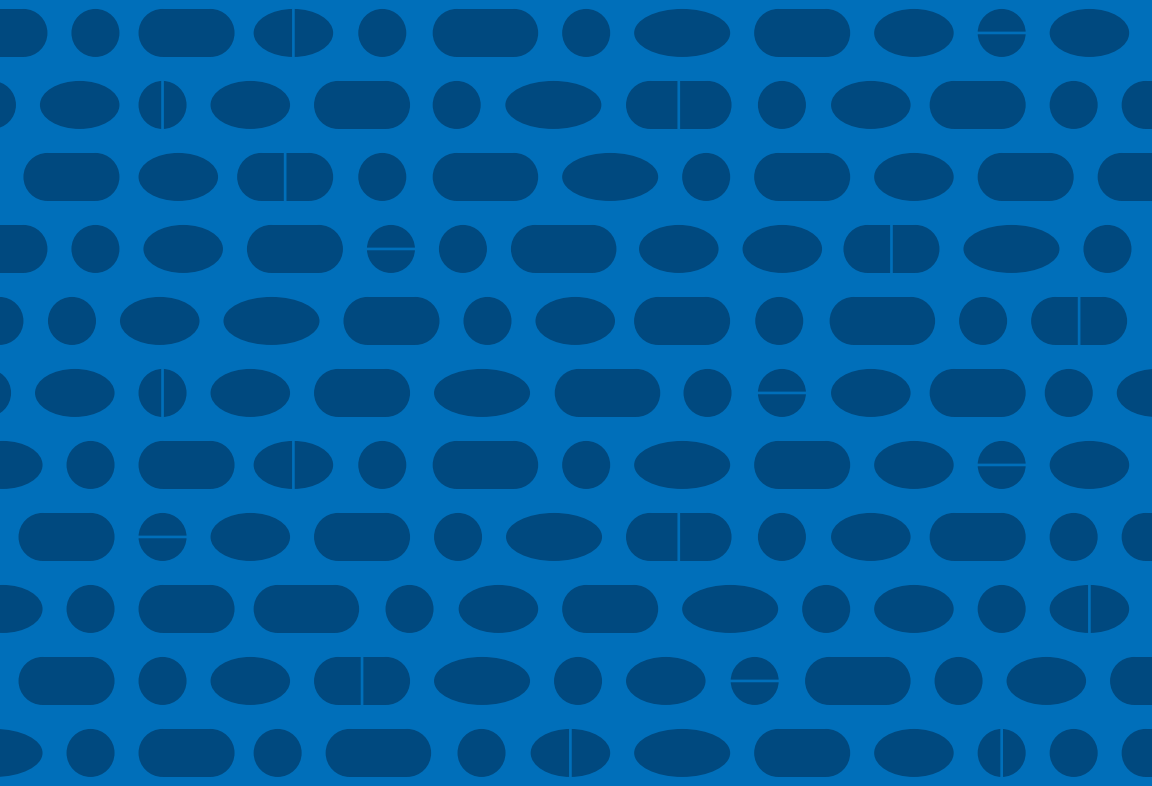
Complete Sample Preparation Guide for Analysis of Elemental Impurities

USP 232/233, 2232

ICH Q3D Step 4 Guidelines



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Introduction

This guide is intended to help the pharmaceutical industry to better understand the new methodology described in USP Chapters <232> and <233> for the determination of elemental impurities in drugs, drug products and drug raw materials. The objective is to educate quality control and production personnel about permitted daily exposure (PDE) levels, based on routes of administration defined in Chapter <232> and how samples should be characterized using the analytical procedures described in Chapter< 233>. The guide will also offer suggestions as to the most convenient way to get the samples into solution together with the best instrumental technique to use in order to comply with these guidelines and meet the requirements of the regulatory agencies involved.

In addition, for background information purposes, it's important to understand how the USP works and the process of updating compendial methods. We will therefore give an overview of the USP mission and provide an historical perspective of heavy metals testing and why the traditional methodology using Chapter 231 is being replaced by Chapters <232> and <233>. The guide will also discuss the current approval status of the chapters, together with the role of the International Conference on Harmonization (ICH), a consortium of pharmaceutical industries from Europe, Japan, and the US which has its own guideline for elemental impurities in pharmaceuticals for human use. In particular it will discuss the proposed alignment process of the USP methods with the ICH guidelines and how it's impacting the global pharmaceutical industry.

Mission of the USP

The U.S. Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed throughout the world. Since its founding in 1820, USP has helped secure the quality of the American drug supply, and building on that legacy, today it works with scientists, practitioners, and regulators of many nations to develop and revise standards that help protect public health worldwide. USP's standards are recognized and used in more than 130 countries, and have helped to ensure public health throughout the world for almost 200 years. In the United States, USP's drug standards are enforceable by the Food and Drug Administration, whereas outside the US, other global pharmacopeial and regulatory agencies have that responsibility.

USP publishes its public pharmacopeial standards through the USP–NF, which is combination of two compendia - United States Pharmacopeia (USP) and The National Formulary (NF). The USP was originally published in 1820 as the Pharmacopoeia of the United States of America, a compendium containing monographs for drug substances, drug products, biologics, biotechnology products, dietary supplements, test methodology, and general information used

to establish quality standards for products that are marketed in the United States (1). Whereas, the NF which was originally published as a separate collection of standards by the American Pharmaceutical Association was purchased by USP and merged into one volume with USP in 1974. Today, the NF section of the compendium contains mostly monographs for items which are typically used only as excipients.

The U.S. FDA designates the USP–NF as the official compendia for drugs marketed in the United States, which must conform to the standards in USP–NF to avoid possible charges of adulteration and misbranding. USP creates and continuously revises USP–NF standards through a unique public–private collaborative process, which involves scientists in industry, academia, and government as well as other interested parties from around the world. The complete USP-NF is revised and updated on an annual basis and its contents become official on May 1 every year.

Heavy Metal Testing

Although the risk factors for heavy metal contamination have changed dramatically, standard methods for their testing and control have changed little for more than 100 years, and as a result, most heavy metals limits had little basis in toxicology. For that reason, one of the most significant standards introduced by the USP in the past seven years has been new methodology for determining elemental impurities in drug products. The new methods, which are based on plasma spectrochemistry, have been summarized in the USP-NF General Chapters <232> (2) and <233> (3) for pharmaceutical products. These two methods will be replacing Chapter<231> (4) a hundred-year old colorimetric test for heavy metals based on precipitation of the metal sulfide in a sample, and comparing it to a lead standard. Let's take a closer look at the method described in Chapter <231>.

Chapter 231

Colorimetric analytical methods have been in use for pharmaceutical materials for over 100 years and are based on measuring color changes of solutions that arise from specific chemical interactions with the analyte elements. The most familiar colorimetric test relevant to analysis of heavy metals is described in the USP-NF General Chapter <231> for heavy metals. The current test is based on a chemical reaction of the heavy metal and compared with a standard prepared from a stock lead solution. It relies on the ability of heavy elements such as lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum to react with thioacetamide, (an organic-based sulfur compound) at a pH of 3-4 to produce a precipitate of the metallic sulfide that is then compared with a lead standard solution. It is used to demonstrate that the metallic impurities colored by sulfide ions under the specific test conditions do not exceed a limit of 10 ppm.

One of the many drawbacks of this approach is the assumption that formation of the sulfides in the sample is very similar to the formation of the lead standard solution and is not affected by the sample matrix. However, since many metals behave very differently, the method requires that the visual comparison is performed very quickly after the precipitate has formed. Unfortunately, analysts can differ in their interpretation of the color change, so different analysts may not consistently read the sample and standard solutions correctly each time.

Another limitation of the technique is that the sample preparation procedure, involving ashing at high temperature and acid dissolution of the sample residue, is prone to sample losses particularly for the volatile elements like mercury. The loss of metals is also matrix-dependent, and because the procedures are time-consuming and labor-intensive, recoveries can vary significantly among differing analysts.

Another colorimetric test, specifically for lead, is described in Chapter <251> (5). This procedure, which selectively extracts Pb from the sample, is extremely

long and uses sulfuric acid, hydrogen peroxide, potassium cyanide, and precipitates lead as the sulfide using dithizone, and carries out an extraction using chloroform. The disadvantages are very similar to the heavy metals test described in Chapter <231> including inconsistent results, and poor detection limit, which again calls into question the usefulness of this method for meeting specifications at very low levels. In addition, it's limited specifically to lead, so the rest of the heavy metals, including arsenic (6), and mercury (7) have their own methods.

The Process for Change

In 2008, the USP supported a workshop at the Institute of Medicine (IOM) and the National Academy of Sciences (NAS) to address limitations of specifications for metals testing as described in Chapter <231> of the USP. The IOM independently formed a committee consisting of individuals with recognized expertise in the areas of risk assessment, analytical methodology, and toxicological science as related to metals testing and exposure. The committee was given a directive to develop and conduct a workshop that would provide the basis for USP to advance its specifications for metals testing. In addition, the committee was asked to involve experts from Europe and Japan, with the goal of coming up with common specifications and analytical procedures for metals testing which would be accepted by the global pharmaceutical and nutraceutical communities. A general consensus by experts at the workshop was that the current methodology for metals testing was inadequate and should be replaced by instrumental methods of greater specificity and sensitivity for a wide range of metals of interest. At the same time, it was acknowledged that with current state-of-the-art methods, metals can be detected at levels much lower than any clinical or toxicological importance. The challenge therefore represented the coupling of method capability, risk assessment, and likelihood of presence of metals of interest in a manner that best protects the public health.

Due to known toxic effects and demonstrated potential for contamination in pharmaceutical ingredients, there was general agreement that lead, mercury, arsenic, and cadmium should be detectable at toxicologically relevant

concentrations. In addition, consistent with the EMA "Guideline on the Specification Limits for Residues of Metal Catalysts", (8) platinum, palladium, ruthenium, rhodium, and rubidium should be detectable based on the likelihood of presence and toxicity. A wider range of metals may be used as organometallic reagents. There was some discussion about the appropriateness of testing for these metals, with a common view that if they were used in a manufacturing process and therefore at risk for presence, that a limit for the specific metal used in the manufacturing process may be required.

Current analytical methods permit the simultaneous detection of a large number of metals and other elements. However, it is unclear how many of these other elements should be included in a pharmacopeial specification. In some instances there is some likelihood of presence (e.g. iron, copper); however, the metal has low toxic potential, while in other instances the element is known to be toxic (e.g. beryllium, uranium), but the likelihood of it being present is very low.

The overall conclusion was that a major revision of USP <231> was strongly recommended. Additionally, further consideration of limits for the testing of other metals associated with the manufacturing process was necessary. It was also a goal that serious effort would be made to harmonize approaches to metals testing across the major pharmacopeias across the world. These efforts would then go forward as a public process, with input sought from the various stakeholders at each step of the implementation process.

Proposed New USP Methodology

The USP proposed two new General Chapters covering elemental impurity limits (Chapter <232>), and analytical procedures (Chapter <233>) in pharmaceutical products and raw materials, which they published in two Stimuli articles outlining the rationale for the revisions and the comments received (9).

These revisions focused on two main areas of work:

- Updating the methodology used to test for elemental impurities in drugs and drug products to include procedures that rely on modern analytical technology

- Setting limits for acceptable levels of metal impurities (including, but not limited to, lead, mercury, arsenic, and cadmium) in drugs and drug products

The USP Metal Impurities Expert Panel, which reported into the USP Chemical Analyses Expert Committee, worked with USP staff and stakeholders to assess methodologies and limits that provide greater patient/consumer protection and could reasonably be deployed across industry laboratories. The limits for exposure should be toxicologically-based and be developed by an expert consensus process to provide quality standards that reflect consensus views about potential health/toxicity concerns. These new chapters were intended to replace the existing methods in General Chapter <231> for Heavy Metals. USP moved forward with these new chapters, gathering comments from the pharmaceutical and nutraceutical manufacturing industries, analytical instrumentation user community, regulatory agencies and other interested global parties. However, based on feedback from all these different stakeholders, there was a certain amount of pushback because the timelines for implementation were considered far too ambitious. Additionally, there were also concerns by the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) about the number of elemental impurities and their permitted daily exposure (PDE) limits defined in Chapter <232>. For this reason, there have been a number of revisions to both Chapter <232> and <233>, which have resulted in implementation timelines being modified and changed a number of times.

However, an announcement by the USP in January 2015 established January 1, 2018 as the new date of applicability of General Chapters <232>, and <233> (10, 11), which was intended to align them more closely with limits and timelines set down by other global pharmaceutical and medical agencies and in particular the Q3D Step 4 Guidelines for Elemental Impurities recently announced by the ICH on December 16, 2014 (12). Through these changes the USP stated that users could either continue to utilize the existing Chapter <231> approach or implement the methodology outlined in the new chapters. The most recent announcement in March, 2016, indicated that the USP will be engaging in an ongoing dialogue with the pharmaceutical industry, the Food and

Drug Administration, together with representatives from the ICH to ensure this alignment process goes as smoothly as possible. To get a better understanding of these issues, let's take closer look at the mission of the ICH and the critical role it has played in helping to guide the USP implementation process.

Role of the ICH

The realization that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times by the global pharmaceutical community. For most countries, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicines. The industry, at the time, was becoming more international and seeking new global markets. However the divergence in technical requirements from country to country was such that the industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products for global use. The urgent need to rationalize and harmonize regulation was also impacted by concerns over rising costs of health care, escalation of the cost of R&D and the need to meet the public expectation that there should be safe and efficacious new treatments available to patients in a timely manner.

Harmonization of regulatory requirements was pioneered by the European Union in the 1980s, as it moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonization was feasible. At the same time there were discussions between Europe, Japan and the United States on possibilities for harmonization. It was, however, at the World Health Organization (WHO) Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, (13) that specific plans for action began to materialize. Soon afterwards, the authorities approached the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) (14) to discuss a joint regulatory-industry initiative on international harmonization, and as a result, the ICH was conceived (15).

Since then, the ICH has played a unique role in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development, so that the benefits of international harmonization for better global health can be realized worldwide. ICH's mission is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

New Global Standards

A final concept paper published in 2009 by the ICH Expert Working Group (EWG), entitled "Guideline for Elemental Impurities" proposed that a new harmonized guideline be developed to provide a global policy for limiting metal impurities in drug products and ingredients. The existing ICH Q3A Guideline classifies impurities as organic, inorganic, and residual solvents. The Q3A and Q3B Guidelines effectively addressed the requirements for organic impurities, while Q3C was developed for residual solvents. The proposed new Guideline, Q3D would provide similar clarification of the requirements for metals.

A harmonized approach for control of metal impurities, including the list of specific metals to be limited and the appropriate limits for these metals, would be beneficial to help avoid the uncertainty and duplication of work for industry to meet requirements that may otherwise differ between the different ICH regions. Some regulatory guidance on specification limits for residues of metal catalysts and reagents was recently provided by Europe, but similar regulatory guidance had not yet been provided from the US or Japan for public review. An ICH Guideline would ensure that new requirements have the necessary input of the regional regulatory authorities, to the benefit of regulators, industry, and public health. An ICH Guideline for metal impurities would emphasize control of supply chains and risk assessment, as was done for residual solvents.

Also consistent with the existing Q3C Guideline, a new Q3D Guideline would focus on the establishment of appropriate limits for specific metals, without necessarily providing details on the analytical procedures to be used. In support of the Q3D Guideline, harmonized analytical procedures should be established by the pharmacopoeias for determining levels of metal impurities, with allowance for use of any appropriate validated procedure for a particular application. It was preferable that interested parties participate in the effort to achieve initial agreement on metal impurities, rather than the regulators and the pharmacopoeias reaching independent decisions which would necessitate subsequent harmonization. Ultimately, a harmonized guideline would provide appropriate safety-based limits for the control of metal impurities, along with consistent expectations for test requirements and regulatory filings.

In order to provide benefit to public health, it was also envisioned that a safety-based approach would be taken for the control of metal impurities. It was especially important to establish appropriate controls for those metals with clearly established toxicological concerns. These metal impurities may arise from the drug substances, excipients, or manufacturing processes used for drug products, and may include catalysts, reagents, ligands, heavy metals or other residual metals. With a focus on safety of the finished dosage form provided to the patient, a new ICH Guideline would assure appropriate control for the specific metals that are likely to be present in particular drug products and ingredients.

ICH Q3D Guidelines for Elemental Impurities

The ICH published the final version of the “Guidelines for Element Impurities” in its Q3D Step 4 document which came out in December 16, 2014, which categorized the various elemental impurities in four different classifications which were intended to facilitate decisions during the risk assessment process. The complete list of 24 elements is shown in **Table 1**.

Element	Class	Oral PDE µg/day	Parenteral PDE µg/day	Inhalation PDE µg/day
Cd	1	5.0	2.0	2.0
Pb	1	5.0	5.0	5.0
As	1	15	15	2.0
Hg	1	30	3.0	1.0
Co	2A	50	5.0	3.0
V	2A	100	10	1.0
Ni	2A	200	20	5.0
Tl	2B	8.0	8.0	8.0
Au	2B	100	100	1.0
Pd	2B	100	10	1.0
Ir	2B	100	10	1.0
Os	2B	100	10	1.0
Rh	2B	100	10	1.0
Ru	2B	100	10	1.0
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1.0
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3.0

Table 1: ICH Permitted Daily Exposures for Elemental Impurities

Unlike USP Chapter <232>, in the ICH Guidelines, the impurities are categorized based on their risk assessment.

Class 1: The elements, As, Cd, Hg, and Pb, are human toxicants that have limited or no use in the manufacture of pharmaceuticals. Their presence in drug products typically comes from commonly used materials (e.g., mined excipients).

Class 2: Elements in this class are generally considered as route-dependent human toxicants. Class 2 elements are further divided in sub-classes 2A and 2B based on their relative likelihood of occurrence in the drug product, with Class 2A most likely and 2B least likely

Class 3: The elements in this class have relatively low toxicities by the oral route of administration but may require consideration in the risk assessment for inhalation and parenteral routes.

It's also important to understand that the ICH guidance for the pharmaceutical industry is to apply a risk-based approach to control elemental impurities and their PDEs. ICH Q3D recommends that manufacturers conduct a product risk assessment by first identifying known and potential sources of elemental impurities. Manufacturers should consider all potential sources of elemental impurities, such as elements intentionally added, elements potentially present in the materials used to prepare the drug product, and elements potentially introduced from manufacturing equipment or container closure systems. Manufacturers should then evaluate each elemental impurity likely to be present in the drug product by determining the observed or predicted level of the impurity and comparing it with the established PDE. If the risk assessment fails to show that an elemental impurity level is consistently less than the control threshold, additional controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product. These additional controls could be included as in-process controls or in the specifications of the drug product or components. ICH Q3D also discusses options for different dosage forms and special circumstances that might affect the risk assessment conclusions. The major differences between ICH Q3D and Chapters <232> and <233> are summarized in **Table 2**.

Description	ICH Q3D	USP <232>, <233>
Methodology Approach	A Guideline	Enforceable Standards
List of Elements	Includes 24 elements and PDEs outlined in three delivery categories	Currently includes 15 elements (Not including Ti, Au, Se, Co, Ba, Sn, Li, Sb, Ag) outlined in three delivery categories * * Upcoming revision to include all 24 ICH elements
Analytical Procedure	Analytical methods not provided (pharmacopeial procedures or suitable alternatives should be used)	Provides analytical methods, procedures and validation protocol
Exclusions/Inclusions	Includes Total Parenteral Nutrition (TPN) products	Excludes Total Parenteral Nutrition (TPN) products
Date of Official Implementation	June, 2016 for new pharmaceutical products December 16, 2017 for existing pharmaceutical products	January 1, 2018 for all pharmaceutical products

Table 2: The major differences between ICH Q3D and Chapters <232> and <233>

To better understand these major differences between ICH and USP methodology, let's begin, by taking a closer look at the most important components of Chapters <232>, and <233>.

USP General Chapter <232>

This chapter specifies limits for the amount of elemental impurities in drug products, drug substances, active ingredients and excipients. These impurities may be present naturally, derived from the production catalysts, introduced inadvertently through the manufacturing process or they could be environmental contaminants in the pharmaceutical raw materials. When elemental impurities are known to have the potential to be present, compliance to the specified levels is a requirement. Additionally, due to the ubiquitous nature of arsenic, cadmium, lead, and mercury, those four elements at a minimum, must be monitored. The elemental impurity levels in the drug products, unless otherwise specified in an individual drug product monograph, must show compliance with the limits specified and be made available to the regulatory agency upon request.

A total of 15 elemental impurities (Cd, Pb, As, Hg, In, Os, Pd, Pt, Rh, Ru, Cr, Mo, Ni, V, Cu) are specified together with their toxicity limits, defined as maximum permitted daily exposure (PDE) levels in µg/day for the four major drug delivery categories. The PDE limits are shown in **Table 2**. (**Note:** these represent the updated, partially-aligned (with ICH guidelines) limits, proposed in Pharmacopeial Forum 40 (2), and posted on the USP elemental impurities website).

Element	Oral Daily Dose PDE (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalation Daily Dose PDE (µg/day)
Cadmium	5.0	2	2
Lead	5.0	5	5
Arsenic (Inorganic)	15	15	2
Mercury (Inorganic)	30	3	1
Iridium	100	10	1
Osmium	100	10	1
Palladium	100	10	1
Platinum	100	10	1
Rhodium	100	10	1
Ruthenium	100	10	1
Chromium	11000	1100	3
Molybdenum	3000	1500	10
Nickel	200	20	5
Vanadium	100	10	1
Copper	3000	300	30

Table 2: Elemental Impurities for Drug Products Defined in USP Chapter <232>, based on an arbitrary adult human body weight for either sex of 50 kg (110 lb)

These PDE limits are related to the toxicity of the elemental impurity and its bioavailability. The extent of exposure has been determined for each of the elemental impurities of interest for the three major routes of administration: oral, parenteral (intravenous), and inhalational. However, they do not apply to parenteral nutritional supplements, dialysates or conventional vaccines.

It's also worth pointing out that parenteral drug products with maximum daily volumes up to 2 L may use the maximum daily volume to calculate permissible concentrations from PDEs. For products whose daily volumes may exceed 2 liters (e.g., saline, irrigation solutions etc), a 2-L volume may be used to calculate permissible concentrations from PDEs. Note also that Total Parenteral Nutritional (TPN) products are no longer included in this list (refer to USP40, 1st supplement for details). The other two routes of administration, mucosal and topical, which are not called out in the list of PDEs, are considered to be the same as oral for the purpose of this standard.

Note: More information about routes of administration of drug products can be found in USP-NF General Chapter <1151> Pharmaceutical Dosage Forms (16)

Speciated Forms

This chapter also addresses speciation, although does not specify an analytical procedure. Each of the elemental impurities has the potential to be present in differing oxidation states or species. However, arsenic and mercury are of particular concern because of the differing toxicities of their inorganic and organic forms. The arsenic limits are based on the inorganic form, which is the most toxic. Arsenic can be measured using a total-arsenic procedure under the assumption that all arsenic contained in the material under test is in the inorganic form. Where the limit is exceeded using a total-arsenic procedure, it should be demonstrated using a suitable procedure to separate the species, that the inorganic form meets the specification.

The mercury limits are based upon the inorganic mercuric (2+) oxidation state. Methyl mercury, the most toxic form is rarely an issue for pharmaceuticals. Therefore the limit was established assuming that if mercury was present in the drug compound it would exist as the most common inorganic form. However, if there is a known potential for the material to contain methyl mercury (such as drugs/compounds derived from fish or kelp), an appropriate speciation procedure would be required.

Compliance Options with Chapter <232>

In order for the drug product 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 impurities in pharmaceutical materials:

Drug Product Analysis Option: The results obtained from the analysis of the drug compound scaled to a maximum daily dose, are compared to the daily dose PDE values shown in **Table 2**. Each impurity should be no more than the PDE.

Summation Option: Separately add the amounts of each elemental impurity (in µg/g) present in each of the components of the drug product. The result of the summation of each impurity should be no more than the daily dose PDE. It should be emphasized that before products can be evaluated using this option; the manufacturer must ensure that additional elemental impurities cannot be inadvertently added through the manufacturing process or storage of the product.

Individual Component Option: This option is available to LVP products only, which should meet the requirements when each drug substance and raw material meets the limits provided in the LVP Component Limit column in **Table 2**. If all compounds in a formulation meet the limits shown, then these components may be used in any proportion, with no further calculation necessary. While elemental impurities derived from the manufacturing process or the storage containers are not specifically provided for in this option, the drug product manufacturer should ensure that these sources do not contribute significantly to the total content of elemental impurities.

Acceptable Levels Based on Final Use

The acceptable levels for these impurities depend on the material's ultimate use. Therefore, drug product manufacturers must determine the acceptable level of elemental impurities in the drug substances and excipients used to produce their products. The values provided in **Table 3** represent concentration limits for components (drug substances and excipients) of drug products based on a maximum daily dose of ≤10 g/day. These values serve as default concentration limits to aid discussions between drug product manufacturers and the suppliers of the components of their drug products.

Element	Concentration Limits (µg/g) for Oral Drug Products with a Maximum Daily Dose of ≤10 g/day	Concentration Limits (µg/g) for Parenteral Drug Products with a Maximum Daily Dose of ≤10 g/day	Concentration Limits (µg/g) for Inhalational Drug Products with a Maximum Daily Dose of ≤10 g/day
Cadmium	0.5	0.2	0.2
Lead	0.5	0.5	0.5
Inorganic Arsenic	1.5	1.5	0.2
Inorganic Mercury	3.0	0.3	0.1
Iridium	10	1.0	0.1
Osmium	10	1.0	0.1
Palladium	10	1.0	0.1
Platinum	10	1.0	0.1
Rhodium	10	1.0	0.1
Ruthenium	10	1.0	0.1
Chromium	1100	110	0.3
Molybdenum	300	150	1.0
Nickel	20	2.0	0.5
Vanadium	10	1.0	0.1
Copper	300	30	3

Table 3: Concentration limits for components of drug products dosed at a maximum daily dose of ≤10 g/day.

USP General Chapter <233>

This chapter deals with the analytical procedure, sample preparation, instrumental method and validation protocols for measuring the elemental impurities using one of two plasma based spectrochemical techniques – Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES); 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. Before we describe the instrumentation requirements, let's first take a look at the recommended sample preparation procedures.

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. It should also be pointed out that all liquid samples should be weighed.

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. A closed vessel digestion procedure is prescribed as the method of choice in this instance. Closed vessel digestion permits for a more complete digestion while containing volatile elements. Microwave digestion is typically used to perform closed vessel digestions. The sample preparation scheme should yield sufficient sample to allow quantification of each element at the elemental impurity limits specified in Chapter <232>.

Closed Vessel Digestion: A closed vessel approach is used for samples requiring concentrated acids in a closed apparatus. The choice of what concentrated mineral acid to use depends on the sample matrix, and its impact of any potential interferences on the analytical technique being used. One procedure that has been used is listed in method <233> as follows; however, manufacturer methods using microwave digestion have proven to provide a faster and more simplified approach:

Weigh accurately 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 min 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.

General Sample Preparation Guidance

The ideal scenario is that the sample under investigation is in a liquid form, so it can be analyzed by direct aspiration or perhaps by simply diluting in an aqueous or organic solvent. However, if the sample is a solid or powdered material, the chances are that it will have to be brought into solution using concentrated mineral acids, and a closed vessel, microwave digestion procedure.

Why Dissolve Samples?

- Solid sampling techniques are notoriously prone to sampling inhomogeneity – taking multiple portions of the solid material under test and dissolving them represents the best option for working with a homogeneous sample

- Solution-based analytical techniques need a homogenous sample, which is representative of the sample matrix under test – taking one-off solid samples such as a tablet, can produce erroneous results, because it may not be truly representative of the batch of samples

- Measurements take a finite amount of time where the signal must stay constant – dissolving the sample and obtaining a clear solution is the best way to achieve signal stability

Microwave Digestion Considerations

Chapter <233> actually recommends the use of closed vessel microwave digestion in the case of insoluble pharmaceutical and nutraceutical final products and excipients in order to completely destroy and solubilize the sample matrix. Microwave digestion systems are commonly used for trace elemental analysis studies in a multitude of application areas to get the samples into solution because they are easy to use and can rapidly process many samples, which makes them ideally suited for high sample throughput pharmaceutical production environments (17).

Why Microwave Digestion?

So let's remind ourselves why closed or pressurized microwave digestion offers the best way to get samples into solution:

- Dissolution temperatures above boiling point of the solvent can be achieved
- The oxidation potential of reagents is higher at elevated temperatures, which means digestion is faster and more complete
- Under these conditions, concentrated nitric acid and/or hydrochloric can be used for the majority of pharmaceutical materials

- Microwave dissolution conditions and parameters can be reproduced from one sample to the next
- Safer for laboratory personnel, as there is less need to handle hot acids
- Samples can be dissolved very rapidly
- The digestion process can be fully-automated
- High sample throughput can be achieved
- Less hazardous fumes in the laboratory

Choice of Acids

The choice of acids used for the preparation of digested samples is also important. Typically concentrated nitric and/or hydrochloric acids are used in various concentrations, depending on the sample type. The presence of hydrochloric acid is useful for stabilization of the platinum group elements, but can sometimes produce insoluble chlorides, particularly if there is any silver in the sample. The presence of chloride can also be detrimental when ICP-MS is the chosen technique as the chloride ions combine with other ions in the sample matrix and the argon plasma to generate polyatomic spectral interferences. An example of this is the formation of the $^{40}Ar^{35}Cl$ polyatomic ion in the determination of ^{75}As and $^{35}Cl^{16}O$ in the determination of ^{51}V. These polyatomic interferences can usually be removed by the use of collision or reaction cell technology (CRCT) if the ICP-MS system offers that capability. However CRCT can slow the analysis down because stabilization times have to be built into a multielement method to determine analytes that require both cell and no-cell conditions.

Nitric acid and hydrogen peroxide are often used for the dissolution of organic matrices as they are both strong oxidizing agents that effectively destroy the organic matter. However, care must be taken when testing for osmium as this can form volatile osmium oxides which are easily lost from the sample. In some cases hydrofluoric acid (HF) may need to be used to dissolve certain silicate-based excipients and fillers that have been used in the final product. In cases where HF is required, specialized plastic (PTFE) sample introduction components need to be used, including the use of buffering agents like boric

acid to dissolve insoluble fluorides and neutralize excess HF. It should be emphasized that HF is a highly corrosive acid and extreme caution should be taken whenever it is used (18).

Microwave Digestion Systems

There are many microwave digestion systems available. The most popular systems are based upon a manually operated batch design. These are preferred when similar materials are being prepared in large numbers. An automated sequential approach has proven to be a good choice for many users performing closed vessel acid digestion, because:

- The system uses an auto sampler which permits the system to be loaded with a full batch of samples and then run unattended. This provides the opportunity for end users to do other tasks while the digestion apparatus systematically prepares the samples.

- The system can be loaded with any variety of pills, capsules, powders and liquids. [These samples typically must be run as a separate batch rather than run together as in a sequential system.] The ability to run all of these different sample types once loaded in the autosampler makes it extremely versatile.

- These systems incorporate a simple cap that is snapped onto the vessel prior to placing it in the autosampler. This proves to be much simpler than vessel assembly in batch systems.

The combination of the above have made automated sample preparation systems a very popular option for performing microwave digestion. **Figure 1** shows an example of an automated system. **Table 4** provides an example of a typical digestion method.

Figure 1: Example of an automated microwave digestion system

Digestion Method

A simple digestion procedure has been developed for the automated system (19)

Samples size: up to 0.5 g
Acid: 9 ml HNO_3, 1 ml HCl

Program

Ramp Time	Hold Time	Target Temp	Cool Down
5 minutes	3 minutes	200°C	2 minutes

This provides for a completely digested and cooled sample in approximately 10 minutes.

Table 4: Typical pharmaceutical digestion method

Detection Technique

Two analytical procedures are suggested in this Chapter. Where elemental impurities are typically at the parts-per-million level in the diluted sample, ICP–OES is the recommended technique. Whereas, for elemental impurities 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, such as atomic absorption (AA) as long as it meets the validation requirements laid-out in this 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 or an alternative procedure, 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 impurities procedure for each type of determination are described below. Any alternative procedure that has been validated and meets the acceptance criteria that follow is also considered to be suitable for use.

Acceptability of Analytical Procedures

The following section defines the validation parameters for the acceptability of the analytical procedure to monitor PDE limits. Meeting these requirements must be demonstrated experimentally using an appropriate system suitability procedure and reference material. 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 <232> 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. The optimum dissolved solids content to analyze samples by ICP-MS, is <0.2%. So if 1 g of sample is digested/dissolved and made up to 500 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 1.0 µg/L. The method then suggests using a calibration made up of 2 standards: Standard 1= 1.5J, Standard 2= 0.5 J. So for Pb, that's equivalent to 1.5 µg/L for Std 1 and 0.5 µg/L for Std 2

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 less than (<) 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 correct for 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 (20), 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 is determined by 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 the Chapter <233>, but for clarity purposes, we will 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 this guide, 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 (21) for guidance.

Accuracy

This test is designed to assess the accuracy of the analytical method/ procedure and in particular the impact of the digestion/dilution method on the spiked additions:

- Prepare standard solutions containing target elements at concentrations ranging from 0.5J to 1.5J using suitable calibration/reference materials
- Run calibration using calibration standards
- Prepare samples under test by spiking at concentrations from 0.5J to 1.5J before any sample preparation/digestion is carried out

The technique/procedure is considered acceptable when:

- The spike recovery of three replicates at each sample concentration is 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.

Some Guidance on How to Approach the Analysis of Pharmaceutical Materials

Let's now turn our attention to assessing the best analytical technique for the products and materials under investigation and also to offer some guidance on sample preparation.

Selection of the Appropriate Technique

So which technique is best for your pharmaceutical products and ingredients? If you are an experienced user and have both ICP-OES and ICP-MS in your laboratory, it might be straight forward, based on your knowledge and understanding of each technique. However, if you have been giving the task of evaluating and purchasing a new instrument to carry out this analysis, you will clearly want an instrument that will be suitable for the task in hand, keeping in mind that you probably also have a budget to work with. Additionally, you have to be aware of the expertise of the people you have in your lab and whether they are capable of developing methods and operating the instrument on a routine basis. You will also need to consider the cost of equipping your lab to ensure the

seamless and optimum operation of such a sophisticated and sensitive instrument.

There is a great deal of information in the public domain about the strengths and weaknesses of both ICP-OES and ICP-MS (22), so let's take a brief look at the major differences between them with an emphasis on the analysis of pharmaceutical materials.

Radial View ICP-OES

Radial ICP-OES is a multielement technique that uses a traditional radial (side-view) inductively coupled plasma to excite ground-state atoms to the point where they emit wavelength-specific photons of light that are characteristic of a particular element. The number of photons produced at an element-specific wavelength is measured by high-resolving-power optics and a photon-sensitive device such as a photomultiplier or a solid state detector. This emission signal is directly related to the concentration of that element in the sample. The analytical temperature of an ICP is about 6000 – 7000°K, compared to that of a flame, which is typically 2500 – 4000°K. A radial ICP can achieve similar detection limits to flame AA for the majority of the Chapter <232> suite of elements, but with 5 – 6 orders of linear dynamic range, it has the advantage of offering much better performance for the refractory and rare earth elements. The sample requirement for ICP-OES is approximately 1 mL/min and is capable of aspirating samples of approximately 5 – 10% TDS.

Axial View ICP-OES

The principle of axial view ICP-OES is exactly the same as radial ICP-OES, except that the plasma is viewed horizontally (end-on), or axially. The benefit is that more photons are seen by the detector and as a result, detection limits can be as much as 5 – 10 times lower. The linear dynamic range is the same as a radial ICP-OES, but as a result of the lower detection capability, the LDR is just shifted down an order of magnitude. The major disadvantage of axial-viewing is that more severe matrix interferences are observed, which means the TDS should be kept below 5%. Most commercially-available ICP-OES instrumentation offers the capability of both radial and axial viewing in the same instrument.

ICP-MS

The fundamental difference between ICP-OES and ICP-MS is that in ICP-MS, the plasma is not used to generate photons, but to generate positively charged ions. The ions produced are transported and separated by their atomic mass-to-charge ratio using a mass-filtering device such as a quadrupole. The generation of such large numbers of positively charged ions allows ICP-MS to achieve detection limits at the low part per trillion (ppt) which are typically 3 – 4 orders of magnitude lower than ICP-OES. Another advantage of ICP-MS over ICP-OES is that it is capable of achieving 8 – 9 order of LDR. However, one of the major limitations of ICP-MS is that TDS should ideally be kept below 0.5%, although high matrix sample introduction systems are now commercially-available.

This is not meant to be a detailed description of each technique, but just to give a basic understanding as to how they differ from each other. Let's now focus in on axial ICP-OES and ICP-MS, which are probably going to be the most widely used techniques for conforming to these chapters in pharmaceutical materials. And in particular, taking the 15 elemental impurities defined in Chapter <232> and comparing instrumental limits of quanitation (LOQ) with the calculated J-values for a generic drug compound with a maximum oral daily dose of 10 g/day.

So with this information, let's take as an example the oral drug delivery method and calculate the J-values for each elemental impurity and compare them with the limits of quantitation (LOQ) for each technique to give us an assessment of their suitability. For this analytical scenario, we'll take the LOQ for the method as 10× the IDL. These LOQs were calculated by taking the average of published IDLs from three instrument vendors' application material and multiplying them by 10 to get an approximation of the LOQ. In practice, a method LOQ is typically determined by processing the matrix blank through the entire sample preparation procedure and taking 10 replicate measurements. The method LOQ, sometimes referred to as the method detection limit (MDL), is then calculated as 3× the standard deviation of these 10 measurements. To make this comparison valid, the sample weight was adjusted for each technique, based on

the detection limit and analytical working range. For ICP-OES, we used a sample dilution of 2 g/100 mL, whereas for ICP-MS we used 0.2 g/100 mL. ICP-OES could definitely use larger sample weights, but for high-throughput routine analysis, we are probably at the optimum dilution for ICP-MS.

The comparison data for axial ICP-OES and ICP-MS are shown in **Tables 5** and **6** respectively. The Factor Difference in the final column, which is J-value divided by LOQ is a good indication of whether the elemental target concentrations can be determined with good accuracy and precision… it's a general rule of thumb, that the higher this value, the more reliable the result.

Table 5 shows that axial-ICP-OES offers some possibilities for monitoring oral drugs because the vast majority of the improvement factors are higher than one. These numbers could be further improved, especially for the heavy metals, 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, it was felt that the axial performance was most appropriate for this comparison.

Element	Oral Daily Dose PDE (µg/day)	Concentration Limits (µg/g) for Oral Drug Products with a Maximum Daily Dose of ≤10 g/day	1.0J-Value (µg/L) Based on a Drug Dose of 10 g/day and a Final Sample Dilution of 2 g/100mL	Axial ICP-OES Instrument LOQ (IDLx10) (µg/L)	Factor Difference (J-Value/LOQ)
Cadmium	5.0	0.5	10	1	10.0
Lead	5.0	0.5	10	13	0.8
Arsenic (Inorganic)	15	1.5	30	20	1.5
Mercury (Inorganic)	30	3.0	60	4	15.0
Iridium	100	10	200	10	20.0
Osmium	100	10	200	52	3.8
Palladium	100	10	200	21	9.5
Platinum	100	10	200	12	16.7
Rhodium	100	10	200	47	4.3
Ruthenium	100	10	200	10	20.0
Chromium	11000	1100	22000	2	11000.0
Molybdenum	3000	300	6000	7	857.1
Nickel	200	20	400	6	66.7
Vanadium	100	10	200	4	50.0
Copper	3000	300	6000	4.0	1500.0

Table 5: USP J-values compared to ICP-OES LOQs

In addition, it can be seen in **Table 6** that ICP-MS shows significant improvement factors for all impurities, which are not offered by any other technique. Even for the four heavy metals, there appears to be ample improvement to monitor them with good accuracy and precision. The added benefit of using ICP-MS is that it would also be suitable for the other methods of pharmaceutical delivery, such as intravenous or inhalation, where the PDE levels are typically an order of magnitude lower. It is unlikely that axial ICP-OES would be suitable for these methods of delivery. Additionally, if total arsenic or mercury levels were found to be higher than the PDE levels, it would be

relatively straight-forward to couple ICP-MS with HPLC to monitor the speciated forms of these elements.

Element	Oral Daily Dose PDE (µg/day)	Concentration Limits (µg/g) for Oral Drug Products with a Maximum Daily Dose of ≤10 g/day	1.0J-Value (µg/L) Based on a Drug Dose of 10g/day and a Final Sample Dilution of 0.2g/ 100mL	ICP-MS Instrument LOQ (IDLx10) (µg/L)	Factor Difference (J-Value/LOQ)
Cadmium	5.0	0.5	1.0	0.0009	1111
Lead	5.0	0.5	1.0	0.0038	263
Arsenic (Inorganic)	15	1.5	3.0	0.021	143
Mercury (Inorganic)	30	3.0	6.0	0.0397	151
Iridium	100	10	20	0.0026	7692
Osmium	100	10	20	0.0042	4762
Palladium	100	10	20	0.0124	1613
Platinum	100	10	20	0.0013	15385
Rhodium	100	10	20	0.0008	25000
Ruthenium	100	10	20	0.002	10000
Chromium	11000	1100	2200	0.003	733333
Molybdenum	3000	300	600	0.0096	62500
Nickel	200	20	40	0.0113	3540
Vanadium	100	10	20	0.0286	699
Copper	3000	300	600	0.0024	250000

Table 6: USP J-values compared to ICP-MS LOQs

Current Status of USP Chapters and Implementation Timelines

Over the past few years, the pharmaceutical industry has been very interested in the timely implementation of these new USP chapters, so they can be ready when the final methodologies are officially published in the appropriate

book of compendial standards. In addition, international regulatory agencies such as the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use), European Medicines Agency (EMA), and the European Pharmacopoeia (EP) and Japanese Pharmacopoeias (JP) have been in continued discussions with USP about the list of elements and permitted daily exposure (PDE) limits defined in Chapter <232>. For this reason, there have been a number of revisions to both Chapter <232> and <233>, which resulted in implementation timelines being modified a number of times.

However, a recent announcement published in the Pharmacopeial Forum 42(2) [Mar.–Apr. 2016], proposed that Chapter <232> should fully align with the list of elemental impurities and PDE levels defined in the ICH Q3D Step 4 document "to the greatest extent possible." This means that the ICH list of 24 elements will become the basis for the new list of elemental impurity PDEs in Chapter <232>. These proposed changes are now out for stakeholder review and comments, and are expected to be completed by the early summer of 2017.

However, while this works its way through the approval process, the current and official version of Chapter <232>, which was published in USP 39–NF 34 on May 1, 2016 is basically unchanged from the version in the 2nd Supplement of USP 38–NF 33, posted in December 2015 and contains the old list of 15 elemental impurities.

Additionally, the current official Chapter <233>, which was published in the 2nd Supplement of USP 38–NF 33 on December 1, 2015, contains some minor editorial changes from the previous version. Full implementation of Chapters <232> and <233> is still on target for January 1st, 2018, while ICH Guidelines for existing pharmaceutical products will become official on December 16, 2017.

FDA Position

The Food and Drug Administration (FDA) has recently put out a draft guidance document to explain its regulatory position on the new USP Chapters and ICH Q3D Guidelines. It is not yet an official document, but it has been distributed to all its stakeholders for the purpose of comments and feedback (23).

To summarize the document, the FDA recommends that, until the final implementation of USP Chapters <232>/<233>, the manufacturer of any U.S. marketed drug products (both existing and new medicinal products) follow ICH Q3D recommendations to establish appropriate procedures for identifying and controlling elemental impurities in the drug product based on risk assessment and product-specific considerations, unless the drug product must specifically comply with USP–NF requirements. Additionally, for elemental impurities and their PDEs listed in ICH Q3D but not in General Chapter <232>, FDA recommends that the manufacturer of the drug product follow the recommendations in ICH Q3D until January 1, 2018, when both USP Chapters <232>/<233>, will be officially approved and in the public domain.

In Summary

The goal of this guide is to educate the pharmaceutical industry on the new USP Chapters <232>, <233>, and ICH guidelines covering elemental impurities in pharmaceutical materials. In particular it has been targeted at novice and inexperienced personnel, who are not familiar with much of the terminology, used in the USP and ICH methods and offer some suggestions about the best instrumental technique and analytical procedures to use. Even though USP methodology will not be fully-aligned with ICH guidelines for another 15 months, it should not dissuade pharmaceutical 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 impurities and contaminants. Now is the time to start thinking about investing in the appropriate technique, because it will take 3 – 6 months to evaluate and select the right instrumentation, 3 – 6 months to develop the competence in elemental analysis, and another 3 – 6 months to validate the methodology.

About CEM

Founded in 1978 by the current CEO, Dr. Michael J. Collins, CEM has pioneered the field of microwave chemistry. For nearly 40 years CEM has designed and developed laboratory instrumentation and scientific methods (both microwave and non-microwave based) that are used by major companies, prestigious research institutes, and universities around the world. The company's major products provide unique solutions for compositional analysis of food and chemical samples, acid digestion for elemental analysis, and chemical synthesis of peptides and small molecules.

References

01. United States Pharmacopeia (USP) and The National Formulary (NF) Online (USP-NF): http://www.usp.org/usp-nf
02. United States Pharmacopeia General Chapter <232> Elemental Impurities in Pharmaceutical Materials – Limits: Second Supplement to USP 37–NF 32, December, 2014
03. United States Pharmacopeia General Chapter <233> Elemental Impurities in Pharmaceutical Materials – Procedures: Second Supplement to USP 37–NF 32, December, 2014
04. United States Pharmacopeia General Chapter <231> Heavy Metals Test in USP National Formulary (NF), : Second Supplement to USP 37–NF 32, December, 2014
05. USP General Chapter <251>: Determination of Lead (Pb)
06. USP General Chapter <211>: Determination of Arsenic (As)
07. USP General Chapter <261>: Determination of Mercury (Hg)
08. European Medicines Agency (EMA) Guideline on the Specification Limits for Residues of Metal Catalysts: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000356.jsp&mid=WC0b01ac0580028e8c
09. Stimuli Article on General Chapter on Inorganic Impurities: Heavy Metals Published in Pharmacopeial Forum 34(5): http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/2009-04-22MetalImpuritiesCommentDigest.pdf
10. USP Elemental Impurities Website: Key Issues; http://www.usp.org/usp-nf/key-issues/elemental-impurities
11. United States Pharmacopeia Update Communication, January 14, 2015: http://www.usp.org/usp-nf/key-issues/elemental-impurities

12. ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) Q3D Step 4 - Guideline for Elemental Impurities; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf
13. The 5th World Health Organization (WHO) Conference of Drug Regulatory Authorities (ICDRA), Paris, 1989, http://whqlibdoc.who.int/hq/1991/WHO_PHA_ICDRA_91.1.pdf
14. International Federation of Pharmaceutical Manufacturers & Associations (IFPMA): http://www.ifpma.org/
15. History of the ICH: Official ICH Website: http://www.ich.org/home.html
16. USP-NF General Chapter <1151> Pharmaceutical Dosage Forms, USP37-NF32, 2014
17. CEM Solutions for USP Chapters <232> and <233>: CEM Corporation, Matthews, NC: http://cem.com/USP232
18. The National Institute for Occupational Safety and Health (NIOSH): Safe Use of Hydrogen Fluoride and Hydrofluoric Acid; http://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750030.html
19. Microwave Digestion of Pharmaceutical Samples Followed by ICP-MS Analysis for USP Chapters <232> and <233>, CEM Corp. Application Note: https://cem.sharefile.com/download.aspx?id=sc6d12fed0084ab4b#
20. USP General Chapter <730> Guidelines on Plasma Spectrochemistry: Second Supplement to USP 37–NF 32, December, 2014
21. USP General Chapter <1225> Validation of Compendial Procedures: Second Supplement to USP 37-NF 32, December, 2014
22. Comparison of AS Techniques: Chapter 21 from Practical Guide to ICP-MS: A Tutorial for Beginners, 3rd Edition; ISBN 978-1—4665-5543-3, Robert. J. Thomas, CRC Press, Boca Raton. FL, 2013
23. Elemental Impurities in Drug Products: Guidance for Industry: Food and Drug Administration Document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM50943 pdf, June, 2016