

Workshop on Metals in Pharmaceuticals and Dietary Supplements

USP Headquarters
Rockville, Maryland

April 28-29, 2009

General Presentations

The content of this presentation reflects the ideas and suggestions of the participants at the Metal Impurities Workshop, April 28-29, 2009. These deliberations are advisory and are not binding in any way to the Council of Experts, its Expert Committees and Advisory Panels, or USP staff.

Quality Standards for Medicines, Supplements, and Food Ingredients throughout the World

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Roger L. Williams, M.D.

Chair, Council of Experts
Chief Executive Officer



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Metal Impurities Workshop

- Workshop convened at the request of the Prescription/Nonprescription Stakeholder Forum
- USP welcomes this request
- Workshop represents engagement of all stakeholders (Industry, FDA, USP, Public) in the work on metals impurities standards



General Chapters Expert Committee

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VICE CHAIR: Gregory P. Martin, M.S.

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Fred Xi, Ph.D.

FDA LIAISON

Robert L. Iser, M.S.



Metal Impurities Advisory Panel

CHAIR: Nancy Lewen, B.S.

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MEMBERS

Charles Barton, Ph.D., DABT

Courtney M. Callis, MPH, DABT

Steven J. Dentali, Ph.D.

Anna M Fan, Ph.D., DABT

Dr. Roland Frotschl

Assad Kazeminy, Ph.D.

Richard Ko, Pharm.D., Ph.D.

Dr. Gregory C. Turk, Ph.D.

Robert Wiens, M.S

GOVERNMENT LIAISONS

Renee Blosser, M.S., FDA

Mamata De, Ph.D., FDA

Bruce A. Fowler, Ph.D., A.T.S., CDC

John F. Kauffman, Ph.D., FDA

Jill C. Merrill, Ph.D., FDA



Heavy Metals Project Team Members

Fran Byrne, Chair

Steve Boyajian
Hamid Forouhar
Denise McClenathan
Greg Roberts
Mark Saulter
Richard Shanholtz
Weifeng Wang
Tiebang Wang
John Kaufmann
Priscilla Zawislak

Baxter Healthcare

Activation Laboratories
Irvine Analytical Laboratories
The Procter & Gamble Company
Watson Laboratories
Glaxo Smith Kline
Mylan Pharmaceuticals
Abbott Laboratories
Merck & Co., Inc.
Food & Drug Administration (FDA)
Hercules Inc.



Also Thanks To:

- **FDA** (in addition to those on the Advisory Panel)
 - Charles F. Jewell, Ph.D.
 - Violetta M. Klimek, Ph.D.
 - William R. Mindak
 - John I. Smith, Ph.D.
 - Saleh Turujman, M.D.
- **PDG Representatives**
 - Shigenori Harada, Ph.D. Japanese Pharmacopoeia
 - Michael Wierer, Ph.D. European Pharmacopoeia
 - Chikako Yomota, Ph.D. NIHS, Japan



Also Thanks To:

- **Moderators**

- Matthew W. Borer, Ph.D. Eli Lilly and Company
- F. Scott Lyon Mylan Pharmaceuticals
- Douglas M. Templeton, M.D., Ph.D. University of Toronto
- Michael Wierer, Ph.D. EDQM-PhEur



Workshop Objectives

- Review and discuss metal impurities limits, methodology, risk assessment, harmonization, and implementation strategies
- Encourage dialog among FDA, industry stakeholders, and USP experts and staff
- And finally to advance revisions to the metal impurities standard that will help assure avoidance of or limit exposure to metals that may cause harm.



The Future (?)



Summer 2008	August 2008	Sept 2008	Dec 2008/ Jan 2009	Spring 2009	Nov-Dec 2009	Feb 2010	Nov 2010
Stimuli Article from Advisory Panel Posted on web	IOM Metals Toxicology Workshop Washington, D.C.	Stimuli Article PF 34(5) Sept-Oct 2008 Annual Scientific Meeting Heavy Metals Session	Stim article comment period ends Advisory Panel meets	Metal Impurities Workshop for public dialog	Draft Chapter Publishes in PF 35(6) Ref Stds(s) in house	Feb 15 comment period ends Advisory Panel meets thereafter	Chapter published in USP 34 with a delayed official date to be determined Ref Stds(s) in catalog

Expert Committee: General Chapters, James DeMuth, Chair

Advisory Panel: Metal Impurities, Nancy Lewen, Chair

Project Team: Heavy Metals and Inorganic Impurities, Fran Byrne, Chair



= Where We Are on Timeline





Thank You

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Definition and Scope of Metal Impurities

Matthew Borer, Ph.D.



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Definition and Scope of Metal Impurities

- Definition - Problem Statement
 - Current State
 - Methodology
 - Limits
- Scope
 - Metals
 - Application



Problem Statement

- We are committed to advancing the current standards (<231>) so that widely agreed upon safe limits for key metal impurities are properly measured, thereby protecting the public health.
- **There has been significant debate about how to achieve this goal.**



Current State

- Provided in your Briefing Book
 - General Chapter <231>
 - Stimuli Article from PF 34(5) September – October 2008
 - Digest of comments on this Stimuli Article
 - Summary of Institute of Medicine Workshop (Aug 2008)
 - USP Advisory Panel draft metals and limits table
 - Slides from USP 2008 Annual Scientific Meeting



Limits

- We want to set limits for appropriate metal impurities (of known toxicity, that are sufficiently likely to be present)
 - Toxicology data
 - Metal species
 - Daily dose and budget fraction
 - Route of administration
 - Patient population

Methodology

- We want analytical techniques that measure selected metal impurities at the limits that we set
 - Selective
 - Sufficiently sensitive
 - Robust
 - Simple and inexpensive

Risk Assessment and Implementation

- The following topics were summarized from public response to the stimuli article in *Pharmacopeial Forum*, Vol. 34(5) [Sept.–Oct. 2008]



Questions/Concerns

- Which metal impurities should be considered and what are the safe upper limits?
- What analytical methods should be used for testing?
- Does any analytical method meet the requirements?
- To what extent is screening of metal impurities required?
- Should control be achieved through testing or process control?
- Should metal impurities be handled as “extraneous contaminants” as defined in ICH Q3A?



Questions/Concerns, continued

- What is the actual magnitude of safety issues (risk)?
- What is the real cost of a different approach (cost/benefit)?
- Should we be consistent with current food regulations?
- Can a General Chapter based on atomic spectroscopy be detailed enough to be a useful referee method?
- How do we address materials that do not pass new tests/limits (if any)?



Meeting Outcomes

- Compile a complete set of questions/concerns
- Document the supporting rationale for our position on these questions/concerns
- Provide a complete list of pros and cons for the remaining questions/concerns
- Resolve and agree on as many questions/concerns as possible





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Metals Limit Setting

Darrell R. Abernethy, M.D., Ph.D.
Chief Science Officer

Metals Limit Setting—Resources Used

- ATSDR—Agency for Toxic Substances and Disease Registry of the US Department of Health and Human Services
- EMEA—Guideline on Specification Limits for Residues of Metal Catalysts or Metal Reagents
- IRIS—Integrated Risk Information System of the US Environmental Protection Agency
- IPCS—International Program on Chemical Safety of the World Health Organization
- JECFA—Joint Expert Committee on Food Additives of the World Health Organization and the Food and Agriculture Organization



Metals Limit Testing—Scope

- Human toxicity associated with exposure to the metal
- Likelihood of presence of the metal in the article to be tested
- Other sources of exposure to the metal
- Additive toxicity from different metals
- Special populations at increased risk for toxicity

Additional Considerations—To be Addressed if Necessary

- Metals with additive toxicity
- Nephrotoxicity
- Unknown sum of total ingestion
- Special populations





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Metals Limit Setting

Douglas Templeton, M.D., Ph.D.
Moderator

Metals Limit Setting

- Metals
- Limits





Thank You

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Metal Impurities Methodology

William F. Koch, Ph.D., FACB
Chief Metrology Officer



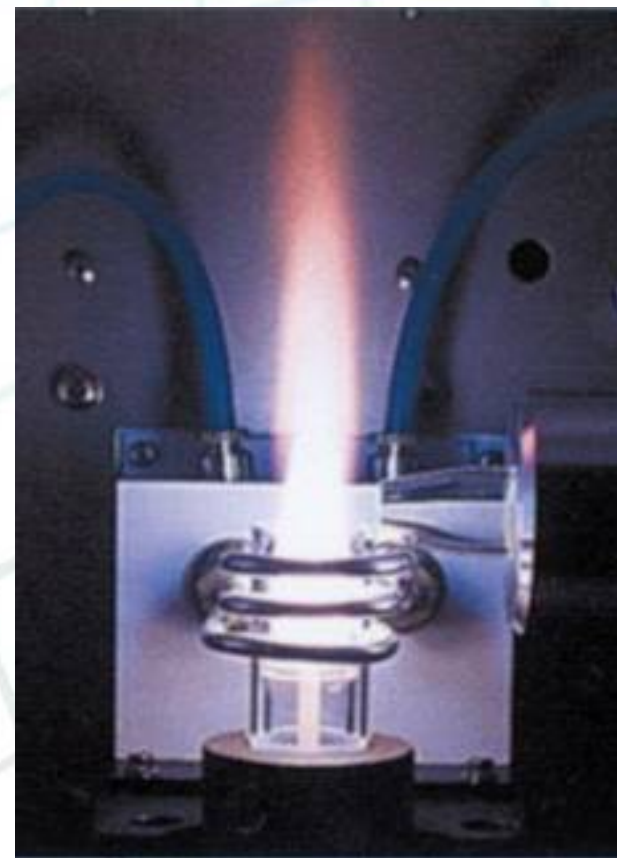
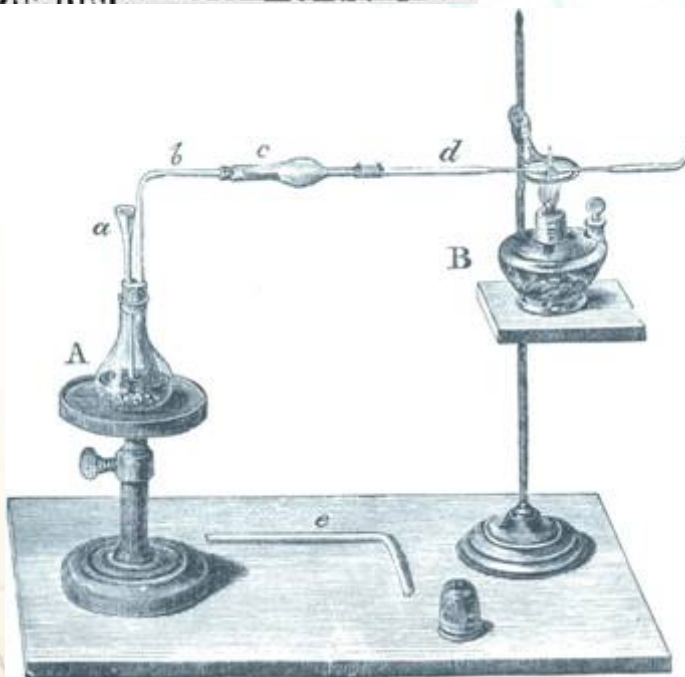
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Methods – Then and Now



- Fire Assay

- Marsh Test



- IC Plasma

Current Compendial Documents

- USP Chapter <231> “Heavy Metals”
- USP Chapter <730> “Plasma Spectrochemistry”
- EP 01/2008: 2.4.8 “Heavy Metals”
- EP 01/2008: 2.2.57, 58 “Inductively Coupled Plasma”
- USP Chapter <1225> “Validation of Compendial Methods”



USP <231> Heavy Metals

- Wet Chemical Method
- Limit test for heavy metals
- Qualitative test
 - Metallic impurities colored as sulfides
 - Ag, As, Bi, Cd, Cu , Mo, Hg, Pb, Sb, Sn
 - Visual comparison with known lead standards
 - L = 0.001% (10 ppm), 2 g sample required



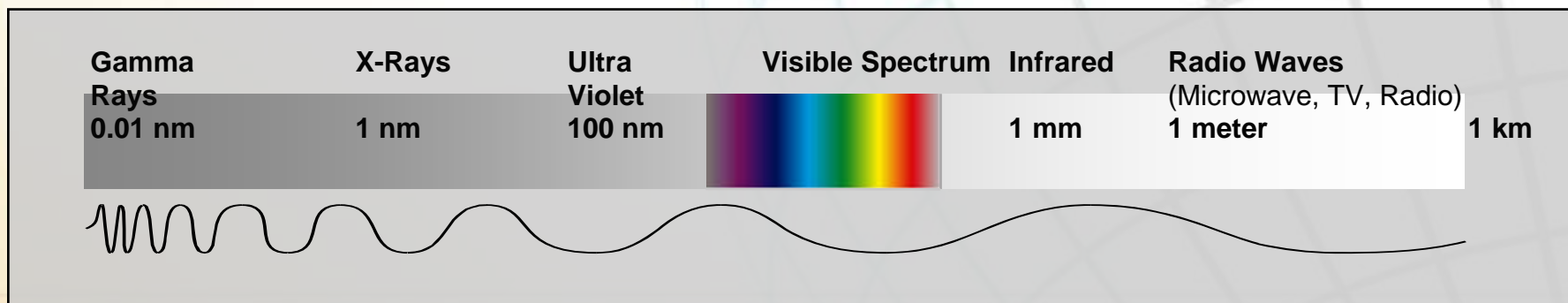
Instrumental Spectroscopic Methods

- Atomic Absorption Spectrophotometry
- Atomic Emission Spectrometry
- Inductively Coupled Plasma-Atomic Emission Spectrometry
- Inductively Coupled Plasma- Mass Spectrometry
- Atomic Mass Spectrometry
- Atomic Fluorescence Spectrometry
- X-Ray Fluorescence Spectrometry
- Neutron Activation Analysis



Instrumental Spectroscopic Methods

- Based on Electromagnetic Spectrum
- Typical detection limits 0.01 – 1 $\mu\text{g/L}$ (ppb) in solution
- Fast (2 minutes)
- Multielement (> 60 elements)
- Definitive, multiple isotope identification



Periodic Table

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac															
			Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu	
			Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr	



Flame Only



Flame & Furnace

Plasma vs. Wet Chemistry

Advantages of Plasma Spectrometry

- **Simultaneous Multielement Analysis**
 - Determination in Single Solution
 - No Chemical Separations
 - Minor Anion Effects
 - Element Specific Emission
- **Rapid Analysis**
 - Analysis Sequence Less Time Consuming
 - Suitable for Routine Analysis
 - All Metals Readily Determined
- **Small Sample Size**
 - Less than Micro- or Ultramicro- Chemical Analysis
- **Better Detection Limits**
- **Comparable or Better Accuracy**
- **Analysis Performed by Technicians**
- **Easier Sample Preparation**
- **Less Chemical Interferences**



Plasma vs. Wet Chemistry

Disadvantages of Plasma Spectrometry

- Relative Method Requires Reference Samples
- Apparatus Costly
- Initial Method Development Requires Effort
- Some Elements Not Readily Detected
 - High Ionization Potential (e.g., F)
 - Low Natural Concentrations
- No Chemical Information (Speciation) Provided
- Concomitant, Spectral, and Other Interferences Require Corrections

Comparison of Methods

	ICP-MS	ICP-AES	Flame AAS	GFAAS
<i>Detection Limits</i>	Excellent for most	Very good for most	Very good for some	Excellent for some
<i>Sample Throughput</i>	All Elements 1-4 min/sample	5-30 Elements 1-10 min/sample	Few Elements 5-15 s/element	Few Elements 2-3 min/element
<i>Linear Range</i>	$>10^8$	10^5	10^3	10^2
<i>Precision</i> -Short term -Long term (4 hours)	1-3% < 3%	0.1-2% < 3%	0.1-1% < 2%	1-5% < 5%

Comparison of Techniques

	ICP-MS	ICP-AES	Flame AAS	GFAAS
<i># Elements</i>	> 75	> 73	> 68	> 50
<i>Sample Usage</i>	Low-Moderate	Low-Moderate	High	Very Low
<i>Semi-Quant</i>	Yes	Yes	No	No
<i>Method Development</i>	Skill Required	Skill Required	Easy	Skill Required
<i>Costs - Capital</i>	\$140,000 – 170,000	\$60,000 – 110,000	\$15,000 – 40,000	\$40,000 – 65,000
<i>- Operating</i>	Medium/high	Medium	Low	Medium



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Metal Impurities Methodology

Michael Wierer, Ph.D.
Moderator

Metal Impurities Methodology

- Current Methods – Heavy Metals, Lead, other Wet Chemistry
- Instrumental Tests for Specific Metals



Metal Impurities Methodology

- **Current Methods – Heavy Metals, Lead, other Wet Chemistry**
 - What has been controlled so far and at what levels?
 - Advantages/disadvantages in keeping an “improved” version of the “sulfide precipitation” tests ?
 - Should other established wet chemical test be kept in monographs
 - Harmonization aspects
 - Could conventional tests be linked to the new methods?

Metal Impurities Methodology

- **Instrumental Tests for Specific Metals (1)**
 - **Sample preparation procedures**
 - Preferences to be discussed in relation to the target sample (API, dosage form, herbals/botanicals)
 - To which detail can this be given in a pharmacopoeia ?
 - Matrix effects
 - Homogeneity of the analyte distribution
 - Safety aspects

Metal Impurities Methodology

- **Instrumental Tests for Specific Metals (2)**
 - Choice of the method
 - Related to required sensitivity (see limits)
 - Related to target sample (API/excipient/dosage form/herbal)
 - Depending on the expected scope (number of elements to be covered)
 - Complexity to operate the method (what can be included in a public standard ?)
 - Cost aspects

Metal Impurities Methodology

- **Instrumental Tests for Specific Metals (2)**
 - Choice of the method
 - Related to required sensitivity (see limits)
 - Related to target sample (API/excipient/dosage form/herbal)
 - Depending on the expected scope (number of elements to be covered)
 - Complexity to operate the method (what can be included in a public standard ?)
 - Cost aspects

Metal Impurities Methodology

- **Instrumental Tests for Specific Metals (3)**

- Can ICP-MS meet limits for Sb, Pb, Hg, Tl ?
- Can ICP-MS meet limits for As and Se ?
- Os reliably quantifiable by ICP ?
- Is multi point calibration needed ?
- Is AAS suitable for routine purposes to control “the big 4” ?
- Can other techniques e.g. Anodic stripping voltametry be used
- Validation requirements to be defined ?
- Performance-based approach
- Which reference standards/materials are needed ?



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Role of USP in Federal Law Implementation Aspects

Matthew B. Van Hook, J.D.
Assistant General Counsel

USP in Federal Food, Drug & Cosmetic Act

- USP an “official compendium”
- Drug with name recognized in USP must comply with compendial identity standards, or be deemed adulterated, misbranded, or both. 501(b) & 502(e)(3)(B)
- To avoid being adulterated, drugs must also comply with compendial standards for strength, quality, or purity, unless labeled to show all differences. 501(b)
- USP does not enforce its standards
- FDA enforces USP standards; compliance focus on manufacturer-approved specs, GMPs, and USP



USP Standards & FDA Compliance

- USP requirements are stated in General Notices; Monograph, General Chapters, Reference Standards
- USP standards apply at any time in the life of an article; when tested, must pass to demonstrate compliance
- However, USP does not set frequency of, or specify circumstances for, testing
 - “Repeats, replicates, statistical rejection of outliers, or extrapolation of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia.”



Examples of USP in GMP Regulations

21 CFR Parts 210 & 211

- GMPs are intended to help assure drug has “identity and strength and meets the quality and purity” claimed. 210.1(a)
- At least one test required to verify the identity of each component of a drug product. 211.84
- For each batch of drug product, requires laboratory determination of satisfactory conformance to final specs, “including the identity and strength of each active ingredient.” Drug products failing to meet established standards or specifications “shall be rejected.” 211.165(a),(f)



FDA Compliance Policy Guide

“Performance Test for Compendial Products”

- Compendial methods required for batch release test only where firm commits to do so (as in a new drug application), or where the official method is the only appropriate test.
- Neither the USP/NF nor the CGMP regulations necessarily require a firm to utilize, as a batch release test, the methods and procedures stated in the official compendia.
- **What is required is that official drug products conform to the appropriate compendial standards. This conformance must be assured by suitable means, including adequate manufacturing process validation and control.**
- **Alternative Methods: in the event of a dispute as to whether or not a drug product meets the standard, the compendial method will be applied as the referee test.”**

CPG 7132.05, Sec. 420.400, Policy ¶1.



Conclusion - What Testing Is Required?

- ***Compliance*** with USP standards is required at all times.
- ***Frequency*** of testing and sampling are left to the preferences of first-party (manufacturer), second-party (buyer) and third-party (FDA/regulator) stakeholders, who “may or may not require additional examination of additional specimens, in accordance with predetermined guidelines or sampling strategies.”
USP General Notices, §3.10
- ***FDA helps promote compliance*** with applicable USP compendial standards, e.g. re GMPs.





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Risk Assessment and Implementation Strategies

F. Scott Lyon
Moderator

Where are Heavy Metals Likely to Occur and When do they Need Control?

- **Material Sources**

- Control for metals “likely to be present” based on natural occurrence
- When will screening methods be required? When will individual metal tests be required?

- **Manufacturing Processes**

- Control for metals known to be used in the manufacturing process (catalysts, reagents and processing equipment)

- **Manufacturer Responsibilities/ Supply Chain**

- Expectations for traceability and consistent quality from all points in the supply chain
- Expectations for manufacturer disclosure of metals used in the process

- **Additional Control for Articles of Risk**

- Enhanced evaluation for high risk items (i.e. certain minerals or botanicals)



When Must the New Heavy Metals Controls be Implemented?

- **Phased Approach**

- Implement highest risk metals (Pb, As, Cd and Hg) first?
- Implement EMEA catalysts and high risk metals first?

- **Implementation time**

- What should be the amount of time allowable for implementation after the standard has been published? When should the standard become official?



How Will the Heavy Metals General Chapter be Interpreted for Enforcement?

- **Regulatory Considerations**

- What are the expectations for presentation of heavy metals methods/ data in regulatory documents (i.e. filings, COA's)?

- **Test Reduction**

- What role does testing have in a heavy metals control system (initial screening, periodic testing, routine testing)?
- What roles do process controls and historical data have in a heavy metals control system? Can these controls justify elimination of testing or reduced testing?

- **Alternate Technologies**

- How will alternate technologies be justified in the absence of a comprehensive referee method?





Thank You
