

Elementverunreinigungen in Pharmaprodukten – Neue Limits und Verfahren zur Bestimmung nach USP

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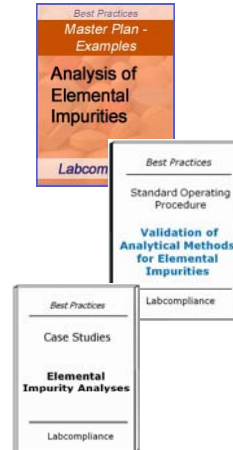
Overview

- FDA Requirements
- Issues with the USP chapter <231>
- Overview of USP chapters for elemental analysis
- Selection of elements and limits – USP/EMEA
- Analytical procedures and referee methods
- Quality control: equipment qualification, method validation, system suitability testing, data integrity
- Recommendations for implementation

Questions and Answers

Reference Material

- Master Plan: Elemental Impurity Analysis
- SOPs
 - Validation of Analytical Procedures for Elemental analysis
 - Analytical Instrument Qualification According to USP <1058>
- Checklist for Elemental Analysis



Reference:

<http://www.labcompliance.com/seminars/audio /240>

To request free reference material, please send an e-mail to Ludwig_huber@labcompliance.com (valid until February 28, 2011)

Why to Control Elemental Impurities

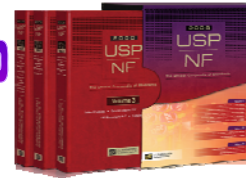
- Toxicity
- Can affect stability of formulation and drug substances
- Required by GMP regulations
 - GMPs should ensure that such drug meets the requirements to **safety, and have the identity and strength and meet the quality and purity characteristic**s that it purports or is represented to possess (21 CFR 210.1)
 - Each lot of components, drug product ... shall be withheld from use until the lot has been **sampled, tested, or examined, as appropriate**, and released for use by the quality control unit. (21 CFR 211.84)
 - Drug products **failing to meet established standards** or specifications and any other relevant quality control criteria **shall be rejected**. (21 CFR 211.165 (f))

Why USP Methodology

US Food, Drug & Cosmetic Act Sec 201 and 501:

- The term “**official compendium**” means the **official United States Pharmacopeia** (Sec 201)
- (b) **Determinations as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium**, except that whenever tests or methods of assay have not been prescribed in such compendium,. (Sec 501)

FDA Requires Testing According to USP



FDA Warning Letter Example

- The computer software your firm uses to determine **metals analysis** is deficient. It has **no security measures to prevent unauthorized access of the software, no audit trails**, and data can be copied or changed at will, with no documentation of the copying or changes
- You (specifically) are not documenting **raw data when you perform inductively coupled plasma emission spectrograph** analyses.
- Your firm does not have a quality assurance program in place to: a) **qualify analytical equipment** prior to their use, and b) calibrate and maintain analytical equipment.

Data integrity

Raw data

Equipment qualification

Ref: www.Fdawarningletter.com (w-058)

History of USP Elemental Analysis

- General chapter <231> uses 100 year old unreliable test method
- 1995: First PF stimuli article identified issues with <231> (Blake)
- 2000: Second PF stimuli article proposed ICP-MS as instrumental alternative (Wang)
- 2004: Detailed article with comparison between <231> and ICP-MS (Lewen)
- **2005: USP General Expert Committee appointed heavy metals subcommittee**
 - Two advisory panels formed for methodology and toxicology
 - Included FDA liaisons
- Independent stakeholder project team formed
- 2008: USP PF Stimuli article with detailed discussion
- April 2009: International workshop with international participation
- **January 2010: Proposals for <232>, <233> and <2232> in PF**

Problems with <231>

- “It was concluded that approximately **50% of the metals may be lost** during the ash process. . . .
- ...Note that **mercury**, which is one of the more toxic heavy metals, was **not recovered** from either set of samples.
- . . . Because of the loss of metals during ignition, the validity of test results obtained with the current USP, JP and EP **general test procedures is questionable.**”

Ref.: “Stimuli to the Revision Process,” Pharmacopeial Forum, Vol. 21, No. 6 (1995) Katherine Blake.

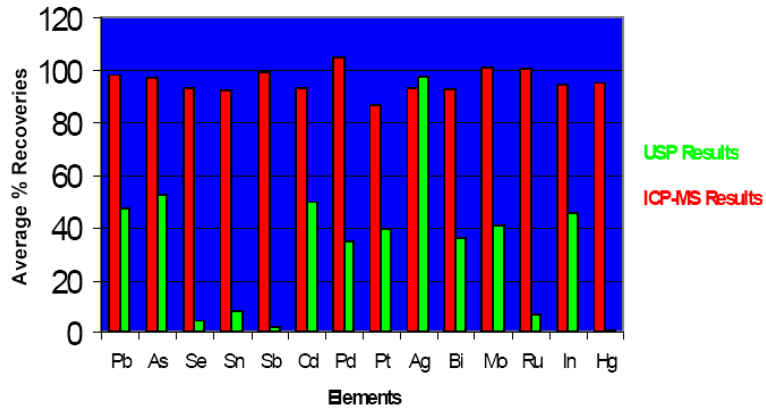
1995

Although still widely accepted and used in the pharmaceutical industry, these methods based on the intensity of the color of sulfide precipitation are **non-specific, insensitive, time-consuming, labor intensive**, and more often than hoped, yield **low recoveries or no recoveries at all.**

Ref: Wang, T. J.Pharm&Biomed Anal. Vol 23 (2000), 867-890

2000

Comparison Between Modern Instrumentation and USP <231> Method



Ref.: Iewen, N et al, J.Pharm & Biomed.Anal. 35 (2004) 739-752

USP <Chapters> Overview

Heavy Metals 231

232

Elemental Impurities
- Limits -

233

Elemental Impurities
Procedures-

2232

Elemental Contaminations
in Dietary Supplements

Terminology: Heavy Metals → Elemental Impurities

Supported by

730

Plasma Spectrochemistry

1058

Analytical Instrument Qualification

1224/5/6

Method Transfer Verification & Validation

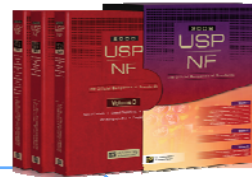
USP General Notices

Revision proposed

- General chapters (232) and (233) will apply to all oral and parenteral articles in USP-NF methodology
 - Elemental Impurities according to 232/233
 - Compounds and detection limits according to 232/233

Where no specific language is given to the contrary, the requirements under the General Notices and General Chapters apply.

USP Implementation Plan



- Stage 1: Feedback to PF Stimuli Papers, April 2010
- Stage 2: Adoption of General Notice to be published in PF
Official release date should coincide with the official EMEA (Sept 2013)
- Stage 3: All references to <231> removed and can not be used any more. Timing coincides with Approval of General Notices

“New chapters are expected to be finalized sometime in 2011 and become official at a later date which has not yet been determined”

Reference: USP’s FAQ Document Related to Proposed Standards for Elemental Analysis

PF = Pharmacopeial Forum
EMEA = European Medicines Agency

<232> - Selection of Elements and Limits

- Elements and Limits based on published evaluations by regulatory bodies
- Element impurities classified by impurities by risk level
 - Class I: highly toxic, high safety concern (the “**big four**” As, Cd, Hg and Pb)
 - Class II: lower safety concern (12 elements)
- Limits defined according to risk level
- Provides three options for determination of compliance to limits (**similar to <467>**)
<http://www.labcompliance.com/seminars/audio/206>

EMA: European Medical Agency

Limits for Class I Impurities

	Component limit (µg/g)	Oral daily dose PDE (µg/day)	Parenteral Component Limit (µg/g)	Parenteral daily Dose PDE (µg/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

Parenteral limits 10x lower

PDE = Permissible Daily Exposure

Elements and Limits for Class II Impurities

	Component limit (µg/g)	Oral daily dose PDE (µg/day)	Parenteral Component Limit (µg/g)	Parenteral daily Dose PDE (µg/day)
Chromium	25	250	2.5	25
Copper	250	2500	2.5	250
Manganese	250	2500	2.5	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 exceeded)	100 (combination not exceeded)	1.0 (combination not exceeded)	10 (combination not exceeded)
Rhodium				
Ruthenium				
Iridium				

From the EMEA "Guideline on the Specification Limits for **Metal Catalysts or Metal Reagents**"

EMA Guideline

- Specification Limits for Residues of Metal Catalysts or Metal Reagents
- First draft: 2000, Final: Sept. 1, 2008
- Contains detailed rationale for limits of 14 metals
- Defines Three Safety Classes, similar concept as ICH Q3C
 - Class I (A, B and C): Metals of Significant Safety Concern known to be carcinogenic
 - Class II: Metals of low safety concern levels tolerated up to exposures in medicines
 - Class III: Metals of minimal safety concern levels well tolerated (e.g., Fe, Zn)

<233> Test&Validation Procedures

- Statement: Procedures in <231> inadequate to meet requirements of <232>
- Provides analytical validation procedures for limit and quantitative tests
- Provides details of two reference procedures (ICP-MS, ICP OES)
- Choice of procedure including sample preparation is responsibility of the user
- Provides performance criteria for alternative methods

Referee Procedures 1 and 2

Techniques

- Procedure 1: ICP-OES (Details in proposed chapter <233> Inductively coupled atomic (optical) emission spectroscopy)
- Procedure 2: ICP-MS (Details in proposed chapter <233>) Inductively coupled plasma – Mass spectrometry

Verification

- Ensure that the procedure is appropriate for use (USP <1226>)

Sample preparation

- The same for procedure 1 and 2
- Closed vessel microwave digestion (if compound not soluble)
- Detailed procedure in proposed chapter <233>

Reagents

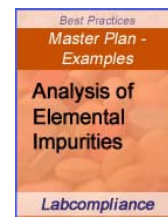
- Free of elemental impurities (reference to USP <730>)
- Traceable to NIST (National Institute for Standards and Technology)

Criteria for Alternative Procedures

- Requires complete validation for each element of interest
- Requires system suitability tests runs with USP reference standards or equivalent at the day of use
- Procedures that meet criteria are equivalent to procedures 1 and 2
- Requirement for testing specified in the individual monograph or in *General Notices*

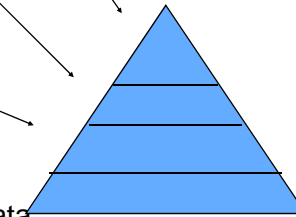
Recommendations for Implementation

1. Study USP 232, 233, and 467
2. Develop a master plan and project plan template for implementation
 - Approach
 - Tasks, responsibilities, deliverables
 - Time schedule
3. Budget for, select and purchase equipment
 - Part 11 and EU Annex 11 compliance
4. Qualify and/or validate equipment and computer systems
5. Develop and validate or **verify test methodology** for elemental impurities

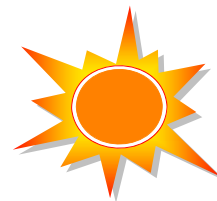


Compliance & Quality Control for Elemental Analysis

- Data integrity, availability and traceability
- System suitability test/quality control checks
 - Verifies that the system performs according to analysts expectations
- Analytical methods validation/verification
 - Proof that analytical procedure does what it purports to do
- Analytical instrument qualification
Computer system validation
 - Forms the base for generating quality data
 - Proof suitability of the instrument for intended use



Thank You



I would like to thank

- *All attendees for your attention*
- *Agilent Technologies for organization and invitation*

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