Digest of Comments Received
On the *Stimuli* Article
"General Chapter on Inorganic Impurities: Heavy Metals"
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This document is provided as background information for the *USP Workshop on Metal Impurities in Drugs and Dietary Supplements*. It reflects comments received by USP to a *Stimuli* article on this topic that was published in *Pharmacopeial Forum* 34(5) (September-October 2008) and pre-published on the USP Web site in May 2008. Because USP does not provide official commentary on *Stimuli* articles, this document does not reflect USP's typical commentary format. Instead, this document is intended to provide a digest of comments received. USP has de-identified and categorized the comments into four categories: General, Toxicity Limits, Methodology, and Implementation. USP has retained the original language of the commenter, with the exception of minor editorial changes, for purposes of providing stakeholders an accurate account of the comments received on this topic.

1. General Comments

1. USP should provide clarified definitions for the terminology of inorganic impurities, metals, elements and heavy metals.
2. Limits and the standards-setting process must be transparent and proactively engage key stakeholders.
3. This topic is developing and changing from week to week. We encourage the USP to open a hot topic page on the USP's web site.
4. USP should not make the new chapter official until an FDA Guidance is officially issued on the topic.
5. Pharmacopeial Education on the revised <231> General Chapter must be available in several forms prior to the General Chapter becoming official.
6. The *Stimuli* article appears to lay out an acceptable, general approach to the determination of these analytes.
7. Approach outlined in the *Stimuli* article appears to advocate multiple-element screening/testing when a risk-based control strategy similar to the ICH approach to Residual Solvents control could be more effective and efficient.
8. Toxicity data is the most scientifically sound method for setting limits.
9. This chapter should be considered a screening method to identify the presence of potentially hazardous elements.
10. It is unnecessary to require such an extensive general screening method for unknown heavy metals from all possible sources.
11. The requirements of an appropriate method should be based solely on the need for specificity, accuracy, precision and LOQ at the toxicological limit. Performance characteristics must not be based on a preconceived notion of what method delivers the lowest detection limit.
12. Publish methodology for trace metal screening and routine control as a new General Chapter (not as a replacement for **<**231>).
13. Remove references to Heavy Metals testing from all monographs, except those determined to be of specific risk.
14. USP's efforts should be on improving *control* rather than adding tests.
15. USP General Notices and General Information Chapter <1086> *Impurities in Official Articles* place the burden on the manufacturer to control contaminants, without the need for specific monograph instructions.
16. Only Method II in current General Chapter <231> has limitations. Serious consideration is required before all of the wet-chemical methods in chapter <231> are removed, when the primary issues are only with Method II.
17. We agree that the procedures and methods outlined in <231> are outdated and no longer appropriate to monitor heavy metals in dietary supplements.
18. The current USP <231> should still be kept as an option for labs that do not currently have state-of-the art atomic spectroscopic instrumentation.

19. Retain the current Heavy Metals General Chapter <231> for the general screening of materials which do not require the testing of specific toxic elements and do not have low level specifications for metals.
20. This chapter should be considered a screening method to identify the presence of potentially hazardous elements.
21. The recognition of vendor certificates is a general *GMP* topic and should not be addressed in this article about inorganic impurities.
22. The scope of the *Stimuli* article is very broad and covers not only the "traditional" heavy metals but also catalysts and other elements such as lithium, beryllium and boron. We recommend that the USP proceed with this effort in phases to allow continued progress but also provide sufficient time to gather input and carefully consider comments as revisions are proposed.
23. What are the real safety concerns and issues that warrant replacing a test that can be run by any lab to one that requires specific equipment, trained personnel and will cost companies considerable amount of money, both on the initial investment and continued support, process, etc.? This has the potential to have a greater negative impact on the pharmaceutical labs that the revised <467> requirements.
24. USP should initially address control and testing strategies for the traditional heavy metals currently addressed by <231> with a focus on lead, cadmium, mercury and arsenic in higher risk, naturally sourced ingredients.
25. We believe that residual catalysts and the other metals/inorganic elements in Table 1 should be addressed in a separate chapter in a later phase of the revision process.
26. Residual levels for many of these elements have been subject to cGMP controls for many years. They are typically monitored during process development and have been reliably controlled during routine production with appropriate processing measures or testing, if necessary.
27. Control is only needed for those metals likely to be present. Knowledge of the material, process and supplier should dictate the need for metal testing. This approach has its roots in the GMPs. There should not be a need for a general screening release method for any of the metals, including General Chapter: <231> Heavy Metals, <206> Aluminum, <211> Arsenic,<241> Iron, <251> Lead, <261> Mercury, <291> Selenium.
28. The USP proposal does not provide guidance on determining concentration limits in the topical ophthalmic drug products. The 10 gram daily dosage would be equal to approximately 300 drops per day, which is approximately 15 times the daily dosage regimen of topical ophthalmic drug products.
29. Classify metals per EMEA Guideline. This would allow the possibility to use less specific tests if metals of low (class 2) and minimum (class 3) safety concern are present.
30. The *Stimuli* article defines sources of inorganic impurities as encompassing catalysts, undetected contaminants from reagents or starting material, equipment or pipe leaching, or those naturally occurring in plant and mineral sources. However, the reference documents for this *Stimuli* article are ICH Q3A and the EMEA Guideline on the Specification Limits for Residues of Metal Catalysts. As the title suggests, the EMEA guideline is limited to metal catalysts. ICH Q3A specifically excludes "extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as GMP issues."
31. The *Stimuli* article states that food and food ingredients will not be addressed. The rationalization for this is not clear, as food materials are consumed in much higher quantities than drug materials. What will be the future USP position on the level of control of inorganic impurities in such materials?
32. If food materials are exempt from the scope of this chapter then, food ingredients such as dextrose, mannitol, gelatin, and sodium chloride that are used as an excipient in a drug product should also be exempted.
33. Colorant, fragrances, coatings, and materials that are present in trace amounts should be exempt from the scope of this General Chapter.
34. Materials used for clinical research should be exempt from the requirements of this General Chapter.
35. The current general screen for metals should be removed from individual monographs, the requirement being governed instead through guidance in the General Notices of USP, similar to the Residual Solvents model.
36. The need to control metal impurities is at the product level, taking into account the metal impurities contributed by the individual ingredients and the final product manufacture. This naturally leads to an "Option 1" and "Option 2" approach for metal impurities, as seen with residual solvents.

37. Only specific metals should be quantitated. It was clear at the Institute of Medicine Meeting (August 26 and 27, 2008 in Washington, D.C.) that there is only adequate data and concern for four metals, As, Cd, Pb, and Hg.
38. The proposed methodology can be applied in lieu of what is the current Heavy Metals testing but also to other tests such as Residue on Ignition, specific ID tests for the presence of metals (such as sodium), or absence of catalysts such as palladium.
39. Pharmaceuticals are just a miniscule part of what we ingest. Humans ingest lead from water and food (about 300 ug lead/day from food alone. Reference: Encyclopedia of Toxicity, Academic Press, Vol 2, pg 231). When you review the data in the paper "Lead in pharmaceutical products and dietary supplements, you can see that lead from the worst case example (e.g., the chewable antacid tablets of 2.7 ug, (or 0.9% of the daily amount consumed from daily food ingestion). It raises the question: "why is the FDA Office of Pharmaceutical Services (OPS) and any FDA Advisory Committee imposing more stringent requirements and specialized testing (e.g., ICP) when it is not supported by either safety or actual data. Therefore, we question the need for such sophisticated and specific metals determination, when the foods we eat in greater quantities containing greater amounts of heavy metals do not and will not have those controls?
40. Why is the USP imposing drinking water standards for lead on pharmaceutical API, excipients and FP's? The drinking water standards are based on consuming a lot more that just a couple of tabs or caps a day or 15- 45 mL of oral liquids. I see this parallel to what happened years ago with 2 ppm benzene on API's, when this limit adopted was supposed to be for FP's and not API's, unless the final product is 100% API.
41. USP is also big on providing requirements for new technologies or equipment that are not readily available in the average lab on individuals (e.g., PDA for HPLC, etc.). Why is this policy not being considered for this Heavy Metals rework?
42. The *Stimuli* article states that the metals listed in table 1 (31 elements!) are important to control. Does that mean that each drug article (drug substance, drug product or excipient) has to be tested for all these elements?
43. How can we define elements as "likely to be present" since it may be not clear from what sources elements come into the drug article (e.g., undetected contaminants, natural occurrence)?
44. Current heavy metals methods are closely harmonized between the USP and EP. Are the proposed ICP methods being harmonized with EP and are they involved with this process? This is important in today's markets and industry.
45. Many contract laboratories charge per element; typically $30-40/element, so even periodic testing or testing only for specific elements would still be very expensive.

2. Toxicity Limits

1. USP should harmonize limits with British, European, and Japanese compendia as well as EMEA.
2. USP should adopt the American Herbal Product Association's interim limits.
3. The Table 1 limits must not be based on method detection limits and instrument capabilities.
4. USP should use established federal and international standards when setting limits.
5. USP should not use Proposition 65 as the safety factors used in this proposition are not generally accepted in the US and international markets.
6. Some of the listed elements are also nutritional ingredients that are governed by the USDA Recommended Daily Allowances (RDA). These exceptions should be clearly stated within the General Chapter. The Table 1 limits must allow for naturally occurring impurities in naturally sourced materials.
7. USP should develop a guideline for assessing toxicology data to ensure transparency of limits. This would also facilitate improvements as new tox data is available.
8. USP should provide much more detailed summary of the rationale behind the proposed limits as well as how they are to be applied.
9. There is no indication in the USP new proposal that factors such as duration of the treatment have an impact on the limits mentioned.
10. Remove the heavy metal concentration limits from the table as the enzyme preparations are offered in a substantial range of daily intake levels, and the industry is well accustomed to converting concentrations limits from dose recommendations when establishing ingredient specifications. There is no benefit in an across-the-board presumptive conversion to concentration limits.

11. The list of USP metal impurities is quite extensive and includes nutrient elements, for which limits should not be set for dietary supplement products, and numerous metals which occur at low levels in all foodstuffs and are not known to pose particular health hazards. For the purposes of establishing limits for botanical containing dietary supplements, the list should be pared down to inorganic arsenic, cadmium, lead, and methylmercury. Other impurities should be considered only if there is a reasonable belief that they may be a problem, in which case measures should be taken by industry as appropriate.
12. There is not enough safety or toxicological data available to support the proposed limits with reasonable degree of certainty.
13. There is no information given in the *Stimuli* article as to how the limits were established.
14. Table of limits is not clear on how to apply these limits on dosage forms and raw materials.
15. The new proposal states that "the level of each inorganic impurity should not exceed the limit defined in Table 1 or otherwise specified in the individual monograph". USP should allow other calculation options as in ICH (Q3C(R3)) and EMEA.
16. Ten micrograms of lead in a supplement or medicine is *not* an amount that any group, particularly USP, should adopt as a standard. We suggest a lead limit of **0.5 mcg** per daily serving of a dietary supplement or medication.
17. It was confusing regarding whether you add the total of heavy metals measured, which could add up to 57 ppm (First, calculate the limit for every element, individually, then multiply the quantification limit by the dilution factor (1g of sample in 20 ml of solution), and after that summarize all individual limits).
18. Table 1 contains far more elements than can be practical to prepare method for use in a quality control situation. A wide range of limits also present enormous challenges to validate a method. Many of the elements in the list are not generally considered toxic (Al, B, Cu, Li, Rb, Sr, Sn, Zn) and several are ubiquitous (Al, Mg, Fe, Cu, Zn). Ir, Os, Pd, Pt, Rh, and Ru should not be included here as most are not remotely ubiquitous.
19. A footnote refers to the EMEA Guideline. This guideline defines limits for Cr, Cu, Ir, Fe, Mn, Mo, Ni, Os, Pd, Pt, Rh, Ru, Zn and V. Why is Vanadium (V) not mentioned in the *Stimuli* article?
20. What is the reason some of the elements that are also listed in the EMEA Guideline have different PDE values in comparison to the EMEA limits (e.g. Cr 150/250 µg/day, Cu 500/250, Fe 15000/13000, Mn 7000/2500, Ni 1000/250 and Zn 15000/13000)? Furthermore, the article defines individual limits for Ir, Os, Rh, Ru (each PDE 100 µg/day), while the EMEA Guideline says that the sum of these four elements has a PDE of 100 µg/day. It should be discussed to harmonize the *Stimuli* article with the EMEA Guideline.
21. The limits are based on a daily dose of 10 grams of the drug product. How to proceed when the daily dose of the drug product is greater or lower than 10 grams per day?
22. Limits are given for oral and parenteral routes of administration. What kind of limits should be used for drug articles that are applied via other routes of administration, including inhalation?
23. The oral and parenteral limits for some elements in Table 1 are difficult or next to impossible to meet even by the most state-of-the-art equipment. This should be taken into consideration when setting the limits in Table 1.
24. What happens if a material currently meets <231> but does not meet the proposed limits? The limits in the article are inconsistent with current limits. Using lead as an example, why is the new limit 1 ppm for oral dosage, while the *Food Chemicals Codex* lists 3 ppm? Has the toxicity of lead increased in recent years?
25. Some of the metals listed, e.g., iron (as iron oxides) and aluminum (as aluminum lakes), are added to excipients at significant levels on purpose without safety concerns. By design, these will exceed the limits in the table. How will these be handled?
26. Delete the second column of the table with limits for ingredients intended for oral intake, which are based on a maximum dose of 10 grams per day. The presumption of not more than 10 grams per day is at times not valid for ingredients of botanical origin.
27. Replace “Parental Limits” to “Parental PDE,” in order to apply the concept to multi-ingredient products, various doses, and both ingredient suppliers and finished product manufacturers without any confusion.

RECOMMENDED MODIFICATION TO TABLE 1

Table 1. Elemental limits for oral and parental materials.

Element	USP Oral Tolerable Daily Intake for Dosage Forms and Components (oral TDI)*, µg/day	USP Parental Tolerable Daily Intake for Dosage Forms and Components (parental TDI)**, µg/day
Class I (metal impurities with wide natural occurrence and generally recognized as presenting significant toxicity)		
Arsenic (As) [as inorganic As]	15	1.5
Cadmium (Cd)	25	2.5
Lead (Pb)	10	1
Mercury (Hg) [total Hg]	defer to toxicologists	defer to toxicologists
Methylmercury (Methyl-Hg)	15	1.5
Class II (metal impurities derived from chemical processing (such as residual reagents or catalysts) or naturally occurring, for which no nutritional value is recognized)		
Antimony (Sb)	20	2
Beryllium (Be)	100	10
Indium (In)	100	10
Iridium (Ir)	100	10
Osmium (Os)	100	10
Palladium (Pd)	100	10
Platinum (Pt)	100	10
Rhodium (Rh)	100	10
Rubidium (Rb)		
Ruthenium (Ru)	100	10
Strontium (Sr)	30,000	3,000
Thallium (Tl)	4	0.4
Tungsten (W)	375	37.5
Class III (metal impurities recognized as micronutrients with a low established upper intake limit)		
Chromium (Cr)	150	15
Cobalt (Co)	1,000	100
Copper (Cu)	500	50
Lithium (Li)	600	60
Molybdenum (Mo)	250	25
Nickel (Ni)	1,000	100
Selenium (Se)	250	25
Class IV (metal impurities recognized as micronutrients with a high upper intake limit or no upper intake limit)		
Aluminum (Al)	50,000	5000
Boron (B)	10,000	1000
Iron (Fe)	15,000	1500
Magnesium (Mg)		
Manganese (Mn)	7,000	700
Tin (Sn)	30,000	3,000
Zinc (Zn)	15,000	1,500

* USP oral TDIs are the identical with USP Oral PDE in Stimuli Article.

*** USP parental TDIs are one-tenth of USP oral TDIs.*

3. Methodology/Instrumentation

1. There is no description of the mentioned method "USP Method 1".
2. Screening of different matrices can be very complex because of the presence of spectral interference from any salts. The technique may therefore require extensive method development work in order to function as a general screening technique for a wide range of pharmaceutical materials.
3. Develop a tiered system, such as is in place for <467>, based on the toxicity of the metals and require different strategies for the monitoring of the metals, including an option for the current <231> and other non-spectrophotometric techniques.

a. Sample Preparation

1. The term "compound" in the sample preparation flow chart is not an appropriate one since it usually implies a single molecular entity. Alternatively, the term "test article" could be used.
2. Many laboratories do not have a closed vessel microwave digester. This should be changed to specify only “microwave digestion”, regardless of open or closed. In addition to the cost, this equipment is not robust and requires specialized training and careful handling.
3. Add a box indicating thorough investigation of different techniques for sample pre-treatment, and at least no organic solvents before microwave digestion.
4. Sample preparation will be a challenge for some dosage forms which will require development of custom sample preparation procedures. As long as proper recoveries of the concerned elements are ensured, the testing labs should be free to use any digestion or dissolution methods deemed necessary or appropriate.
5. USP should conduct a study to develop improved methods of sample preparation where existing methods are inadequate. Sample preparation is a significant factor in the accuracy and reproducibility of results. Reproducibility is not consistent across all product types, including excipients.
6. Not all pharmaceutical substances can be brought into solution with dissolution or closed-vessel microwave digestion. Sometimes ashing/incineration or fusion is required.
7. The safety of the analyst should also be considered. The use of sulfuric acid and hydrogen peroxide in closed-vessel system can be highly explosive. Therefore the EP method c2.4.8, G> preconises to add separately the sulfuric acid and hydrogen peroxide outside the closed-vessel system and to allow to react before transferring in the closed-vessel.

b. Instrumentation

1. The equipment is too expensive. Not every laboratory can afford to buy ICP-MS to meet very low limits of detection.
2. The Atomic Absorption methodology measures only one element at a time, each element being quantified at the specific limit stated in the proposed chapter. There are currently 31 elements listed, this means many separate calibrations to be performed for only one test. The technology is time and staff consuming.
3. ICP instruments are relatively complex to operate. Operation and maintenance of these instruments requires extensive training of QC lab personnel to obtain accurate results on routine samples.
4. The variables and criteria for instrument selection are too ambiguous and open to too much interpretation.
5. It is unlikely that all 31 metals can be analyzed with one ICP/OES method, since instrumental conditions for their detection vary.
6. Osmium analysis by ICP is notoriously unpredictable.
7. Include the proposed system suitability criteria in chapter <730> Plasma Spectrochemistry.
8. ICP-OES has limitations that could affect the reliability of the data when it comes to accuracy versus ICP-MS.
9. Real-world detection limits of Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) will not be able to meet even the oral limits for Sb, As, Pb, Hg, Se, and Tl. Of course, this creates an even more problematic picture for the corresponding parenteral limits, which are 10 times lower.

10. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) has to be used to meet the limit requirements for Sb, Pb, Hg, and Tl. For As (particularly in a Cl-containing material) and Se, even a quadrupole ICP-MS will not be able to meet the required oral and parenteral limits without using some sort of collision/reaction cell technologies, or hydride generation accessories. Even high resolution (sector-field) ICP-MS, not accessible to most testing labs due to its extreme cost, can hardly meet the required oral and parenteral limits for As and Se. High resolution mode has to be used for As and Se in order to ensure interference-free analysis, thus deteriorating even further their sensitivities. As and Se exhibit much poorer sensitivities in ICP-MS than most elements in the first place due to the fact that they are both poorly ionized in the inductively coupled plasma.
11. After instrument selection, should sensitivity, precision or accuracy, etc. be measured for each sample analysis or during a method validation study?
12. In the fourth paragraph of the *Introduction*, it is stated that measurement values within +/- 20% of the certified concentrations of the reference standard are considered acceptable. However, in the sections on *Method reporting limit* and *Drift*, a criterion of +/-30% was used. This apparent inconsistency should be resolved and a consistent number should be used.
13. In *Calibration*, the requirement to use four working standards plus a blank is simply unnecessary. For Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS), the linear range is normally five to 12 orders of magnitude. One working standard plus one blank would be sufficient to ensure accurate results. There is nothing gained by using four standards relative to using just one standard.
14. The use of internal standard is dependent on the method and can be recommended but not required. Calibration is possible with more or less than four standards and should be recommended but not required.
15. The concepts for trueness and uncertainty should be further clarified by USP.
16. We have concerns with the spiked recovery, sensitivity, and individual vs total heavy metals that need clarification. Typically the heavy metals limit is for total (10- 20 ppm). Please confirm that the new limits be for each metal and that the spiked recovery study was for each and not the total?
17. The requirement for further dilution and reanalysis of the sample, if the concentration of an element in the test article solution is greater than 110% of the highest calibration standard concentration, is too restrictive. If prior knowledge of the linear range of the element is known, re-dilution and reanalysis of the sample is not necessary or required if the determined concentration is not over the linear range (even if it is over 110% of the highest calibration standard concentration).
18. The overall structures of the sections under Procedures and Methods are confusing and need to be organized so that the readers can follow easily. For example, it should begin with a scheme for sample preparation, and be followed with a set of instructions for using any one of the several instrumental methods that are currently available, including ICP-OE, ICP-MS, AA, AE, Ion Chromatography or even neutron activation.
19. The USP General Chapter <1225> ”Validation of Compendial Procedures“ defines the required characteristics for a method. There are neither *"Method Reporting Limit*" nor *"Sensitivity Criterion"* defined.
20. For the calculation of the PDE, toxicological safety factors (100 to 5'000) are considered and applied. Therefore it has absolutely no additional safety benefit to introduce the new characteristics *"Method Reporting Limit* " *and "Sensitivity Criterion".*
21. It is necessary to provide the equation to estimate the final concentration (limit) of inorganic impurities in finished products, along the same lines for limit calculation used for Class 2 Residual Solvents (General Chapter <467>).
22. The calculation equations appear to be specific to an instrument that reports a signal in micrograms or nanograms per ml. These units are derived quantities. In fact, the fundamental measure for most of the instruments covered in the article is counts, counts per second or absorbance.
23. Chapter <730> does not discuss the reagent impurity requirements and there are no reagents that can be certified to be completely free of all inorganic impurities.
24. Suggest XRF as an option in determining heavy metals. The wording can even be a little broader....."any suitable, validated methods for this metals analysis using possible instruments of ICP, XRF, etc"
25. The article says "Any procedure.....is considered to be an acceptable procedure to demonstrate compliance." What kind of validation requirements does such a procedure have to fulfill?

c. Reference Standards

1. There is not enough information provided in the *Stimuli* article to fully understand the proposed concept of performance based standards (PBS) and the composition of the performance based USP reference standards to allow an adequate determination of what types of methods will be feasible if they are required to meet performance based requirements.
2. There is a need for USP to provide certified mixtures of the different elements at the relevant concentrations.
3. Is it required to use only the USP Reference Standards or is it sufficient to use reference standards of similar quality since NIST traceable standards are available from variety of vendors?
4. The use of a USP Reference Standard is unnecessary and will result in potentially harmful exposure to analysts and release into the environment from analysis for heavy metals.
5. Using the reference materials that are not the same as the substance to be tested may induce matrix-specific effects which can appear to invalidate a truly valid analysis approach for a given material.
6. It is impractical for USP to create reference standards for all of the materials tested in *USP-NF.*
7. The verification of recoveries with *USP Reference Standards* and *Monitor Solutions* should only be necessary for the validation of user-defined procedures respectively new implemented USP methods or after a change of such validated procedures. This should be described in a separate chapter *"Development of a Specific Method."*

Implementation

1. Allow a five-year implementation timeline for existing approved products to help alleviate the financial burden of method development and optimization, procurement of new equipment and additional staff.
2. Irrespective of how the requirement for metals testing is implemented, the first step of implementation must be the acceptance of appropriate toxicologically based limits. Additionally, metals that are inherent and required in a variety of formulations (Stannous Fluoride in toothpaste, or metals in or as Dietary Supplements) would need to be addressed.
3. The EMEA Guideline differentiates between marketed products and the development of medicinal product where a higher limit might be acceptable. Is there a plan at USP to include such a differentiation?
4. USP should establish an interim period of implementation and use their Heavy Metals Project Team to evaluate potential issues with the recommended limits.
5. Allow the use of skip lot testing and testing on only those heavy metals likely to be present when sound scientific test methods and/or validated synthetic or manufacturing processes have shown to result in the removal potential metal impurities.
6. A criterion that allows non-routine testing should be added (e.g. < 30 % of Table 1 limit in six consecutive pilot plant batches or three consecutive commercial scale batches).
7. Remove the passage “regardless of the source, the control of these impurities may be certified by a vendor, but purchasers also must corroborate the absence of impurities before using these materials in manufactured article.
8. The excipient industry will require this new technology and metal specific limits. Every excipient supplier will not have this technology and it will cause mayhem in the industry, basically falling on the shoulders of Pharma to control and maintain compliance, etc. In addition, like BHA and BHT, excipient suppliers may decide to pull the USP-NF designations from their product, as this can be a huge burden and hold up for release testing.
9. USP should work with excipient manufacturers and API manufacturers and require them to identify any catalysts which are used in the manufacture of their product and additional sources of heavy metals of concern based on toxicity (e.g., lead) which may be present in their product. If the levels are proven, by the manufacturer to be sufficiently low, no additional testing should be required by the recipient company.

10. Since metal residues may originate from several sources it seems to be difficult for manufacturers of drug substances or excipients to perform tests in the whole extent. It should be discussed to assume the explanation of the EMEA "Guideline on the specification limits for residues of metal catalysts (EMEA/CHMP/SWP/4446/2000)" as follows:

    "Since the origin of metal residues is irrelevant regarding their potential toxic effects, the concentration limits in this guideline are in principle also applicable to residues from other sources than catalysts and reagents. However, for these other sources adoption of a concentration limit and a validated method in the specification is only necessary in the very exceptional cases where these residues are known to be insufficiently limited by GMP, GDP or any other relevant provision. Pharmaceutical companies are not supposed to perform extensive tests on metal residue findings of unknown sources to comply with this guideline. They may rely on general information from trustworthy suppliers."

    - In which cases a routine test is required? Can it be replaced by a non-routine (skip) testing?
    - How can the absence of a routine test be supported? It should be discussed to assume the explanation of the EMEA Guideline as follows:

    "If the synthetic or manufacturing processes have shown to result in the removal of a potential metal residue, routine testing of that metal residue may be replaced by non-routine (skip) testing. A metal residue can be considered adequately removed if in six consecutive pilot scale batches or three consecutive industrial scale batches less than 30% of the appropriate concentration limit was found."