybdenum	180	90	7.6	9.0
Nickel	600	60	6.0	6.0
Vanadium	120	12	1.2	1.2
Copper	1300	130	13	13

PDEs based on an arbitrary adult human body weight of 50 kg (110 lb) (* = Not considered a safety concern)

Chapter <2232> Permitted Daily Exposure (PDE)Levels

- The levels of elemental contaminants should be less than the Permitted Daily Exposure (PDE) levels shown in the table below of, unless a specific monograph provides different limits for a supplement that is consumed in larger quantities than 10 g/day

Elemental Contaminant	USP Chapter <2232> PDE Limits (µg/day)
Arsenic (Inorganic)	15
Cadmium	5
Lead	5
Mercury	15 (total)
Methyl Mercury (CH_3Hg)	2

- PDE levels derived from data supplied by the Food Agriculture Organization of the United Nations (FAO/UN) and World Health Organization (WHO), based on a body weight of 50 kg and other safety factors
- Manufacturers are responsible for compliance with other applicable local requirements (e.g. Proposition 65 in California) differing from these PDE values

General Chapter <233>
Elemental Impurities: Procedures

- This chapter describes the two analytical procedures for the measurement of elemental impurities/contaminants
  - **Procedure 1:** ICP-OES
  - **Procedure 2:** ICP-MS
- Applies to pharmaceutical materials described in Chapter 232 and dietary supplements in Chapter <2232>
- Gives guidelines on sample preparation, calibration procedures, spike recoveries, precision and instrumental drift limits
- The chapter also describes criteria for alternative instrumental procedures such as AA, as long as they meet the validation requirements laid-out in this chapter

Chapter 233 Elemental Impurities –Procedures

Sample Preparation

- Neat: Used for liquid samples
- Direct Aqueous Solution: When a sample is soluble in an aqueous/acid medium
- Direct Organic Solution: When a sample is only soluble in an organic solvent
- Indirect Solution: When a sample is not directly soluble in an aqueous or organic solvent
  - Closed vessel digestion procedures (e.g.. microwave)
  - Suggests the addition of gold to determine mercury

Chapter 233 Elemental Impurities –Procedures

Calibration Procedure

- **Calibration**: Two calibration standards required at 0.5J and 2.0J
- Target Limit/Concentration (J-value) is the concentration of the elements of interest, appropriately diluted to the working range of the instrument
  - E.g.: Limit for Pb = 5 µg/day. Based on a suggested dosage of 10 g of supplement/day, that's equivalent to 0.5 µg/g (ppm) Pb. If 1 g of sample is digested/dissolved and made up to 500 mL, that's a 500-fold dilution, which is 1 µg/L (ppb). **So the J-value for Pb is 1.0 µg/L**, based on this dilution factor
- A Calibration is then made up of 2 standards
  - Standard 1= 2.0J, Standard 2= 0.5 J
  - **For Pb: Std 1 = 2.0 µg/L and Std 2 = 0.5 µg/L**

Chapter 233 Elemental Impurities –Procedures

Validation Protocols

- For elemental impurities limit procedures, validation tests should include:
  - Drift (stability of calibration)
  - Detectability (impact of matrix on target elements)
  - Precision (repeatability)
  - Specificity (impact of target elements on each other)
  - Accuracy (using reference materials)
  - Ruggedness (robustness of method)
  - Limit of Quantification (detection suitability of technique being used)
  - Linear Range (suitability of technique to measure over range values using same calibration)

USP Chapter <233> Selected Validation Protocols

- **Drift**: This USP criterion requires comparing results obtained from standardization solution 1 (2J) before and after the analysis of the sample solutions : Specification: < 20%
- **Repeatability**: This USP criterion requires measuring 6 independently prepared samples of the material under investigation, spiked at the target limits (1J spike) – Specification: <20%
- **Ruggedness**: USP defines ruggedness as analyzing the same sample (1J spike) either: on different days; with a different instrument; or by a different analyst: Specification: <25%

So What Technique is the Most Suitable?

USP J-values Compared to Limits of Quanitation for Axial ICP-OES

Element	Conc Limits for an Oral Drug with a Max Daily Dose of ≤10 g /day (µg/g)	J-Value with a Sample Dilution of 2g/100mL (µg/L)	Axial ICP-OES LOQ (IDL x 10) (µg/L)	Factor Improvement (J-Value/LOQ)
Cadmium	0.5	10	1	10
Lead	0.5	10	13	0.8
Arsenic	1.5	30	20	1.5
Mercury	1.5	30	4	7.5
Iridium	10	200	10	20
Osmium	10	200	52	3.8
Palladium	10	200	21	9.5
Platinum	10	200	12	16.7
Rhodium	10	200	47	4.2
Ruthenium	10	200	10	20
Molybdenum	18	360	7	51.4
Nickel	60	1200	6	200
Vanadium	12	240	4	60
Copper	130	2600	4.0	650

USP J-values Compared to Limits of Quanitation for ICP-MS

Element	Conc Limits for an Oral Drug with a Max Daily Dose of ≤10 g /day (µg/g)	J-Value with a Sample Dilution of 0.2g/100mL (µg/L)	ICP-MS LOQ (IDL x 10) (µg/L)	Factor Improvement (J-Value/LOQ)
Cadmium	0.5	1.0	0.0009	1111
Lead	0.5	1.0	0.0038	263
Arsenic	1.5	3.0	0.021	143
Mercury	1.5	3.0	0.0397	76
Iridium	10	20	0.0026	7692
Osmium	10	20	0.0042	4762
Palladium	10	20	0.0124	1613
Platinum	10	20	0.0013	15385
Rhodium	10	20	0.0008	25000
Ruthenium	10	20	0.002	10000
Molybdenum	18	36	0.0096	3750
Nickel	60	120	0.0113	10588
Vanadium	12	24	0.0286	840
Copper	130	260	0.0237	10970

Approval Timelines for Implementation of New Chapters

- The pharmaceutical/nutraceutical industries were concerned about the ambitious timing of these new chapters
- In addition, international regulatory agencies such as the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use), European Medicines Agency (EMA), and the European Pharmacopoeia (EP) and Japanese Pharmacopoeias (JP) were concerned about the list of elements and permitted daily exposure (PDE) limits defined in Chapter <232>
- For this reason, there have been a number of revisions to both Chapter <232> and <233>, which resulted in implementation timelines being modified a number of times
- However, a recent announcement by the USP Chemical Analysis Expert Committee stated that it is the intention to align Chapter <232> Elemental Impurities—Limits with the ICH Q3D Step 4 directives…. by January, 2018

So What is the Current Status of the New Chapters

- Chapters were published in the First Supplement to USP 36–NF 31 on February 1st, 2013
- Exact details of Chapters won't be known until there is full alignment with ICH Q3D Step 4 directives
- This will likely happen on December 1st, 2015 with the publication of 2nd Supplement to USP 38–NF 33
- The plan is to fully implement these Chapters by January, 1, 2018, when they will become applicable to all drug products and nutraceuticals

ICH Q3D Step 4 Guidelines - 16 Dec, 2014

Element	Class	Oral PDE µg/day	Parenteral PDE µg/day	Inhalation PDE µg/day
Cd	1	5.0	2.0	2.0
Pb	1	5.0	5.0	5.0
As	1	15	15	2.0
Hg	1	30	3.0	1.0
Co	2A	50	5.0	3.0
V	2A	100	10	1.0
Ni	2A	200	20	5.0
Tl	2B	8.0	8.0	8.0
Au	2B	100	100	1.0
Pd	2B	100	10	1.0
Ir	2B	100	10	1.0
Os	2B	100	10	1.0
Rh	2B	100	10	1.0
Ru	2B	100	10	1.0
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1.0
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3.0

USP 232
Element
Cadmium
Lead
Arsenic (Inorganic)
Mercury (Inorganic)
Iridium
Osmium
Palladium
Platinum
Rhodium
Ruthenium
Molybdenum
Nickel
Vanadium
Copper
Chromium

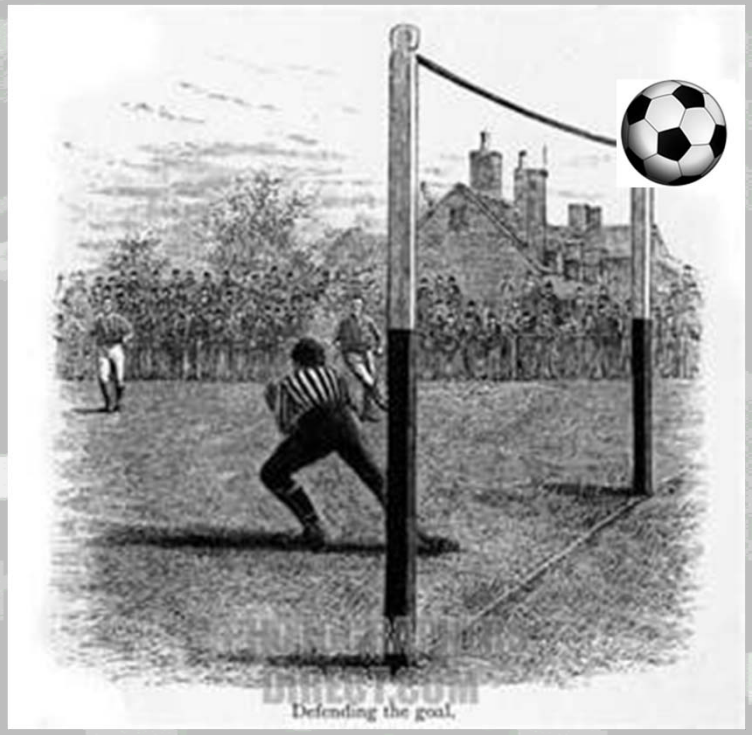
Assuming USP Don't Move the Goalposts Again, the New Chapters Should be Fully Implemented by January 1, 2018

Questions About USP Chapters 232/233

Dr. Zaidi Kahkashan

USP Scientific Liaison for *Elemental Impurities in Pharmaceutical Materials*

Email: kxz@usp.org



Questions About USP Chapter 2232

Dr. Christopher Okunji

USP Scientific Liaison for *Elemental Contaminants in Dietary Supplements*

Email: coo@usp.org

Robert Thomas: robert.james.thomas@scientificsolutions1.com
