White Paper 71654

Understanding New USP Chapter <2232> for Trace Elemental Contaminants in Dietary Supplements and Nutraceutical Products

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Introduction

This white paper is intended to help the dietary supplements and nutraceutical industries better understand the new methodology described in United States Pharmacopeia (USP) Chapter <2232>, which sets limits for elemental contaminants in dietary supplements. The objective is to offer guidance on the best technique to use for this application and to provide guidance in how to optimize the analytical procedures in order to meet the requirements of the regulatory agencies involved.

Mission of the USP

The USP is an internationally-recognized scientific organization that sets standards for medicines, food ingredients and dietary supplements manufactured and distributed throughout the world. USP's drug standards are used in more than 140 countries. The Food and Drug Administration (FDA) is responsible for enforcing all USP regulations in the United States.

Since the USP was first formed, one of its main missions has been to help manufacturers and suppliers of dietary supplements ensure the quality and purity of their products, by providing appropriate standards and reference materials through its compendium of pharmacopeial standards and National Formulary (USP-NF). These standards help limit the introduction of potential contaminants and adulterants, and serve as a quality benchmark in the buying and selling of dietary supplement products and their ingredients in the global marketplace.

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Overview of USP Chapter <2232>

One of the most significant standards introduced by the USP in the past five years has been to set limits for the four elemental contaminants in dietary supplements: arsenic (As), cadmium (Cd), lead (Pb) and mercury (Hg). The new limits are summarized in the USP-NF General Chapter <2232>[1] which replaces Chapter <231>,[2] a hundred-year old heavy metals colorimetric test based on metal sulfide precipitation which is visually compared to a lead standard. Chapter <2232>, together with Chapters <232>,[3] which sets limits for elemental impurities in pharmaceutical materials, and Chapter <233>,[4] which describes the two plasma-based analytical procedures suitable for both Chapters, have recently gone through a lengthy evaluation, review and approval process.

Even though Chapter <2232> was approved in August 2013, and is currently published in the second supplement to USP37-NF32, final implementation is waiting on the approval of Chapter <233>, which has stalled due to concerns by other international pharmacopeias about permitted daily exposure (PDE) limits defined in Chapter <232> and a disagreement with the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) about the alignment process. In addition, there has been pushback from the industry in the U.S. because it considers the timelines for implementation of all three chapters to be far too ambitious.

It is important to emphasize that Chapter <2232> is for informational and guidance purposes only (as in all USP chapters above 1000). It is at the discretion of the regulatory agency (FDA in the U.S.), whether they would require dietary supplement and nutraceutical manufacturers or suppliers of raw materials to comply with the full testing procedures described in the chapter, when it is eventually implemented.

Implementation of Methodology

Based on recent USP communications,[5] and guidelines from the ICH whose goal is to harmonize the regional variations into a standard global method,[6] it is expected that all three chapters will be fully implemented on January 1, 2018. This means that as of the publication date of this white paper, U.S. manufacturers of pharmaceutical products and dietary supplements have approximately 2½ years to adopt these new methods. This has stimulated a great deal of activity by the pharmaceutical and nutraceutical industries to invest in either ICP-OES or ICP-MS instrumentation to ensure they have all their methods and procedures in place before the final implementation date. In addition, in the state of California, Proposition 65 mandates that manufacturers and suppliers of nutraceutical products ensure that their herbal and dietary supplements contain less than defined maximum allowable levels (MAL) of four heavy metals to ensure they are safe for human consumption.[7,8] However, it is expected that the PDE limits defined in Chapter 2232 will take precedence over Proposition 65 MALs. Table 1 shows a comparison of the PDE limits defined in USP Chapter 2232 together with Proposition 65 maximum levels. Table 2 shows the component limit of any single ingredient or individual raw material based on a dosage of 10 grams of dietary supplement per day. The product meets the requirements when each component used in production of the finished dietary supplement meets the limits given in the table.

It should be noted that arsenic may be measured using a non-speciation procedure, under the assumption that all arsenic contained in the supplement is in the inorganic form. If the arsenic limit is exceeded using a non-speciation procedure, compliance with the limit for inorganic arsenic shall be demonstrated on the basis of a speciation procedure by using an IC-ICP-MS or a HPLC-ICP-MS system. Likewise, methyl mercury determination is not necessary when the content for total mercury is less than the limit for methyl mercury. When the total mercury content is higher than the methyl mercury limit, a speciation method is required.

Figure 1. Thermo Scientific™ iCAP™ RQ ICP-MS.

Table 1. USP Permitted Daily Exposure (PDE) Limits and California Proposition 65 NSRL (No Significant Risk Levels for carcinogens) and MADL (Maximum Allowable Daily Levels) for the four heavy metals.

Elemental Contaminant	USP Chapter <2232> PDE (µg/day)[1]	Safe Harbor Levels Under California Proposition 65 (µg/day)[7,8]
Arsenic (Inorganic)		10 (NSRL)
Cadmium	5	4.1 (MADL)
Lead	10	15 (NSRL)
Mercury	15 (total)	—
Methyl Mercury	2	0.3 (MADL)

Table 2. Individual component limit of any single raw material used in the manufacture of the dietary supplement.

Elemental Contaminant	USP Chapter <2232> Individual Component Limit (µg/g) Based on a Dosage of 10 g/day
Arsenic (Inorganic)	1.5
Cadmium	0.5
Lead	1.0
Mercury	1.5 (total)
Methyl Mercury	0.2

Chapter 2232 Requirements

In order for a dietary supplement to comply with the limits for elemental contaminants as described in this chapter, the levels in the finished product should be no more than the PDE limits. The following three options are available for determining compliance with the limits for elemental contamination in dietary supplements:

Finished Product Option

In this option, the finished dietary supplement is analyzed according to the procedure in Chapter <233>.The results obtained from the analysis of a typical serving size, based on the maximum daily dosage of the supplement recommended on the label (servings/day) should be no more than the PDE values shown in Table 1.

Individual Component Option

This option is applicable to a finished dietary supplement with a maximum daily intake of less than 10 g of the finished product. Carry out the analysis of the individual ingredients of the dietary supplement. The product meets the requirements when each component used in production of the finished product meets the limits given in the Table 2.

Summation Option

This option can be used for the finished dietary supplement dosage that is consumed in quantities greater than 10 g/day, or where the acceptance limit for any contaminant in any component of the dietary supplement exceeds the individual component limit. Carry out the analysis of the individual ingredient and calculate the amount of each elemental contaminant (in µg/daily dosage) present in the dietary supplement. The amount of each elemental contaminant in the daily dosage should be no more than the PDE values given in Table 1.

USP General Chapter <233>

General Chapter <2232> contains no information on how to carry out the analysis of the dietary supplements. The nutraceutical analytical community must become familiar with Chapter <233>, which deals with the sample preparation, instrumental method and validation protocols for measuring the elemental contaminants using one of two plasma based spectrochemical techniques – Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) or Inductively Coupled Plasma Mass Spectroscopy (ICP-MS) – or any other alternative technique, as long as it meets the data quality objectives of the method defined in the validation protocol section. In addition, before any technique is used, it must be confirmed that the overall analytical procedure is appropriate for the instrument being used and the samples being analyzed by meeting the Alternative Procedure Validation described in this chapter. Analytical procedures for the determination of the oxidation state, organic complex, or speciated form of the elemental impurity are not included in this chapter, but examples may be found elsewhere in USP–NF and in the open literature. Let's take a closer look at the methodology described in Chapter <233>.

Sample Preparation Procedures

The selection of the appropriate sample preparation procedure will be dependent on the material being analyzed and is the responsibility of the analyst. The procedures described below have all shown to be appropriate for both pharmaceutical- and nutraceutical-type materials.

Neat

This approach is applicable for liquids that can be analyzed with no sample dilution.

Direct Aqueous Solution

This procedure is used when the sample is soluble in an aqueous solvent.

Direct Organic Solution

This procedure is appropriate where the sample is soluble in an organic solvent.

Indirect Solution

This is used when a material is not directly soluble in aqueous or organic solvents. It is preferred that a total metal extraction sample preparation be carried out in order to obtain an indirect solution, such as open vessel acid dissolution or a closed vessel approach (eg: microwave digestion), similar to the one described below. The sample preparation scheme should yield sufficient sample volume to allow quantification of each element at the elemental impurity limits specified in Chapter <232>.

Closed Vessel Digestion

The benefit of closed vessel digestion is that it minimizes the loss of volatile impurities. The choice of which concentrated mineral acid to use depends on the sample matrix and its impact on any potential interferences on the analytical technique being used. An example procedure that has been shown to have broad applicability is described below:

Accurately weigh 0.5 g of the dried sample in an appropriate flask and add 5 mL of the concentrated acid. Allow the flask to sit loosely covered for 30 minutes in a fume hood then add an additional 10 mL of the acid, and digest using a closed vessel technique until digestion is complete (please follow the manufacturer's recommended procedures to ensure safe use. Make up to an appropriate volume and analyze using the technique of choice.

Alternatively, a leaching extraction may be appropriate as long as it is scientifically validated metal dissolution studies of the specific metal in the drug product under test.

Detection Technique

Two analytical procedures are suggested in this Chapter. Where elemental contaminants are typically at the parts-per-million level in the diluted sample, ICP–OES is the recommended technique. For elemental contaminants at the parts-per-billion level or lower in the diluted sample, ICP–MS is the preferred technique. The chapter also describes criteria for an alternative procedure as long as it meets the validation requirements laid-out in the chapter. Whichever technique is used, the analyst should verify that the procedure is appropriate for the instrument and samples being analyzed by meeting the Procedure Validation requirements described below.

Validation Protocol

All analytical procedures, including ICP-OES, ICP-MS and alternative procedures must be validated and shown to be acceptable, in accordance with the validation protocol. The level of validation necessary depends on whether a limit test or a quantitative determination is specified in the individual monograph. The requirements for the validation of an elemental contaminant procedure for each type of determination are described below. Any alternative procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use.

Acceptability of Analytical Procedures

The following section describes the validation protocols for the suitability of an analytical procedure to monitor the PDE limits. Meeting these requirements must be demonstrated experimentally with an appropriate system suitability procedure using reference materials. The suitability of the method must be determined by conducting studies with the material under test supplemented/spiked with known concentrations of each target element of interest at the appropriate acceptance limit concentration. It should also be emphasized that the materials under test must be spiked before any sample preparation steps are performed.

Suitability of Technique

To understand the suitability of the technique being used and whether its detection capability is appropriate for the analytical task, it's important to know the PDE limit for each target element, and in particular, what the USP calls its J value. In Chapter <233>, the J-value is defined as the PDE concentration of the element of interest, appropriately diluted to the working range of the instrument, after the sample preparation process is completed.

So let's take the determination of Pb by ICP-MS as an example. The PDE limit for Pb defined in Chapter <2232> is 5 µg/day. Based on a suggested dosage of 10 g of the drug product/day, that's equivalent to 0.5 µg/g Pb. If 0.2 g of sample is digested/dissolved and made up to 100 mL, that's a 500-fold dilution, which is equivalent to 1 µg/L. So the J value for Pb in this example is equal to 1 µg/L.

The method then suggests using a calibration made up of 2 standards: Standard 1= 2.0J, Standard 2= 0.5J. So for Pb, that's equivalent to 2 µg/L for Std 2 and 0.5 µg/L for Std 1.

The suitability of a technique is then determined by measuring the calibration drift by comparing results for Standard 1 before and after the analysis of all the sample solutions under test. This calibration drift should be <20% for each target element.

It should also be pointed out that no specific instrumental parameters are suggested in this section, but only to analyze according to the manufacturer's suggested conditions and to calculate and report results based on the original sample size. However, it does say that appropriate measures must be taken to use a sample weight that's optimum for the technique being used, to ensure that the sample matrix does not produce any deleterious effects on the sample introduction components that might negatively impact signal stability. In addition, it suggests that suitable correction procedures should be employed for minimizing interferences, such as matrix-induced wavelength overlaps in ICP-OES and argon-based polyatomic interference with ICP-MS. For guidance, it references the use of *General Chapter <730> on Plasma Spectrochemistry*,[9] which is a general method in the USP-NF describing both ICP-OES and ICP-MS, techniques for the determination of elemental impurities in pharmaceutical materials.

The suitability of the technique and analytical procedure is then determined by a set of validation protocols, which cover a variety of performance and quality tests, including:

- Detectability
- Precision
- Specificity
- Accuracy
- Ruggedness
- Limit of Quantification
- Linear Range

Each test is explained in great detail in Chapter <233>, In the following sections, we give a brief description of each one. It should also be noted that where appropriate reference standards are specified in the chapter, certified reference materials (CRM) from a national metrology institute (NMI) or reference materials that are traceable to that CRM should be used. An example of an NMI in the United States is the National Institute of Standards and Technology (NIST).

Instrumental Detectability

This section deals with both non-instrumental and instrumental detectability. However for clarity purposes, we will just describe the instrumental test.

- Prepare a *Standard Solution* of target elements at J and a matrix matched blank
- Prepare an *Unspiked Sample*
- Prepare a sample spiked at 1.0J – *Spiked Sample Solution 1*
- Prepare a sample spiked at 0.8J - *Spiked Sample Solution 2*

The technique/procedure is considered acceptable when:

- *Spiked Sample Solution 1* gives a signal intensity equal to or greater than the Standard Solution
- *Spiked Sample Solution 2* gives a signal intensity less than the *Spiked Sample Solution 1*
- The signal for each *Spiked Sample* is not less than the *Unspiked Sample*

Precision/Repeatability

- Prepare six separate test sample solutions and spike each one at a target concentration of 1.0J
- Acceptance criterion: RSD for the six individual samples should be < 20%

Specificity

The procedure, sometimes referred to as selectivity must be able to assess the impact of each target element in the presence of other components that may be present in the sample, including other target elements, matrix components, and other interfering species. It refers to USP-NF General Chapter <1225>Validation of Compendial Procedures[10] for guidance.

Accuracy

This test is designed to assess the accuracy of the analytical method/procedure and in particular when samples are above the normal calibration range.

- Prepare standard solutions containing target elements at concentrations ranging from 0.5J to 2.0J using suitable calibration/reference materials
- Run calibration using calibration standards
- Prepare samples under test by spiking at concentrations from 0.5J to 2.0J before any sample preparation is carried out

The technique/procedure is considered acceptable when:

- The spike recovery of three replicates at each sample concentration is between 70%-150%

Ruggedness

The effect of random events on the analytical precision of the method shall be established by performing the 'Repeatability' test:

- On different days or
- With different instrumentation or
- With different analysts

Note

It should be emphasized that only one of these three experiments is required to demonstrate ruggedness.

Acceptance Criterion

RSD should be <25% for each element

Limit of Quantification (LOQ) and Linear Range

The LOQ and linear range capability is demonstrated by meeting the Accuracy requirement.

Selection of the Appropriate Technique

So which technique is best for elemental contamination levels typically found in dietary supplements? For an experienced user with both ICP-OES and ICP-MS in their laboratory, it might be straight forward, based on the operator's knowledge and understanding of each technique. However, for new users who have been given the task of evaluating and purchasing a new instrument to carry out this analysis, they will clearly want an instrument that will be suitable for the task in hand, keeping in mind that there might be budgetary restrictions. Additionally, there is the expertise of the people in the lab to take into consideration and whether they are capable of developing methods and operating the instrument on a routine basis. The cost of equipping the lab to ensure the optimum operation of such a sophisticated and sensitive instrument is also an important factor to consider.

So let's take a more detailed look at the detection capability of axial ICP-OES[11] and ICP-MS[12] techniques for compliance purposes in nutraceutical materials. And in particular, taking the 4 elemental contaminants defined in Chapter <2232> and comparing instrument detection limits (IDLs) with the calculated J-values for a dietary supplement with a maximum oral daily dose of 10 g/per day. The comparison data for axial ICP-OES and ICP-MS are shown in Tables 3 and 4 respectively, based on an optimum sample preparation/dilution factor of 2 g/100 mL for ICP-OES and 0.2 g/100mL for ICP-MS. The Factor Difference in the final column, which is the J-value divided by the IDL, is a good indication of whether the elemental target concentrations can be determined with good accuracy and precision. The higher this value, the more reliable the result. It should be emphasized that IDLs are not a true reflection of the measurement capability of the technique in real samples. It is generally accepted that a method detection limit (MDL), where a blank is taken through the entire sample preparation process, is a better assessment of the limit of detection (LOD) in the sample matrix under test. However, the IDLx10 is often used as a good approximation of this value.

Thermo Scientific™ iCAP™ 7000 ICP-OES Analyzer (left)

iCAP Q ICP-MS (right)

Table 3. USP J-values compared to axial ICP-OES IDLs.

Element	PDE (µg/day)	Concentration Limits (µg/g) for a Supplement with a Maximum Daily Dose of ≤10 g/day	1.0J-Value (µg/L) Based on a Supplement Dose of 10 g/day and a Final Sample Dilution of 2 g/100 mL	Axial ICP-OES Instrument Detection Limits[11] (µg/L)	Factor Difference (J-Value/IDL)
Cadmium	5.0	0.5	10	0.07	143
Lead	5.0	0.5	10	1.06	9
Arsenic (Inorganic)	15	1.5	30	1.43	21
Mercury (Inorganic)	15	1.5	30	0.14	214

Table 4. USP J-values compared to ICP-MS IDLs.

Element	PDE (µg/day)	Concentration Limits (µg/g) for a Supplement with a Maximum Daily Dose of ≤10 g/day	1.0J-Value (µg/L) Based on a Supplement Dose of 10 g/day and a Final Sample Dilution of 0.2 g/100 mL	ICP-MS Instrument Detection Limits[12] (µg/L)	Factor Difference (J-Value/IDL)
Cadmium	5.0	0.5	1.0	0.0001	10,000
Lead	5.0	0.5	1.0	0.0009	1111
Arsenic (Inorganic)	15	1.5	3.0	0.0009	3333
Mercury (Inorganic)	15	1.5	3.0	0.0099	303

Table 3 shows that axial-ICP-OES offers some possibilities for monitoring dietary supplements because the improvement factors of all four elements are higher than one. These numbers could be further improved, by using a much higher sample weight in the sample preparation procedure without compromising the method. As all commercially-available ICP-OES instrumentation has both axial and radial capability, we determined that the axial performance was most appropriate for this comparison.

In addition, it can be seen in Table 4 that ICP-MS shows significant improvement factors for all four contaminants, over the ICP-OES technique. The added benefit of using ICP-MS is that if the total arsenic or mercury levels are found to be higher than the PDE levels, it is relatively straightforward to couple ICP-MS with HPLC to monitor the speciated forms of these elements.

In Summary

The objective of this white paper is to educate the dietary supplement and nutraceutical manufacturing communities on the new USP Chapter<2232> on setting limits on elemental contaminants in dietary supplements and on Chapter <233>, describing the analytical procedure to carry out the determinations. In particular it has been targeted at personnel, who are not familiar with the terminology used in the USP methods and also to offer some suggestions about the best instrumental technique and analytical procedures to use.

It will be interesting to see how USP methodology will eventually be aligned with ICH directives, but the recent announcement delaying implementation should not discourage global nutraceutical manufacturers to have appropriate analytical capability in place as soon as possible in order to show compliance to regulators that their products are free from elemental contamination. For up-to-date information on these new chapters, please check the Key Issues page on USP elemental impurities website.[13] In addition, Thermo Scientific has its own USP Landing Page which gives the most recent status of the USP and ICH alignment process, together with product solutions to meet these directives.[14]

Thermo Scientific has various instruments to test for elemental contaminants in dietary supplements that are mentioned in this white paper. For more information on the products visit the links below.

ICP-OES: http://www.thermoscientific.com/en/products/inductively-coupled-plasma-optical-emission-spectrometry-icp-oes.html

ICP-MS: http://www.thermoscientific.com/en/products/inductively-coupled-plasma-mass-spectroscopy-icp-ms.html

IC-ICP-MS: http://www.thermoscientific.com/en/products/modular-systems.html

LC-ICP-MS: http://www.thermoscientific.com/en/products/hplc-uhplc-systems.html

Other Resources

IC-ICP-MS for Speciation Analysis

White Paper: http://www.thermoscientific.com/content/dam/tfs/ATG/CMD/cmd-support/icap/7000/whitepapers/WP70553_Final.pdf

White Paper: http://www.thermoscientific.com/content/dam/tfs/ATG/CMD/cmd-support/icap/7000/whitepapers/WP-IC-ICP-MS-Elemental-Speciation-WP70481_E.pdf

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