Mandates for Elemental Impurities

Current Recommendations & Requirements

FDA (USP) <232> & <233> / EMA (EP) Ch. 5.2 / & ICH-Q3D Step 4 version

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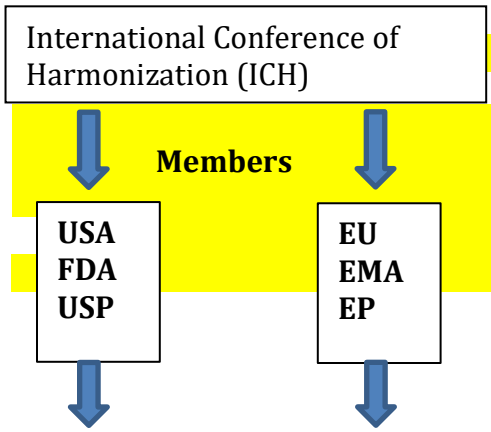
INTRODUCTION



Q3D – Guidance on Elemental Impurities
Step 1, 2, 3 & 4

* 24 metals with emphasis on As, Pb, Cd & Hg
*3 Classes of Toxicity
*Guidelines for Risk Assessment
* ICH only issues guidelines, each "member" interprets and adopts.
* USP and EU versions are different.
* Step 5 is for the member nations to implement the guidelines.

Jan. 1st, 2018 **June, 2016 and December, 2017**

HIGH LEVEL COMMENTS:

1. Elemental Impurities in Drug Substances is a Consumer Issue and concern is on the rise!
2. The primary mandate of the FDA is to protect the food and drug supply of the United States and with more and more drugs coming in from China and India there is heightened concern over the safety and security of the drug supply.
3. There was no previous comprehensive guideline for the overall protection of the drug supply against the presence Elemental Impurities. ICH developed these guidelines in response to that. They are only guidelines. The actual interpretation and enforcement is left to the member states.
4. The FDA will ultimately incorporate these mandates into their review of cGMP with current levels of enforcement penalties to increase!
5. This process started in Europe in 2008 with first (and final) enforcement June of 2016.
6. This process started in the USA in 2010 with first (and final) enforcement January of 2018.
7. This paper is a commentary on the outcome of this process. The opinions expressed are those of my own but the factual evidence in support of those opinions is found in the addendums that are included with this course.

WHY SO MANY DELAYS?

The enforcement of USP <232> and <233> has been delayed multiple times since its first proposed implementation date of Dec. 2013 to May of 2014, then to December of 2015 and now, after consideration of comments from Drug Manufacturers to January 1st, 2018.

- The initial delays were caused by severe industry reaction to the proposals.
- There were delays due to the complications encountered with method development and application.
- This last delay has allowed for the adoption and partial harmonization of USP <232> with the ICH Q3D Step 4 Version. For further details, please refer to addendum #22 (implementation plan for elemental impurities General Chapters <232> and <233>.)

Similarly, the European version of these mandates has been delayed multiple times and **now contains significant revisions.** Along the way a great deal of uncertainty over compliance requirements and future enforcement by the EMA and the FDA has occurred.

In regard to the FDA, The confusion has been complicated by a "soft tone" coming from the USP and the FDA on the subject in order to "keep the peace" and keep the process moving forward. While the USP has refined and clarified their official position through various means, these position-statements issued by the USP do not change what the law actually states. Nor do they determine how the FDA may **ultimately** act through local auditing and enforcement. (For additional information, please refer to addendum #21 (USP FAQ's for Gen. Chapter <232> and <233> and also addendum #17 (Commentary to the 2nd Supplement of USP 38) covering pages 15-30 which deals specifically with issues concerning General Chapter <232> and <233>.)

Therefore it is important that as this initiative and the enforcement of it evolves through a multi-year-implementation process, those charged with the responsibility of compliance must understand **what these standards actually state** and therefore the implication as to **how the FDA could enforce these rules if they so choose to in the future, under ICH, USP or GMP guidelines.** This paper will cover the issues associated with this multi-year, multi-compendial, multi-agency rollout. It will also stress the realities of the mandates themselves and the risks involved with a control strategy that is not rigorously applied to the final drug product as well as the entire manufacturing and supply chain.

OBJECTIVES:

- Explain the ICH-Q3D Step 4 version and how it relates back to the USP and EP mandates.
- Explain the most recent requirements from the EMA regarding the adoption and harmonization of ICH-Q3D Step-4 version with the EMA: CHMP/SWP/4446/2000 (Feb 2008) in respect to registration of Pharmaceuticals for human use.
- Explain the requirements for USP <232> and how that will change with the adoption and harmonization of the ICH Q3D, Step 4 version for Elemental Impurities.
- Evaluate future implications for the Drug Substance, Excipient & Drug Product Manufacturer in regard to their own operation as well as 3rd party vendors and suppliers. What are the inherent risks of taking the "risk based" approach? How can suppliers help?
- Review the requirements for USP <233> in regard to instrumentation and challenges with method development, sample preparation and validation.

REFEERNCES:

Part I: ICH Q3D: Addendum #1-5.
Part II. EMA Mandates: Addendums #6-11.
Part III. USP Mandates: Addendums #12-25.

SUMMARY OF CHANGES

I. **International Conference on Harmonization (ICH) endorsed topic Q3D, Impurities: Guideline for Metal Impurities, and published its final Step 4 Version, on** 16 December 2014. It has now been accepted and adopted as part of the Step 5 process by the USP, EP and presumably the JP will follow. Implementation and enforcement is quite another issue! (Please refer to Addendum #1 for additional information).

II. **On Feb 26th, 2015 EMA published CHMP/QWP/109127/2015 "Elemental Impurities in Marketed products, Recommendation s for Implementation." This harmonized and adoption by EMA and CHMP of ICH Q3D as a "Scientific Guideline for risk assessment" will become effective June 2016 for new marketing authorization for new products containing a new active substance and or a new product with an established active substance and December of 2017 for all marketed drug products including new applications for products already approved.** (See Addendum # 6, 7 & 8 for more information) - Note: CHMP = Committee for Medical Product for Human Use

European Medicines Agency (EMA) published guidelines on Specification Limits for Residues of Metal Catalysts or metal Reagents: CHMP / SWP / 4446 / 2000; Was effective September 1, 2008 for new products with full compliance of all products by September 2013 - then delayed until April of 2014 and now delayed until 2016 for new products and 2017 for old products. Currently this is still included in the European Pharmacopeia (EP) as Chapter 5.20 and analytical method Chapter 2.4.8 and has not yet been revised. **This has officially been replaced by EMA/ CHMP/ ICH/ 353369/ 2013 issued Jan 1 of 2014** (See Addendum #6 &8 for more information)

III. **United States Pharmacopeia (USP) revised General Chapters <232> and <233>** on Elemental Impurity Limits and Procedures in April 2012. (Please refer to Addendums #13 & 16). They were originally to become effective in February, 2013 but that was changed to May 1, 2014. This was further delayed until December 1, 2015 and now, Jan. 1, 2018. (Please refer to Addendum 22 for more details).

USP issued a revised version of <232> and <233> (Feb 2015) as a draft copy to the 2nd supplement to USP 38 ("revised notes" See addendum #14) **and then finally they issued the actual 2nd supplement containing further revisions to General Chapters <232> and <233>** (see addendum #13 & 16)**. The latest revision was more rigorously harmonized with ICH Q3D step 4 version. The draft copy** (addendum 14) **and the final version as issued in the 2nd supplement to USP 38** (addendum #12) **have significant differences from each other and the original issue of the General Chapter. This has caused an enormous amount of confusion.**

As of the date of Jan. 1, 2018, elemental impurities will be controlled in official drug products according to the principles defined and requirements specified in the two General Chapters and in the ICH-Q3D Step-4 guideline**.** In addition on that same date, General Chapter <231> will be omitted and all references to it in general chapters and monographs will be deleted. Early adoption of these requirements are permitted by USP and once implemented that products and its ingredients will no longer need to comply with applicable <231> requirements.

Note: DP = Drug Product (final finished drug product)
Note: DS = Drug Substance, or "API"

I.) What does the ICH-Q3D Guideline for Metal Impurities Actual Say! (REF: Addendum #1)

ICH Q3D: Permitted Concentrations of Elemental Impurities for Option 1

Reported in µg/g (ppm)

Table A.2.1: Permitted Daily Exposures for Elemental Impurities[1]

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
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

[1] PDEs reported in this table (µg/day) have been established on the basis of safety data described in the monographs in Appendix 3, and apply to new drug products. The PDEs in the monographs are not rounded. For practical purposes the PDEs in this table have been rounded to 1 or 2 significant figures. PDEs less than 10 have 1 significant figure and are rounded to the nearest unit. PDEs greater than 10 are rounded to 1 or 2 significant figures as appropriate. The principles applied to rounding in this table may be applied to PDEs derived for other routes of administration.

[2] Classification as defined in Section 4.

Permitted concentrations of Metal Impurities in drug products, drug substances and excipients

Table A.2.2: Permitted Concentrations of Elemental Impurities for Option 1

The values presented in this table represent permitted concentrations in micrograms per gram for elemental impurities in drug products, drug substances and excipients. These concentration limits are intended to be used when Option 1 is selected to assess the elemental impurity content in drug products with daily doses of not more than 10 grams per day. The numbers in this table are based on Table A.2.1.

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
Tl	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

About the ICH-Q3D Step 4 Guideline:

1.) The document has three parts:
   a. Evaluation of toxicity
   b. Establishment of PDE's for each element of toxicological concern.
   c. Application of risk based approach to control elemental impurities in drug products.

2.) The scope of ICH-Q3D includes:
   a. New finished drug products as defined in ICH Q6A and Q6B and new drug products containing existing drug substances. (See Addendum #2 & 3 for more information)
   b. Drug products containing **purified proteins** and polypeptides (including the same from recombinant and non-recombinant origins). Also included is the derivatives and products of which they are components (e.g., conjugates)
   c. Drugs products containing synthetically produced polypeptides, polynucleotides and oligosaccharides.

3.) The guideline does not apply to: herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation and elements that are intentionally included in the drug product for therapeutic benefit. Furthermore, the guideline does not apply to products based on genes (gene therapy), cells (cell therapy) and tissue (tissue engineering). Finally, this guideline does not apply to drug products sued during clinical research stages of development.

4.) The guideline for risk-based approach presents **a process to assess and control elemental impurities using the principles of risk management as described in ICH-Q9** (See Addendum #5 for more information)

5.) Methods used to establish PDE (oral, parenteral and inhalation) are provided

6.) Allowance for the same methodology to be applied to other routes of exposure

7.) Justification for higher PDE's in certain cases.

8.) Element **Classification by toxicity** as well as likelihood to occur in the drug product. This is very different from previous the EMA classification.
   i. Class I: **As, Cd, Hg and Pb** (known human toxicants). These four elements require evaluation during risk assessment, across all potential sources of elemental impurities and routes of administration.
   ii. Class II: Generally considered route dependent human toxicants.
      a. Class IIa – **Co, Ni and V**: these elements of high probability of occurrence in the drug product and this require risk assessment across all potential sources of elemental impurities and routes of administration.
      b. Class IIb – **Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl:** these elements have a reduced probability of occurrence in the drug product related to their low

abundance and low potential to be co-isolated with other materials. They can be excluded from the risk assessment unless they are intentionally added.

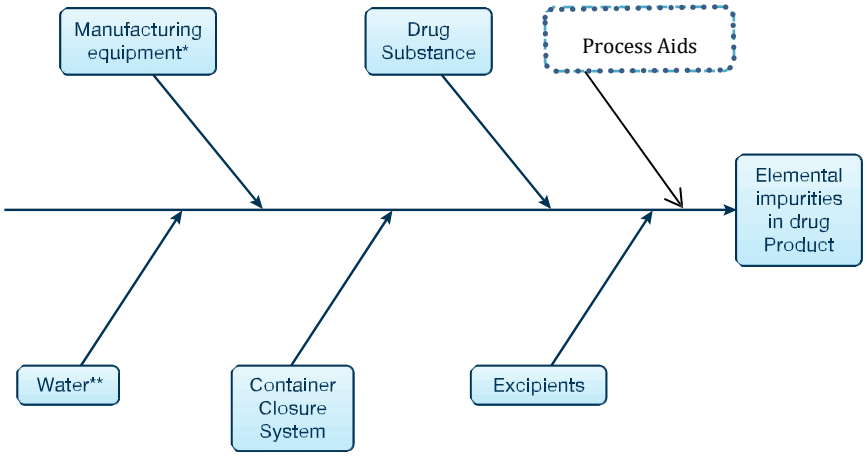
iii. Class III: **Ba, Cr, Cu, Li, Mo, Sb and Sn**: these elements in this class have relatively low toxicities by the oral route of administration but may require consideration in the risk assessment for inhalation and parenteral routes.

9.) Metals not included in this guideline: Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn. Low in toxicity or covered by other guidelines. Al for compromised renal function; Mn and Zn for patients with compromised hepatic **function. W impurities in therapeutic proteins etc.**

ABOUT RISK ASSESSMENT

1.) Elements of Risk Assessment:

a. Based on ICH Q9 (See Addendum #5 for more information)
b. Based on scientific knowledge and principles
c. Required to document in an "appropriate manner" (the level of formality and effort of the risk assessment should be proportional with the level of risk. Therefore, formal and informal tools and procedures are acceptable.
d. Formal tools for risk assessment are described in ICH Q8 and Q9. (See Addendum #4 & 5)
e. ICH-Q3D lists specific areas to review and leaves others up to you!
    i. Elements intentionally added
    ii. Elements unintentionally added
        1. Through drug substances
        2. Water
        3. excipients
    iii. Manufacturing equipment
    iv. Container closure system
    v. Final Process Aids



2.) What is not mentioned and should be is “other” processing aids that could potentially add metals. They are inferred in other places but do not make this list. This stands in contrast to the more strict USP <232> guidelines (which calls for the evaluation of all potential sources).

Figure 2: Primary sources of elemental impurities in drug substances (DS)

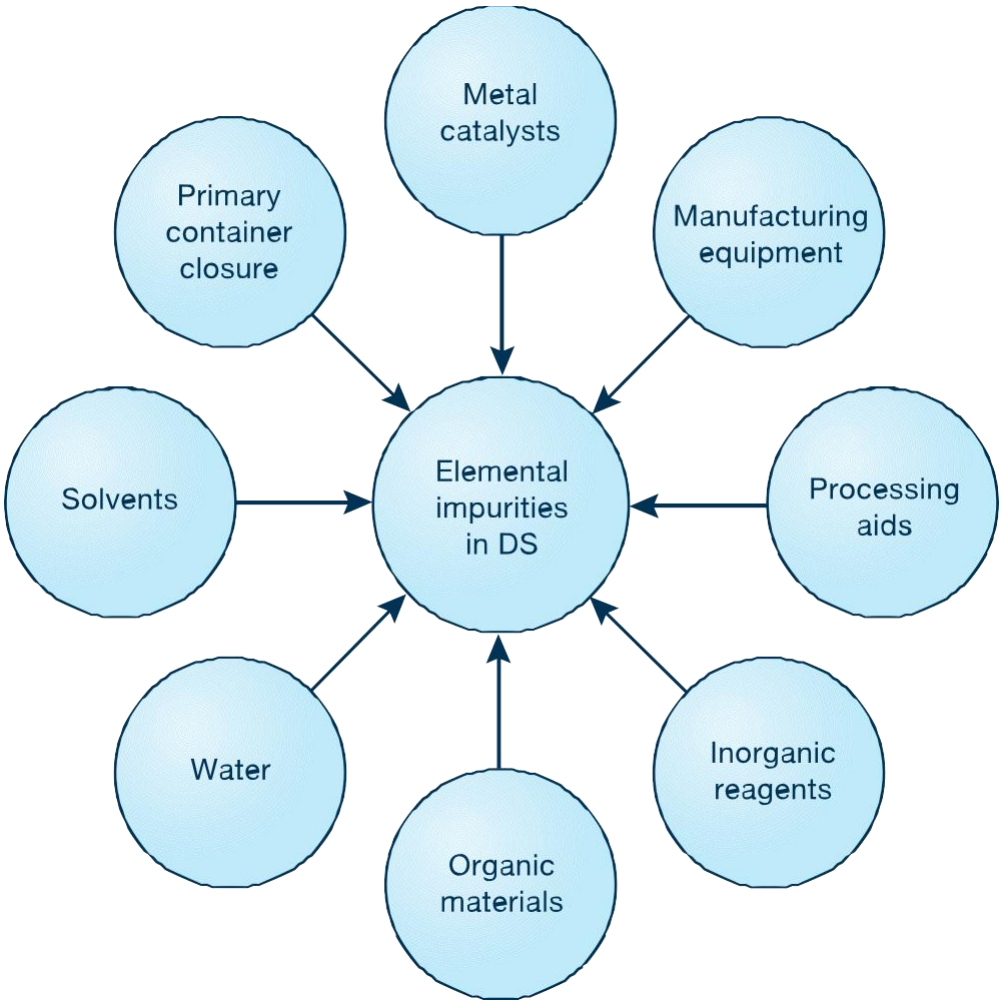


Table 5.1: Elements to be Considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

3.) ICH allows for use of supplier information: “Risk assessment can be facilitated with information provided by suppliers!

4.) It also goes on to say that the risk assessment should include “prior knowledge” of elemental impurity concentration ranges from specific sources (sources should already be providing data and potentially testing on a regular basis!)

5.) Control thresholds begin at 30% PDE’s. **(Note: USP does not allow for this)**

a. Over which you need control
b. Under which you can test to confirm its removal from the assessment or ignore.
c. When threshold exceeded additional controls must be put in place which include a series of actions that include testing, setting of specifications, changing formulations or packaging etc.

6.) Speciation is not covered nor required however, it can be used to reduce levels below the PDE.
7.) ICH-Q3D calls for pharmaceutical analytical procedures such as the USP <232> or suitable procedures.
8.) Lifecycle Management: the guideline calls for science and risk based approach to each lifecycle stage promoting continues process improvement across the entire product life cycle.

FOR MORE INFORMATION: Refer to Addendum #1

I.) EMA Mandates for the adoption of ICH-Q3D guidelines for Elemental Impurities

History

European Medicines Agency (EMA) published guidelines on Specification Limits for Residues of Metal Catalysts or metal Reagents: CHMP / SWP / 4446 / 2000; (please see Addendum #8) effective September 1, 2008 for new products with full compliance of all products by September 2013 then delayed until April of 2014. This is now part of the European Pharmacopeia (EP) as Chapter 5.20 and analytical method Chapter 2.4.8.

This original issuance was the summation of over 8 years of collaborative work with government, private agencies and scientists in Europe in regard to controlling the presence of elemental impurities (heavy metals) in Pharmaceutical components and finished Pharmaceutical products for human use.

KEY ELEMENTS of the previous document that were sometimes overlooked:

- The objective of the guideline was to recommend maximum acceptable concentration limits for the residues of metal catalysts or metal reagents that may be present in the Pharmaceutical substances (active or excipient) or in the drug products. The metals originally addressed where ones of toxic concern ONLY used regularly as process catalysts or reagents during the synthesis of pharmaceutical substances where their use may lead to residues in the final DS or DP. This has been expanded to all metals of concern regardless of the cause of exposure of route of exposure.
- The guideline classified metal residues into three categories based on their individual levels of safety concern. These have now changed.

- It provided reporting guidelines and testing strategies – this has now been completely supplanted by the ICH-Q3D guidance.
- It specifically focused and mentioned the following: DS, excipients, manufacturing equipment and piping, bulk packaging, the environment, and solvents!
- The purpose was to control residues with limits, validated testing methods in order to guarantee acceptable product quality.
- One of the key concepts of this document was the thought that by limiting concentrations of elemental impurities in the derivatives to the DP you would limit exposure in the DP. Focusing on the supply chain was always a key ingredient as with the original issuance with the EMA document (as well as with USP <232>. It was not until the enormous push-back by the Pharmaceutical industry did the focus change to the final DP.
- **Another key element was reliance on other guidelines such as GMP and Residual Solvents to preserve the integrity of the DP.** The new mandates were meant to compliment, not replace any other standard regarding the identification and control of contaminants.

- The guideline always had a broader scope: **"Since the origin of metal residues is irrelevant regarding their potential toxic effects, the concentration limits in this guidance are in principle, also applicable to residues from other sources than catalysts and reagents…. Where insufficiently limited by GMP, GDP or any other relevant provision."**
- **Finally, the guidance was clear on the reliance of suppliers: "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."**

This Guidance is now replaced with EMO/CHMP/ICH/353369/2013 (Addendum #7&9). There is an introduction and then a link to the balance of the ICH document.

Major Changes to EMA requirements:

1.) DEADLINES OF JUNE 2016 & DECEMBER OF 2017!!! (see addendum 6, 7 &9)

Assessments are required by June 2016 for new marketing authorization for new products containing a new active substance and or a new product with and established active substance and December of 2017 for all marketed drug products including new applications for products already approved.

2.) The ICH Document calls for 24 elements to be evaluated where the former EMA document listed only 14. (see addendum #1)

3.) **IPEC issued a strong rebuttal to EMA's adoption due to supply chain issues!** (See addendum #10).

4.) **A very different type of 3-part classification system for toxicity of metals is used:** The three class system of toxicity is now:

   a. Class 1: Elements of high toxicity by all routes of administration
   b. Class 2: Elements with rout dependent toxicity
      i. Possible from different sources
      ii. Less likely unless intentionally added to the manufacturing process
   c. Class 3: Elements with low toxic potential by oral route

5.) In addition, many of the metals have moved in regard to these classes.

6.) Limits have changed substantially from the previous version.

7.) **The overall emphasis by the EMA is still "Assess and then test" not "Test and Assess".** They strongly emphasize an assessment of risk and a control strategy rather than redundant testing. ICH-Q3D does call for some testing* but the emphasis seems opposite of the older position of the USP/FDA (which too, has shifted). (*See pg. 8 & 10 in Addendum #1). ICH calls for periodic testing and the establishment of specifications for DS, Excipients etc... Testing is also inferred in the establishment of validated data, risk assessments and the like.

8.) The guideline <u>more intentionally</u> covers elemental impurities from many possible sources (including equipment, water, and packaging) and not simply from intentional sources such as Metal Catalysts and Reagents as per the previous EMA standard. **This applies to solvents used in the drug manufacturing process (the final DP) as well as the DS (API's). If solvents are used in the manufacturing process of the final drug product than they should also be specifically reviewed.**

9.) **Within the transition period, the drug manufacturer must perform a risk assessment of his products in terms of elemental impurities.** In doing so, **many** potential sources, such as starting materials for active substances, excipients, reagents, catalysts, process water, equipment, container closure systems, etc. are to be taken into account. This risk assessment should provide the basis for a control strategy that ensures that the respective permitted daily exposure limits (PDEs) specified in the guideline is strictly adhered to.

10.) By Law the risk assessment must be made available during an inspection upon request.

11.) The application for a variation to the regulatory authority is not required if a risk analysis has shown that:

   a. no further monitoring for elemental impurities in starting materials, intermediates, active ingredients, excipients and finished products is required, and that these do not have to be replaced or exchanged for others,

b. No change in the manufacturing process is necessary.
c. **In all other cases, a variation is needed.**

12.) For the analyses of elemental impurities, specific procedures are to be used i.e. USP <233>. Non-specific compendia test for heavy metals will **no longer** be accepted.

Other Changes: EMA's interpretation of ICH Step 4 Guidelines Q3D on Elemental Impurities

1. **Previously did not address the heavy metals of highest toxicological concern (Arsenic, Cadmium, Mercury and Lead). It now does!**
2. Categorize listed metals based on classes of toxicity (Class 1, Class 2 and Class 3) and mode of administration.
3. Increase in 14 to 24 metals with most PDE limits being changed (17 of the 24 metals have "tighter" thresholds with more stringent PDE values). Six elements were given higher thresholds in the Q3 version and adopted by the EMA.
4. Nickel has been moved to a 2A category and its limit cut to 1/3 previous level. This means higher controls for certain products as Ni is frequently used as a metal catalyst in API synthesis and is also present in metallic materials in many parts of the production process.
5. The PDE for Thallium has also been considerably reduced with regard to inhalation.
6. Further partly drastic reductions concern the elements Iridium, Osmium, Rhenium and Platinum by 10x! Some of these metals are also used as catalysts in chemical synthesis.
7. The older EMA guidelines allowed for exemption based on control and validation. The new version expands the scope of review and still allows for exemptions based on meeting a 30% threshold of PDE values. **NOTE: THIS IS NOT ALLOWED UNDER USP GUIDELINES!**

Meeting EMA (EP) Guidelines:

1.) Conduct your Risk Assessment (for additional help refer to Addendum 11 & 1)

a. **Review your manufacturing process**
b. **Determine if metals listed are used intentionally anywhere in the process.**
c. **Determine if the metals listed can be introduced inadvertently anywhere in the process.**
d. **Review your entire supply chain**
e. **Press vendors for data and or their own "risk assessments"**

2.) Develop a control strategy that should at the very least include the top 4 elements (As, Pb, CD, Hg) if not the top 7 (Co, V, Ni)

3.) Create your report.

4.) **The rule is applied to all drug products, drug substance, drug components and processing aids**: Pharmaceutical companies should be requesting the application of the standard to suppliers of API's and Excipients who themselves should be conducting their own evaluations.

5.) Limits for DP, DS and Excipients have now been harmonized with ICH

Analytical Procedures for EMA and How to Report

- You must now use a specific approved Pharmaceutical compendia method such as **pharmacopeia procedures: EP chapter 2.3.20 mirrors USP <233> - See Section IV for further details.**

- **Statements should no longer be acceptable Regarding Reporting of Metals:**
  1. "Only Class 3 metals are likely to be present. All are below option 1 limits for <oral> or <parenteral> exposure" (then provide metals present and define which exposure route).
  2. "Only Class 2 metals (X, Y, etc.) are likely to be present. All are below Option 1 limit for…"
  3. "Class 1 metal (Z) is likely to be present. The metal is present in a concentration of (X ppm) which is below the <acceptable criteria>." (Provide identity of metal, actual conc. Found, applied acceptable criteria, etc.)

Recommendations:

Risk assessments required under Q3D are complex and comprehensive. Drug Product manufacturers and Drug Substance (API) manufacturers should look for and rely on vendors willing and able to supply valuable and reliable data.

III.) FDA: USP General Chapters <232> and <233>

(References: addendums 12-25)

The USP has now adopted the same basic principles as found in ICH-Q3D:

a. Evaluation of toxicity data for each metal impurity.
b. With the establishments of PDE's for each metal of toxicological concern (PDE = Permitted Daily Exposure)
c. Perform a complete assessment of product, manufacturing process and supply chain.
d. Development of a control strategy for all metals in all components, drug substances and final drug products.
e. Perform all testing according to <233> protocols or develop validated alternate methods

The USP and ICH is calling for Five (5) levels of control:

1. Control of Raw Materials
2. Control of the manufacturing process (of the drug)
3. In-Process Controls (i.e. testing)
4. Control of the drug substance (i.e. APIs)
5. Control of the final drug product

UPDATES & REVISIONS:

1.) The process with USP has had many variations, changes, and supplements. One must take care to study them all! These are all included in the addendum.

a. Read the original General Chapter <232> – Addendum #13
b. Read the revised notes to the 1st supplement issued Feb 2015 – Addendum #14
c. Read addendum #12 – 2nd supplement to USP 38 – includes important changes and clarifications to previous versions and supplements.
d. Read the 2nd supplement to USP <233>
e. Read Supplement #3 – Correspondence number C163959 – Addendum #23

Unfortunately, there are significant differences in each of these versions which have given rise to a great deal of confusion!!! The understandings of the application of these changes are also made clearer by the "commentary to the 2nd Supplement USP 38" – Addendum #17 and FAQ's (addendum #21).

2.) The most recent version is still only a partial harmonization of metals (15 of the 24) but a harmonization of PDE's for those same elements of concern.

3.) Officially, USP has adopted ICH Q3D Step 4 version guidelines for Risk Assessment with certain (more rigorous caveats regarding testing and control strategy. **The latest change to the wording of <232> (see addendum #23) says that regardless of the approach used to assess (such as using a risk based control strategy or not) "Compliance with the limits specified is required."**

4.) **USP announced by way of General Notice 5.60.30** (see addendum #18) **the final, enforceable implementation of USP <232> and <233> effective January 1, 2018.**

5.) As mentioned, the USP however, did NOT accept all 24 metals listed in the ICH-Q3D Guideline, but simply harmonized the Risk Approach, creation of PDE's, and 15 of the 24 metals. **They did however accept all changes to limits published in the Step 4 version.**

6.) Concurrent with the ICH Q3D guidelines, AND MADE MORE CLEAR in the last correspondence (see addendum #23) **the USP allows for the acceptance of data from sources of supply obtained from reliable vendors. "Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance or excipient manufacturers, who may provide test data or if applicable risk assessments." (see addendum #23)**

7.) **In difference to a more general EMA and ICH "view" the USP <232> still calls for absolute more testing although they have adopted the view of a Risk Assessment and Control Strategy. They**

specifically call out for testing and absolute data in the final clarification statement (Addendum #23) and when a risk assessment is used the vendor must follow table #2 limits. It is CLEAR from this information that the FDA and USP would prefer the presence of absolute data from vendor and then on the final drug product by the Drug Manufacturer NOT simply validating out of doing any testing!!! Clarity over how the FDA will demand risk-analysis data is to be seen! (Another review of the Comments to the 2nd Supplement to USP 38 is very helpful – Addendum #17 as well as the USP FAQ's (see addendums #21).

In all these documents the USP states the following:

a. The USP revised its standards for elemental impurities in the interest of better protecting public health. **(See Addendum #17 "Commentary to 2nd Supplement USP 38)**

b. **They want Lead, Mercury, Arsenic and Cadmium always considered in any risk based analysis.**

c. **Drug Manufacturers are ultimately responsible for assuring conformance to FDA requirements and USP standards no matter what the source.**

8.) While the limits have changed, <u>NOT ALL METALs ARE INCLUDED.</u>

a. The top 7 are which are the most important (Pb, CD, Hg, As, Co, V, Ni) – are included.

b. **What about the balance? The USP has publically said that these metals will be included in a future general chapter of number greater than 1000 (meaning a general informational chapter).** Like the extra metals from older ICH versions that the ICH should always be considered, these metals should be viewed only if intentionally added or if there is other mitigating factors where it becomes responsible to control the content.

c. Keep in Mind that the USP <232> calls for Drug Manufacturers to ultimately establish:

i. Safety of all PDE's

ii. **Their own PDE's**

iii. **Specifications for all suppliers.**

Table 1. Elemental Impurities for Drug Products

Element	Oral Daily Dose PDE[a] (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalational Daily Dose PDE (µg/day)	2S (USP38)
Cadmium	5	2	2 2S (USP38)	2S (USP38)
Lead	5	5	5 2S (USP38)	2S (USP38)
Inorganic arsenic [a]	15	15	2 2S (USP38)	2S (USP38)
Inorganic mercury [a]	30	3	1 2S (USP38)	2S (USP38)
Iridium	100	10	1 2S (USP38)	2S (USP38)
Osmium	100	10	1 2S (USP38)	2S (USP38)
Palladium	100	10	1 2S (USP38)	2S (USP38)
Platinum	100	10	1 2S (USP38)	2S (USP38)
Rhodium	100	10	1 2S (USP38)	2S (USP38)
Ruthenium	100	10	1 2S (USP38)	2S (USP38)
Chromium	11000	1100	3 2S (USP38)	2S (USP38)
Molybdenum	3000	1500	10 2S (USP38)	2S (USP38)
Nickel	200	20	5 2S (USP38)	2S (USP38)
Vanadium	100	10	1 2S (USP38)	2S (USP38)
Copper	3000	300	30 2S (USP38)	2S (USP38)

[a] See *Speciation* section. 2S (USP38)

Table 2. Example Concentration Limits for Components of Drug Products with a 10-g Maximum Daily Dose 2S (USP38)

Element	Concentration Limits (g/g) for Components Used in Oral Drug Products	Concentration Limits (g/g) for Components Used in Parenteral Drug Products	Concentration Limits (g/g) for Components Used in Inhalation Drug Products 2S (USP38)
Cadmium	0.5	0.2	0.2 2S (USP38)
Lead	0.5	0.5	0.5
Inorganic arsenic [a]	1.5	1.5	0.2 2S (USP38)
Inorganic mercury [a]	3	0.3	0.1 2S (USP38)
Iridium	10	1	0.1 2S (USP38)
Osmium	10	1	0.1 2S (USP38)
Palladium	10	1	0.1 2S (USP38)
Platinum	10	1	0.1 2S (USP38)
Rhodium	10	1	0.1 2S (USP38)
Ruthenium	10	1	0.1 2S (USP38)
Chromium	1100	110	0.3 2S (USP38)
Molybdenum	300	150	1 2S (USP38)
Nickel	20	2	0.5 2S (USP38)
Vanadium	10	1	0.1 2S (USP38)
Copper	300	30	3 2S (USP38)

[a] See *Speciation* section. 2S (USP38)

PLEASE NOTE: There was an error in the publication of the 2nd Supplement to USP 38: The units for the next Table should be ug/g not g/g.

In the Supplement #3 (addendum #23) these tables are corrected once again for wording and units (Oral daily Dose is corrected for table one and the units for table 2).

Table 1: Permitted Daily Exposures for Elemental Impurities

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
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

Recommendations for Elements to be Considered in the Risk Assessment

The following *Table 2* identifies elemental impurities for inclusion in the risk assessment. This table can be applied to all sources of elemental impurities in the drug product.

Table 2: Elements to be Considered in the Risk Assessment

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

9.) In addition to the newly revised USP wording (addendum #23) regarding components is as follows:

"The acceptable levels of elemental impurities depend on the material's ultimate use. Therefore, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance manufacturers or excipient manufacturers, who may provide test data, or, if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer to demonstrate compliance with this chapter in the final drug product. Drug substance or excipient manufacturers who choose to perform a risk assessment must conduct that risk assessment using *Table 2* in this chapter. Elements that are inherent in the nature of the material, as in the case of some naturally-sourced materials, must be considered in the risk assessment." (USP40)

The values provided in *Table 3* are example concentration limits for components (drug substances and excipients) of drug products dosed at 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. [NOTE—Individual components may need to be limited at levels different from those in the table depending on monograph-specific mitigating factors.]

Table 3: Permitted Concentrations of Elemental Impurities for Individual Component Option

Element	Class	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Inhalation Concentration (µg/g)
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
Tl	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

▪ 13 (USP40)

10.) **What the USP is saying in this revision is that while the Law is intended for final drug products, but that does not mean that that drug substances, excipients and processing aids (solvents) are exempt from review.** The USP <232> maintains that ***"the acceptable levels for these impurities depend on the materials ultimate use"*** and that ***"Drug product manufacturers must determine the acceptable level of elemental impurities in the drug substances and excipients used to produce their products."***

OBJECTIVE: 1.) know (test) 2.) Document 3.) Control

PATH: 1.) Risk Assessment 2.) Control Program 3.) Report

Knowing and Assessing requires someone to do the testing!!!

11.) In this sense 2nd List serves (only) as an ***"aid in the discussion between drug product manufacturers and the suppliers of the components of their drug products."*** **The USP <232> therefore requires that Drug Manufactures ultimately develop their own specific (internal) requirements not only for their final drug products but for all drug components from their suppliers.**

12.) While the last revision to the USP <232> becomes official on August 1st. 2015 and was to have an official implementation date of December 1st, 2015, the new **(partially)** harmonized version will become effective January 1st, 2018. Which one should an early implementer follow? The USP states that early adoption of the standard is permitted and that all previous versions can be discounted.

13.) The revised <232> allows for a risk based control strategy but "due to the ubiquitous nature of **Arsenic, Cadmium, Lead and Mercury, they (at the minimum) must be considered in the risk based control strategy**. Regardless of the approach used, compliance with the limits specified is required. (No risk based strategy can eliminate these for elemental impurities). YOU MUST ASSESS AND TEST FOR THESE 4!!!

14.) It should also be noted that in difference to stated opinions in recent publication out of Europe where solvents are deemed "low risk" (Pharmaceutical Technology Europe, March 2015 issue – (See Addendum #11) and that the chance of presence of elemental impurities is small (due to distillation) this is in fact contrary to the fact for many solvents being used in the Pharmaceutical process. The "mood" in Europe seems to reflect the old position of a focus on the intentional introduction of elemental impurities versus the unknown and unintentional introduction over actual data and continues to lean "risk based analysis" toward the position of known introduction of elemental impurities. If a solvent is used in the manufacturing process: granulation, coating, washing of pill casings, synthesis of an API, cleaning equipment, to feed microbes or to purify proteins (just a few examples) then surely they need to be included in the risk analysis.

15.) Rather The USP <232> **and to a lesser degree** ICH Q3D requires that any analysis of manufacturing process and supply chain **takes into consideration all sources of exposure to heavy metals including those used intentionally, those introduced inadvertently and those occurring naturally or as a result of environmental exposure.** This includes **"the container closure system." The main difference between the EP (EMA) and the USP (FDA) standards is the requirement for "absolute data" (test everything) don't "assume". Risk based plans must show robustness. It will be interesting to see how the FDA chooses to audit these plans in the future against the actual <232> call for factual test data.**

16.) Concentrations of Arsenic and Mercury are allowed to be differentiated if in excess by way of speciation (that is, by oxidation state, organic complex or a combination there of) if in excess of the published PDE limits.

17.) Topical and mucosal applications will adhere to the same PDEs as Oral (table 1) except as indicated in the individual monograph. "Consider the oral PDE as a starting point".

18.) Parenteral drugs with a maximum daily volume up to 2L may use the maximum daily volume to calculate permissible concentrations from PDE's.

19.) The USP's original position was that the new <232> General Chapter would apply to all USP monographs, not just those with a previous specification for heavy metals. This mirrors the USP General Chapter <467> (Residual Solvents.) However, the USP and the FDA has indicated publically that they want to see <232> applied **ONLY** to final drug products, drug substances, excipients and other components of the manufacturing process or final product.

Meeting USP Guidelines & OTHER Key Points:

1. The USP <232> General Chapter calls for absolute analytical (quantitative) data according to USP <233> General Chapter requirements **even if incorporated into a risk assessment and control program.**

2. The FDA is allowing a risk-based approach (Risk Based assessment) for the control of elemental impurities in drug products. Regardless the USP <232> mandate is written in such a way that testing still applies to all components and substances to be conducted by "someone": either the Drug Manufacturer or the Supplier. **The need to be "aware" and capable of controlling the presence of Heavy metals in all components and substances is different than the approach taken by Pharmaceutical companies to bring the final drug product into compliance.** Please note that in the final ruling the wording relative to the supply chain has changed: "if, by process monitoring and supply-chain control manufacturers can demonstrate the absence of impurities, then further testing (MAY) not be needed." **If the supplier cannot do it than the Pharma company will have to take on the responsibility for it. While this may be possible for some components and process aids, it is virtually impossible for others (such as solvents).**

3. The FDA will allow alternate validated procedures for specific metal compounds if shown to be equal or better than the results provided using USP <233> methods and show to meet 233 testing guidelines. This is important because some metals are difficult to "extract" and prepare and/or be analyzed for use with ICP-MS. However the method must be validated according to the USP 233 guidelines. This will require a considerable amount of work.

4. **"Assurance of compliance to specified Levels is required."** **Each** lot of the DP must be fully tested unless absolute data can support the absence of the metal from the product, process and components with accurate validation. **This applies to all raw materials as well.**

5. If the USP ultimately adopts product monograph specific limits then individual components may need to be limited at levels below those in the tables depending on monograph-specific mitigating factors. This does not alleviate the requirement under <232> for the Drug Manufacturer to ultimately **CREATE** standards for the vendors.

Meeting USP <232> Guidelines:

1. **Perform Your Risk Assessment (if selling into Europe you need to do this anyway)**
2. **Evaluate your entire Mfg. Process**
3. **Evaluate your entire supply chain.**
4. **TEST, TEST, TEST**
5. **Get your suppliers to do the same!!!**
6. **Formulate your Control Strategy**
7. The presence of listed metals must (ultimately) be determined in every component, process, intermediate and final product. Establish PDE's for your products and Limits for your suppliers!

TESTING YOUR DRUG PRODUCT

See next section and…See Addendum # 15 and #16

CONCERNS:

1. The "Risk Based Approach" is needed to get through the mass of work now but has significant risks:

In the event of contamination the final product must be scrapped and cannot be reworked. In the event of a product recall companies will lose millions and be faced with stiff fines and even civil lawsuits

In addition, ENSURING that all heavy metals have been released in the sample prep procedures will be required (see next section and also addendum #15)

2.) A Risk Based approach is needed for drugs with many components but may not be the best approach for Drug Substances, Excipients, Solvents and less complex drugs.

3.) A Risk Based approach will NOT alleviate the ultimate burden of total validation of all sources, components and suppliers. Companies should begin to press their suppliers in regard to the new standards and ultimate testing of finished packaged lots supplied to the Pharmaceutical Company.

Ultimately Pharmaceutical companies will have to evaluate all elements of the drug-supply chain and defend them through the audit process.

Regarding EXCIPIENT VENDORS

In addition to previous statements regarding the application of General Chapter <232> to non-drug substances (and the need to test and report for heavy metals), the ICH-Q3D Publication specifically requires suppliers of excipients (at a minimum) to compile validation data on the levels of elemental impurities. In addition both the USP and ICH have reinforced through various statements and publications that excipients must be included in the risk analysis and for the USP in testing.

Upon publication of EMA's acceptance of ICH Q3D guidelines, IPEC immediately published another position paper pushing back on these mandates (see Addendum #10)**. Previously IPEC recommended not providing any data to Drug Product Manufacturers. Now that are simply threatening they can't do the work in time (EMA's timeline) and that drug shortages will result.**

In difference to this, BioSpectra is already in full compliance with USP <232>, EMA and ICH-Q3D standards for our World Grade Solvent line and tests each finished lot of material for all metals on all three standards as well as all other compendia tests!

1) The new USP <232> and ICH-Q3D standards pose a big challenge for many excipient suppliers due to the variable nature of heavy metals in their raw material (mining in particular). Most suppliers perform extremely infrequent (yearly) tests and only for one or two heavy metals. Variation of 1-50 ppm for certain heavy metals is common for individual lots coming from the same mine as well as from the same product from different sources. Ultimately these sources must perform lot-to-lot testing or the burden will fall on the Pharmaceutical companies buying and using this product.
2) Many other excipients have variable sources of nutrient supply (soil, ocean, etc.) and should be tested lot-to-lot.
3) Solvent based excipients in particular are subject to a whole host of exposure through the manufacturing, purifying and handling process.
4) Metals from excipients cannot be easily purified and are usually present (example, those that are solid material.)
5) Metals from excipients are highly variable, especially those that are mined.
   Reason for variability is the source for excipients:
   a. Mining ores
   b. Ocean

c. Plants – soil
d. Synthetic process

Example: Kaolin Mine in Czech Republic: 12-55 ppm Pb. / Talk Mine in the French Pyrenees (less than 10 ppm Pb but tested only once per year).
Example: Calcium Carbonate has high levels of CD
Example: Potassium Chloride has high levels of Pb

Note: in contrast to this, High Purity Ethanol is derived from corn:

- That is consumed by yeast
- Purified through a destructive distillation process
- Final product tested extensively

6) Many excipient suppliers do not have the capability to test for metals nor the desire as the Pharma business is the 3rd, 4th or 5th market.
7) IPEC is concerned that more suppliers will drop USP monographs making it more difficult to obtain supply. This will also shift more of the burden to the Pharmaceutical companies.
8) Therefore, any supplier already doing all this testing lot-to-lot (like BioSpectra) will become a valuable asset and supplier to the Pharmaceutical industry.

Review Points: USP <232>, EMA (EP) and ICH-Q3D

Heavy metals contamination is a "consumer" issue. The general population has a limited but potent (emotional) understanding of heavy metal toxicity (see Addendum **19**, "inside the mind of the FDA). There is no "acceptable level" of heavy metal contamination in the mind of many consumers especially parents particularly for metals such as Pb, As, Cd and Hg where "general knowledge" of toxic side effects are understood. In addition there is a lot of variability and uncertainty behind the generation of PDE's. Over time, increased public awareness will only increase skepticism, fear and anxiety of the general public. The ultimate impact of increased consumer education and response will result in stricter enforcement, tighter thresholds and a call for more complete data.

1. The FDA's primary objective (today) is for "TEST", "CONTROL" and "DOCUMENT". In time the public will become aware of the current standards and demand further scrutiny and transparency. In the meantime, drug manufacturers need to review their entire production process as well as their entire supply chain for each drug (a massive effort.) Chain of custody considerations will become acute for non-dedicated systems and vendors who do not perform lot-by-lot testing of raw materials. **Supply Chain Security will become a paramount issue in the coming years!**

2. The FDA is concerned about the use of technical grade solvents used **for DP and DS and other drug components. T**hey want to see the Industry begin to change its posture and think "Consumer

Safety" first. This may require a review of suppliers, a change in buying patterns and a renewed discussion between the Purchasing Department and the Quality Group over quality mandates.

3. The FDA is very concerned about abuses in cGMP practices. High level regulatory action and massive fines underscore the FDA's resolve to force the industry to change their thinking and behavior. (IMPAX, RAMBAXY, GSK, other)

4. Regulatory enforcement will continue to stiffen: The director of the FDA has already asked the Justice Department to help them begin "criminal prosecution" of "responsible parties" for flagrant abuses of cGMPs. This is not a new trend but a new "reality". The FDA is now following suit with other major Federal Agencies such as the EPA, OSHA, DOT and others.

5. The FDA's position will be "measured" and therefore will go slow at first. They understand that this is a massive change for the Pharmaceutical industry. They will want to see final drug products tested first. Then they will begin to enforce the "general clause" on API's, excipients and all other drum components. Ultimately they want the Pharmaceutical industry to embrace these changes and begin to enforce them on their suppliers. **(See addendum #17, 19 & 21).**

6. These new regulations **may** cause many suppliers of excipients and solvents to eventually "drop" the USP, EP or other grade certifications due to compliance issues. In other cases raw materials may be found to be too high or variable in heavy metals. This may require reformulation of certain drugs. **This will require drug manufacturers to redefine buying patterns for solvents used in the drug manufacturing process. (Sandoz' recall of 1M packages of generic Zyrtec).**

7. We know that cost of compliance is "high" for everyone in the industry: many products do not lend themselves easily to digestion and release of heavy metals and so method development for sample preparation and testing will also slow down progress.

8. Ultimately Pharmaceutical companies must segregate solvent purchases for API manufacturing and other critical control processes. They must also begin to "Police" the wide abuse of USP certification for solvents and other products that are clearly not being manufactured under cGMP or being fully tested according to USP specifications through the manufacturing process and/or the final batch and lot.

9. The USP <232> calls for a "dialog between the manufacturer and supplier". Get started now!

Future Perspectives

1. What is really a SAFE level of exposure? Is there really enough toxicological data to support the PDE's that have been set by the USP, EMA or ICH? This can and probably will change in the future. **THEREFORE KNOWING ABSOLUTE LEVELS OF METAL IMPURITIES IN ALL COMPONENTS WILL BE ABSOLUTELY NECESSARY IN THE FUTURE.** Don't formulate around current PDE's as they could change in the future. Therefore, Risk based testing is "very risky".

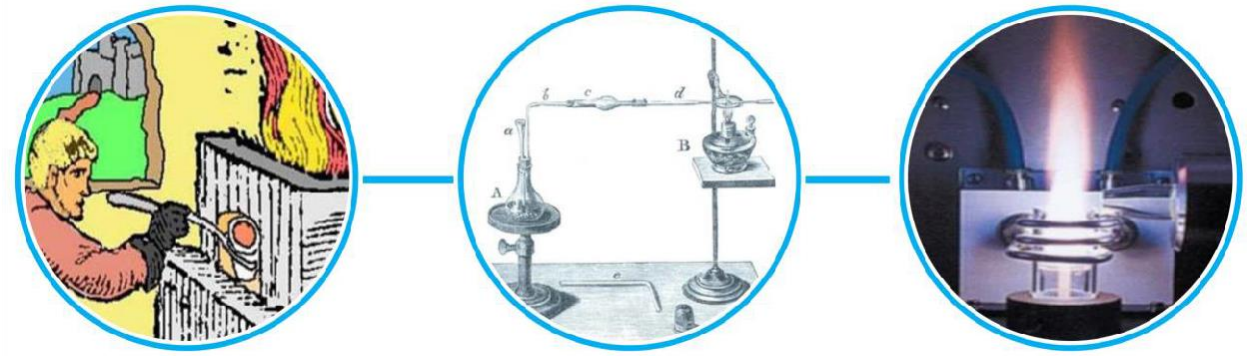
2. The FDA has made it clear where responsibility lay by stating in the USP <232> that Pharmaceutical companies are ultimately responsible for the **SAFE LEVEL OF IMPURITIES.** Companies with the highest tolerance levels to metal impurities and the lowest tolerance level to the principles of compliance set forth by the USP <232> and ICH-Q3D will be at risk.

3. This current debate over whether or not excipients and other components are included in the USP <232> mandate is a "fool's bargain". It's already stated clearly in the mandate and therefore it is only a matter of time before it is enforced.

Recommendations:

1.) Pharmaceutical companies should share and merge data under some consortium in the form of a database: (See Addendum #9)
2.) Pharmaceutical companies should use vendors who are willing and able to submit actual data! 3.) If that is not possible then Pharmaceutical companies should press their suppliers now for their own risk assessments and validation of same.
4.) Audit your suppliers!
5.) Get your risk assessment in place and then… keep going!
6.) If you are using solvents in the drug manufacturing process – TEST
7.) Make sure your API manufacturers are including solvents in their risk assessments and or testing protocols. Mark sure they are using higher quality solvents.

IV.) Analytical Procedures for USP <233>



Fire Assay ***Marsh Test*** ***IC Plasma***

Methods – Then and Now

Current pharmacopeia procedures (ex. USP <231> and EP 2.4.8) allows for qualitative wet chemistry tests based on visual comparison with known standards and not quantitative instrumental results. These qualitative tests are highly variable and subject to human error. Issues surrounding the USP <231> are well established in the literature to provide unreliable results in many applications. Subsequently, USP 231 will be "retired". The method dates back to 1905 and was never validated.

Additional USP chapters for the control of specific metals and other inorganic impurities have been added over the years. Significant among these additions has been USP chapter <730> Plasma Spectrochemistry which gave laboratories the opportunities to use techniques such as inductively coupled plasma with either mass spectroscopy or atomic (or optical) emission spectroscopy (ICP-MS and ICP-AES, (OES)). (see Addendum #25 for additional information on plasma spectroscopy)

The new general chapter <233> now requires these instrumental analytical techniques: ICP-AES or ICP-MS. The sophistication of the instrumentation requires system validation, sample preparation techniques and proper digestion of the samples to release the metals. This is posing some significant challenges to some suppliers through the entire drug supply chain. Ultimately, failure to provide this data will require the Drug Manufacturer to perform the work either on a routine basis or through a through validation of the source.

About ICP Methods

The advantage of ICP methods is that they can provide specific detection and quantification for each of the elements specified in chapter <232> eliminating the subjectivity of other semi-quantitative methods. The ICP techniques are also quicker in most cases and require a smaller sample size and give a better detection limit for all the elements of interest.

USP General Chapter <233> sets out general conditions for testing, covering preparation, analysis and the parameters for validation. The preparation methods referred to in the General Chapter are neat, direct aqueous solution, direct organic solution and indirect solution. For BioSpectra we have found that the solvents we work with require indirect solution preparation.

Neat samples are in such a state that they can be used without further preparation. More commonly used solutions will need to be prepared prior to analysis and the simplest of these procedures is preparation of a direct solution whereby a product is diluted with water/dilute acid or an organic solvent to give a solution for analysis. This did not work for us with our solvents.

In many cases, it is desirable to treat the sample by breaking down any organic meal contained within it; such a step typically reduces the matrix effect which might otherwise give rise to false positive and false negative results. When prepared in this way it is referred to as an indirect solution. These solutions are generally prepared using a microwave digester. The sample is heated to temperatures up to 250C and pressures of up to 55 bar. Under these conditions the sample matrix is effectively destroyed and the metal atoms are released into solution. After the sample is cooled, it is made up to a suitable volume with water, ready for analysis.

Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) a.k.a. (ICP-OES): Optical Emission Spectroscopy

ICP-AES: in this technique a samples solution is fed into an argon plasma which has temperatures of approximately 10,000C. The sample matrix is destroyed under these conditions and individual atoms are released. These atoms are then excited to a higher energy state. As the excited atoms cool, they return to a "ground state." The process releases energy in the form of light (i.e. atomic or optical emissions). The wavelength of which is specific to a particular element. When the light falls on a detector, it can be quantitated and the amount of analyte can be evaluated.

Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

Inductively coupled plasma mass spectrometry (**ICP-MS**) is a type of mass spectrometry which is capable of detecting metals at concentrations as low as one part in 10^{12} (part per trillion). This is achieved by ionizing the metal atoms in an Argon plasma (inductively coupled plasma) which are then fed into a quadrapole (MS) which separates the ions according to their mass-to-charge ratio. Following separation, the ions fall onto a detector and the sample can be quantified. Compared to atomic absorption techniques ICP-MS has greater speed, precision, and sensitivity.

Differentiating the new techniques

Both ICP-AES and ICP-MS are able to analyze several elements simultaneously. As a result, sample throughput can be very quick: typically 2-3 minutes per sample. Generally it is fair to say that ICP-AES instrumentation is cheaper than ICP-MS but both instruments have relatively high running costs due to the consumption of argon in the plasma. The key difference between the instruments is the

detection limit. The ICP-MS typically has detection limits 100 to 10,000 times lower than that of the ICP-AES. Both techniques HOWEVER, are capable of analyzing to the levels required by USP but ICP-MS can offer a much lower detection limit. The main limitation of the ICP-MS is that samples have to be in liquid form which necessitates digesting solid samples.

USP Chapter <233> states that for both techniques, steps must be taken to remove matrix interferences. For ICP-AES these interferences can occur from overlapping wavelengths. In this case, alternative wavelengths can be used for analysis. Also many instrument manufacturers have correction techniques built into the operating software. In the case of ICP-MS, the sources of matrix interferences come from the fact that different species can have the same mass/charge ratio as a specific metal ion. For example, argon-chloride appears as at the same mass as arsenic giving false positives. To remove these interferences, many instrument manufacturers use special cells within the instrument that can add gases to the ions and mitigate the interferences.

Mass spectrometry (MS)
is an analytical technique that measures the mass-to-charge ratio of charged particles (a type of molecular fingerprint). An **Inductively Coupled Plasma** (**ICP**) is a type of plasma source in which the energy is supplied by electric currents which are produced by electromagnetic induction, that is, by time-varying magnetic fields.

- BioSpectra has enhanced and improved our technical sophistication levels by investing in the Perkin Elmer NexION 300D ICP-MS along with dedicated personnel to operate it.
- BIOSPECTRA reconfigured and rebuilt our laboratory to create dedicated space for this instrument and accommodate for required environmental conditions.
- IQ/OQ/PQ for the instrument was completed by qualified personnel from Perkin Elmer.

NexION 350 Series ICP Mass Spectrometers

There is no question that ICP-MS is the most suitable multi-element technique for determining elemental impurities at these levels in pharmaceutical products. The desired limits, even for the large volume parenterals (LVP), which are the lowest specifications of all the different drug

delivery methods, can be reached. It can be seen that the PerkinElmer NexION® 350 ICP-MS detection capability is approximately 2-5 orders of magnitude lower than compendial requirements depending on the element of interest. The added benefit of ICP-MS for this application is that it can be seamlessly coupled to a liquid chromatographic (LC) separation system to determine the different forms of arsenic and mercury, **if required.**

It should be noted that even though there are four different models of NexION 350 ICP mass spectrometers, the configuration recommended for this application is the NexION 350X, which includes a single-channel universal collision/reaction cell. This enables the instrument to be used in either the Collision (KED) mode or the Reaction (DRC) mode using one cell gas, in addition to the Standard/normal ICP-MS mode. In fact, the detection limits in Table 2 were carried out by a combination of Collision mode and Standard mode. The Collision mode was used for elements like arsenic, which have the potential to be negatively impacted by the argon-chloride (ArCl) interference in a sample digested/diluted with hydrochloric acid, while the elements like the PGM's, which are known to be free of polyatomic spectral interferences, were determined using the Standard mode.

Additionally, one of the many unique features of the NexION's Universal Cell Technology™ is the capability known as Extended Dynamic Range (EDR) – this patented feature is very useful if the requirement is for both trace metal impurities and major nutritional elements in pharmaceutical or nutraceutical products. With EDR, the dynamic range can be extended for elements which are present at high concentrations. This means that for the analysis of dietary supplements, the nutritional elements like Ca, Mg, Na and K can be determined in the same multielement method as the suite of toxic contaminants (Cd, Pb, As, Hg) described in the proposed new Chapter <2232>, Elemental Contamination of Dietary Supplements, which is still in the review/comments stage.[7]

Another advantage of using NexION 350 ICP-MS technology for this application is the extremely good, long-term signal stability. The patented Triple Cone Interface translates into a well-defined ion beam, providing less dispersion of the ions, therefore preventing deposition on internal components. When combined with the novel Quadrupole Ion Deflector ion optics, which ensures particulate and neutral species never enter the Universal Cell or mass analyzer, the result is unsurpassed stability with real-world samples.

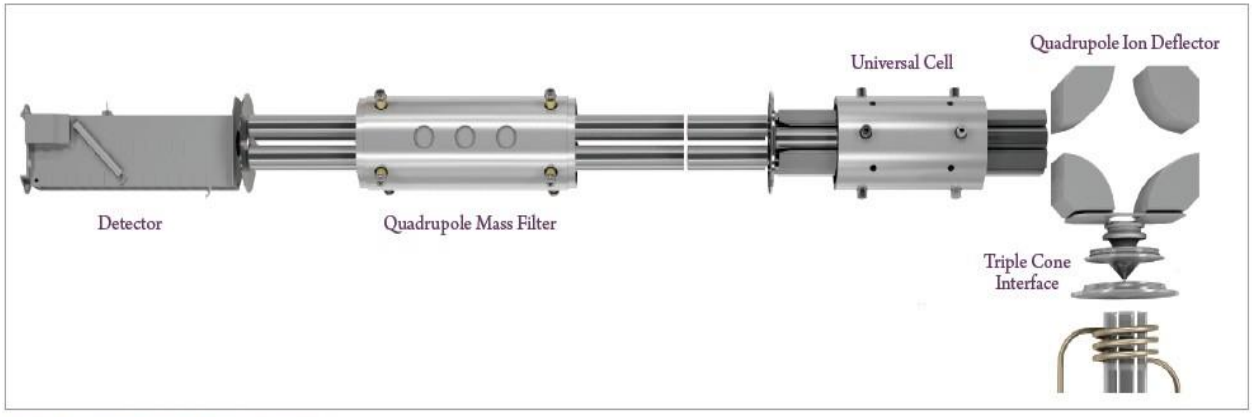


Figure 3. NexION 350 ICP-MS ion optics.

With NexION's design, no matrix particulates enter the mass spectrometer, dramatically reducing routine maintenance. The only components that need cleaning are the interface cones. When compared with other systems, which require tedious and time-consuming cleaning of the ion lens, cell and cones, the NexION 350 ICP-MS is ideally suited to the demands of the high-throughput QC pharmaceutical lab. And to keep the system running at peak performance, NexION ICP-MS Software provides alarms that can be set to remind the operator when it's time for the few preventative maintenance tasks required, such as roughing pump oil changes and tubing replacement. The system will even display how many hours various components have been used and when they might need attention. There is no question that the design of the interface and ion optic region on the NexION 350 ICP-MS is a direct result of PerkinElmer's proven experience in the development of ICP-MS instrumentation for real-world applications over the past 25 years.

Microwave Digestion

PerkinElmer also offers the Titan MPS™ Microwave Sample Preparation System, capable of the high-performance closed-vessel digestion required by USP <233>. Using the unique DTC™ and DPC™ contact and connection-free sensing technologies, the Titan MPS system accurately monitors the sample temperature in each digestion vessel to provide outstanding reaction control and deliver consistent digestion results. The TFM™ vessels employed in the Titan MPS are robust and simple to use, come with a one-year warranty and deliver the lowest background available to ensure the ability to meet the USP <232> detection requirements.

Figure 4. Titan MPS Microwave Sample Preparation System.

USP <233> Elemental Impurities – Procedural notes: (ref: Addendum #11, 12 & 16)

1. Instrumental methodology is very generic in nature with no details about instrumental parameters or the best masses to use. It basically includes a number of QC/QA validation protocols to ensure the method is working correctly including spike recovery, accuracy, and precision. **IN SPITE OF THIS THE USP WILL ALLOW THIS TO BE CONSIDERED A COMPENDIAL METHOD AS LONG AS YOU ARE FOLLOWING 233 PROTOCOLS!!!**
2. Target (element) limits (known as "J" values) defined as the acceptance value for the elemental impurity being evaluated, based on weight, number of doses and frequency of taking / administrating the drug that is, by approximating the Daily dose PDE / Maximum Daily dose.
3. Samples are diluted to the concentration does not exceed 2x J (2J) the target limits.
4. Speciation is not required (unless necessary to bring contamination levels into range).
5. Must use appropriate reference materials (ultra-pure reagents).
6. Samples are prepared and appropriate measures taken to correct for matrix-induced interferences. A collision / reaction cell may be used to reduce polyatomic spectral interferences.
7. Calibration using two matrix-matched calibration standards and a matrix-matched blank whenever possible.

8. Sample Preparation: Analysts are free to use whatever means of sample preparation is appropriate for their samples and target elements for their samples. Where digestion is required, closed-vessel digestion is the most appropriate method.***
9. All procedures, both compendial and alternate **must be verified for appropriateness** of the sample by meeting the Procedure Validation Requirements (as states in <233> Elemental Impurities Procedure.) Validation requirements in <233> supersede those found in <1225>

*** BioSpectra analyzes higher volatile solvents (acetone, ethanol, etc.) which require care due to volatility and appropriate digestion due to carbon spectral interferences from the solvent's high carbon content and the fact that the plasma might be extinguished by the higher vapor pressure of the volatile organic solvents. In these cases, pre-treatment is required with use of microwave digestion to insure release of all metals. In some cases the solvent is viscous (glycerin) which can cause the opposite problem in terms of volatility – not enough creating issues of appropriate nebulization. The use of pretreatment microwave digestion also removes this issue.

Solvents are evaporated and reconstituted in trace grade, nitric acid as most metals are not stable in solution for any of the solvents. As an example Hg is lost in an open vessel digestion.

Very few solvents can be evaporated on the digestion hot plate. They do not evaporate, melt the plastic when heated, or are too dangerous to heat in the open hood.

Certain solvents, such as glycerin cannot be nitrated directly (as they form dangerous reactions).

Therefore, Digestion via microwave ensures that all the organic matter is evaporated and nothing but the actual metals of interest is left. Microwave digestion allow for a single preparation for all elements of interest.

Procedure 2: ICP-MS

- Two standardization solutions: 0.5J and 1.5J
- Sample appropriately prepared
- Follow instrument manufacturer's recommendations for instrument parameters

Note: the alternate method must provide results at the same precision level of the mandated methods or better.

Note on Verification:

If you use method #1 or #2 you are allowed by the USP to accept these as validated even though they are non-specific methods. Verification procedures are incorporated therein. If however you cannot use these methods you must follow the rigors of validating your new procedure.

Validation of Alternate or Compendial Procedures - Follow guidelines found in USP <233> Elemental Impurities – Procedures:

(For additional details please refer to Addendum #15, 16 & 20)

NOTE: The parameters of acceptance criteria presented in Chapter <233> take precedence OVER USP Chapter <1225> Validation of Compendial Procedures.

NOTE: Any alternative procedure MUST be validated according to <1225> and must demonstrate same level of accuracy. Once this is done it can be considered equivalent to the compendia procedures for the purposes of <233>. This is lot more work than the verification requirements below.

1. Detectability / Stability: Can your procedure "see it"? (range of detection) 15% Stability of the method by measuring an appropriate concentration level of spike relative to the target limits before and at the end of analyzing a batch of samples.
2. Repeatability: Can your procedure repeat the same results (vs. drift) by measuring 6 independent samples of the material under investigation, spiked at the target limits defined and measuring the recovery and precision of the measurements: RSD, NMT 20%
3. Accuracy: Can your procedure accurately achieve a known number by spiking the material under investigation at appropriate concentration levels related to the target limits and measuring the % accuracy. Limits allowed: 70 to 150%
4. Ruggedness: does the procedure work on different instruments or different days and different analysts? NMT 25%
5. Specificity: The procedure must be able to differentiate between the target element and the other elements in the presence of components that are expected to be present in the matrix.

V.) ADDENDUMS

I. ICH

1. Q3D_Step_4
2. Q6A_test procedures and acceptance criteria
3. Q6B_Guideline
4. Q8_Guideline
5. Q9_Guideline

II. EC/EP/EMA

6. EMA, 26 Feb 2015, CHMP, QWP, 109127, 2015
7. EMA, January 2015, CHMP, ICH, 353369, 2013
8. EMA.CHMP.SWP.4446.2000. Feb 2008 guidline for metal catalysts and reagents
9. GMP news 1,2,3 &4
10. IPEC Federation Publishes Position Paper on EU Risk Assessment Guidelines for Excipients
11. Pharma Tech Europe Artical on ICH implementation, challenges, opportunities

III. USA / USP / FDA

12. 232, 2nd supplement to USP 38
13. 232, original General Chapter
14. 232, revised notes, 1st supplement issued Feb 2015
15. 233, 2nd supplement to USP 38
16. 233, original general chapter
17. Commentary to 2nd Supplement USP 38, relative to 232 and 233
18. General Notice, 5.60.30
19. MK057_USP_232_Inside the mind of the FDA rev 1.4_ 09.10.2015_pd
20. USP 1225 Validation procedures
21. USP FAQs from 2014 and 2015
22. USP Implementation Plan for Elemental Impurities Gen Chapters 232 and 233
23. USP Supplement 3, Correspondence Number C163959
24. XXX notes regarding toxicity
25. XXX USP General Chapter 730