

Heavy Metals Update



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- Plasma Spectrochemistry
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Background

- Do we need <231>?
- Does GMP Obviate <231>?
 - Ingredient Contamination “sneak by”
 - Sb in H₃P₀₄
 - Pb in excipient
 - Paint chip in drum, leaching from pipes. Etc.
- Environmental (Natural Product)
- Drug Substance synthetic process (e.g., catalysts)

Catalyst Use is Widespread

Name	Metal/Catalyst
Cipamfyline	Sn
Efegatran	Pd
Forasartan	Pd
Fosphenytoin	Pd, Ag (earlier step)
Llepcimide	Te
Mivobulin	Pd
Sulopenem	Pd
Valsartan	Sn, Pd

<231> - Problematic for Many Years

- PF 28 (6) p-2029: Microwave Muffle Furnace Technology for use in the test for residue on Ignition by: Colin Donaghy & Mathew Smart (GSK)
- PF 29 (4) p- 1328: An Atomic Spectroscopic Method as an alternative to both heavy metals <231> and USP residue on Ignition <281> by: Tiebang Wang (Merck)
- PF 30 (5) p-1876: Change to USP general chapter on heavy Metals <231> by: PA6
- PF 30 (6) p-2271: ICP-OES as an alternative to heavy metals test by: Martha Shenkenbergen & Nancy Lewen

Issues With Both USP and EP Methods

	USP Method II (ignited at 550° C)	EP V.3.2.8 Method C (ignited at 750° C)
Tin (Sn)	66%	0%
Arsenic (As)	63%	70%
Mercury (Hg)	0%	0%
Antimony (Sb)	57%	61%
Cadmium (Cd)	60%	57%
Lead (Pb)	56%	46%
Bismuth (Bi)	62%	56%
Copper (Cu)	69%	54%

Plasma Spectrochemistry- An Alternative Method to Heavy Metal

ICP/ICP-MS

- Element Specific
- Quantitative
- Cost Issue
- Dilute & Shoot (70-80% of API)

Plasma Spectrochemistry

- The USP published a new chapter on Inductively- Coupled Plasma in Pharmacopeial Forum, Volume 28(6) {Nov. – Dec. 2002}
- USP/NF 2005 1st Supplement
Official: April 1, 2005

Metals Advisory Panels' Activities

■ Heavy Metals <231> Advisory Panel

- 2007-2008
- Panelists recruited from industry and GC-EC
- Objective to investigate instrument-based methods to replace Heavy Metals <231>
- Resulted in Stimuli Article published in Pharmacopeial Forum 34 (5) [Sept-Oct., 2008] proposed new instrument-based chapter to replace <231>

■ Metal Impurities Advisory Panel

- 2008-Present
- Panelists recruited from agencies, industry, USP staff, includes 3 professional toxicologists
- Objective to develop USP standards to replace Heavy Metals <231>

Topics Addressed by Advisory Panel

- Eliminate “heavy metals” as a test and adopt an “inorganic impurities” method?
- What metals do we need to monitor?
- What concentration limits do we need to meet?
- Do we need a wet-bench approach?
- Can we use an instrumental approach?
- Do we provide results for individual elements?
- How do we reconcile results from any new procedure with results obtained previously using <231>?
- How does daily dosage impact monitoring?

Advisory Panel Discussed Several Different Methods for Sample Preparation

- Microwave Digestion (both open- and closed vessel)
- Hot Plate
- Parr Bomb
- Pre-Digestion

Advisory Panel Discussed Potential Detection Techniques

- Atomic absorption (flame, graphite furnace, cold vapor)
- ICP-OES
- ICP-MS
- XRF
- LIBS
- Ion Chromatography
- Flame Emission Spectroscopy

Results of Team's Experiments

- Dilute-and-shoot (direct dilution) and closed-vessel microwave digestion provided the best results and options for sample preparation procedures- flow chart provided to assist analysts with sample preparation procedures
 - Analysts are free to go directly to closed vessel microwave digestion, if they so desire
- ICP-OES and ICP- MS are options for analytical determinations

USP Metal Impurities Advisory Panel's Recommendations

- The USP Metal Impurities Advisory Panel has made the following recommendations in development of the USP Metal Impurities standard:
 - API and excipients will be tested for Arsenic, Cadmium, Lead, Mercury PLUS...
 - EMEA Metal Catalysts, including their scope as outlined in the EMEA Guideline (12 Catalysts; EMEA list with EMEA limits, less iron and zinc). Additional metals listed in table under consideration.
 - Establish multiple options for limit calculation following the USP <467> Residual Solvent model.
 - Develop 4 new general chapters, General Notices implementation strategy and publish 2 stimuli articles

Elemental Impurities Advisory Panel Accomplishments To Date

- 2 Stimuli Articles
 - Elemental Impurities-Comments and Responses
 - Elemental Impurities-Information
- 4 new general chapters
 - Elemental Impurities-Limits <232>
 - Elemental Impurities-Procedures <233>
 - Elemental Contaminants in Dietary Supplements <2232>
 - Elemental Impurities-Other Elements <1232>:to be developed over new few years
- PF 36 (1) [Jan.-Feb. 2010]

Stimuli Article: Elemental Impurities- Comments and Responses

- The Advisory Panel recommends the adoption of the General Notices revision with an extended implementation date. They recommend that the committee consider an official date that coincides with the official date of the EMEA Metal Catalyst guideline (September, 2013)

Stimuli Article: Elemental Impurities- Comments and Responses

- The Advisory Panel recommends that all of the references to the General Chapter <231> Heavy Metals be removed from USP-NF monographs in a manner to coincide with the official date approved for the General Notices revision.

Stimuli Article-Information

■ **Methods for Establishing Exposure Limits**

- European Medicines Agency (EMA) guidance, “Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents” (2008)
- 10g/day dose for drug products for calculation of ppm limits
- 50 kg person for extrapolation from animal data on body weight-basis
- 70-year lifetime
- 10% bioavailability for extrapolation from the oral permissible daily exposure (PDE) to the parenteral PDE

Elemental Impurities-Limits <232> Class 1 Impurities and Limits

Element	Oral Component Limit ($\mu\text{g/g}$) per 10-g Dose	Oral Daily Dose PDE ($\mu\text{g/day}$)	Parenteral Component Limit ($\mu\text{g/g}$) per 10-g Dose	Parenteral Daily Dose PDE ($\mu\text{g/day}$)
Arsenic	1.5	15	0.15	1.5
Cadmium	0.5	5	0.05	0.5
Lead	1	10	0.1	1
Mercury	1.5	15	0.15	1.5

<232> Class 2 Impurities and Limits

Element	Oral Component Limit per 10-g Dose ($\mu\text{g/g}$)	Oral Daily Dose PDE ($\mu\text{g/day}$)	Parenteral Component Limit per 10-g Dose ($\mu\text{g/g}$)	Parenteral Daily Dose PDE ($\mu\text{g/day}$)
Chromium	25	250	2.5	25
Copper	250	2500	25	250
Manganese	250	2500	25	250
Molybdenum	25	250	2.5	25
Nickel	25	250	2.5	25
Palladium	10	100	1.0	10
Platinum	10	100	1.0	10
Vanadium	25	250	2.5	25
Osmium	10 (Combination not to exceed)	100 (Combination not to exceed)	1.0 (Combination not to exceed)	10 (Combination not to exceed)
Rhodium				
Ruthenium				
Iridium				

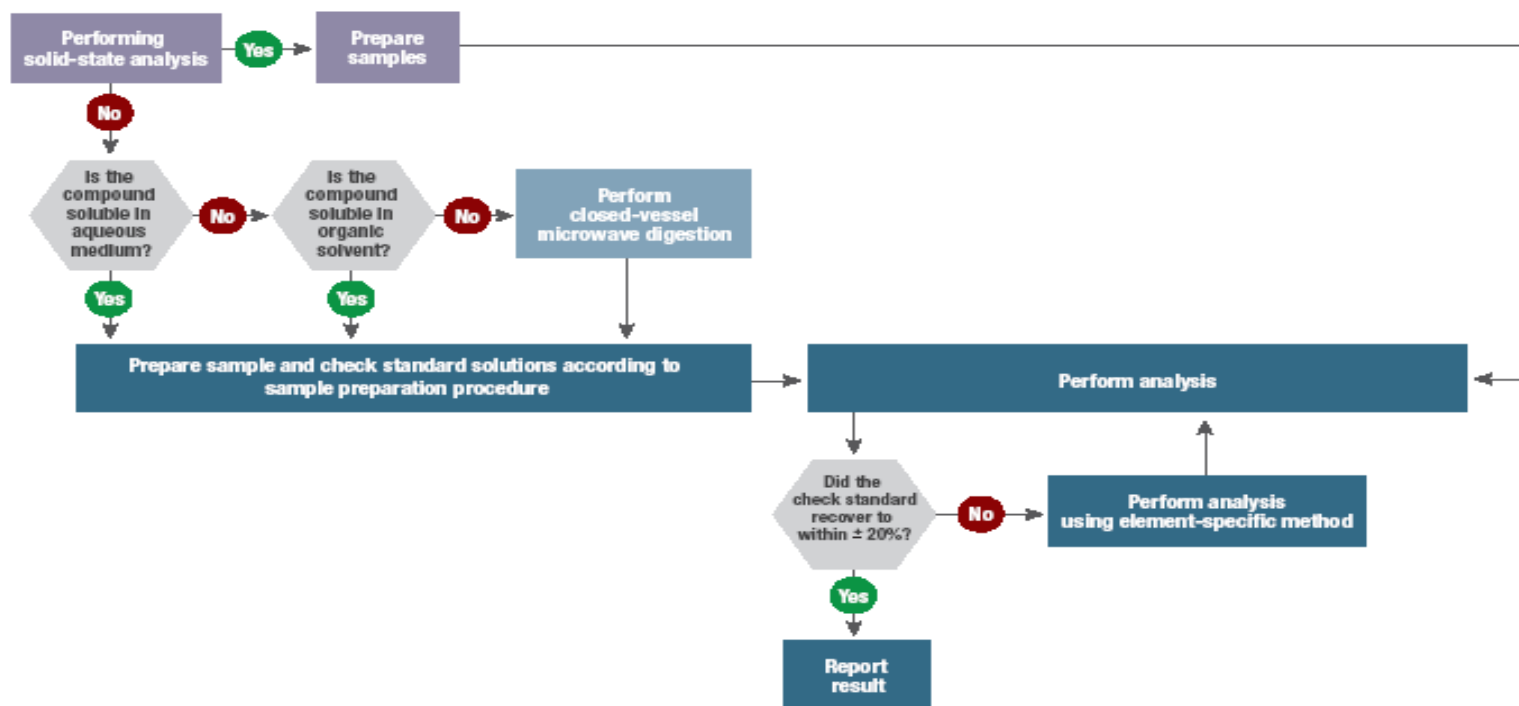
Elemental Impurities-Limits <232>

- Options for Describing Limits
 - Individual Component Option
 - Summation Option
 - Daily Dose Option

Elemental Impurities –Procedures <233>

- Like <467> Residual Solvents, provides procedures as a starting point
- Provides both a limit and quantitative test
- Does not address speciation
- USP procedures need to be verified, <1226>
- User procedures need to be validated, <1225>
- Chapter provides validation acceptance criteria
- Dietary supplement chapter refers to this chapter for all but methyl mercury and speciation issues

Sample Preparation



Sample Preparation

- **Closed Vessel Microwave Digestion**

“This sample preparation procedure is designed to be used for samples that need to be digested; this procedure also applies to samples that are not soluble in Nitric Acid. (Note: weights and volumes provided may be adjusted to meet the requirements of the microwave digestion apparatus being used provided that proportions remain constant.)”

Elemental Impurities-Procedures <233>

■ Limit Test Validation Summary

Parameter	Test	Acceptance Criteria
Accuracy	Response comparison of spiked sample with standard	80-150% of standard response
Precision	Response of 6 spiked samples	RSD<20% (n=6)
Specificity (False Negative)	None	Accuracy and Precision
Specificity (False Positive)	Demonstrate lack of signal from other elements	Not specified

Elemental Impurities-Procedures <233>

■ Quantitative Validation Summary

Parameter	Test	Acceptance Criteria
Accuracy	Comparison of spike sample with standards at 0.5 J, 1.0J, 1.5J	80-150% recovery
Precision (Repeatability)	Analysis of 6 individual sample preps spiked at 1.0J	RSD<20% (n=6)
Precision (Intermediate Precision)	Repeatability test performed by: separate analyst, different system, different day (only one required)	RSD<25% (n=12)
Specificity (False Negative)	None	Accuracy and Precision Met
Specificity (False Positive)	Demonstrate lack of response when other elements are present	Not specified
LOQ	None	Accuracy Met

Elemental Impurities-Procedures

<233>

■ Referee Procedures

“When a user does not have a procedure that meets the criteria for performance described, then one of the referee procedures shall be employed. The procedures include: *Procedure 1*, which can be used for elemental impurities generally amenable to detection by ICP-OES and *Procedure 2*, which can be used for elemental impurities generally amenable to detection by ICP-MS.”

Elemental Impurities-Procedures

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■ **Method 1: ICP-OES**

–Calibration solution 1: 2J of the element(s) of interest in a solution of similar acid concentrations to sample solution (e.g. 7.5% aqua regia) where J is the limit corrected for dosage and dilution. For mercury analysis, it is recommended to add gold as a stabilizer.

–Calibration solution 2: As per Calibration solution 1, except 0.1J element concentration(s).

–Check standard solution: Prepared per the Calibration solutions except at 1-ppm for all elements. To be analyzed at specified intervals throughout the course of the analysis for system suitability. Acceptance criterion is measured concentration 80-120% of target concentration

–Blank solution: solution prepared with acid concentrations matching the Calibration and Check standard solutions.

Elemental Impurities-Procedures <233>

- • **Method 2: ICP-MS**

- Prepare Calibration solutions 1 and 2, and Blank solution per description in Method 1.

- Calibration solution 1 to be used as for system suitability with acceptance criterion of 80-120% of target concentration(s).

Elemental Impurities-Procedures <233>

■ Reagents:

- All reagents used for the preparation of sample and standard solutions should be free of elemental impurities in accordance with *Plasma Spectrochemistry <730>*.
- Commercial, NIST-traceable elemental stock standards, at a recommended concentration of 100 µg/mL or greater or appropriate USP Reference Standards, either single element or multi-element are used as reagents.

Thank You

Questions?