

Harmonized Guideline on Limit and Testing of Elemental Impurities in Pharmaceutical Substances: A Review

Reddy MM*, Reddy KH and Reddy MU

Department of Chemistry, Sri Krishnadevaraya University, Ananthapur, Andhra Pradesh-515003, India

*Corresponding author: Reddy MM, Department of Chemistry, Sri Krishnadevaraya University, Ananthapur, Andhra Pradesh-515003, India, Tel: 9705360365; E-mail: musirikemahesh@gmail.com

Received date: May 03, 2016; Accepted date: July 18, 2016; Published date: July 20, 2016

Copyright: © 2016 Reddy MM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Testing of elemental impurities as heavy metals has been in use for many years. Lack of sensitivity and reproducibility are the main limitations of current heavy metals procedure USP <231>. The procedure described for heavy metals will detect Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu and Mo. The new chapters are designed for safer limits and enhanced detection limits. ICH was proposed a draft consensus guideline and under step 2b version in the year 2013 and posted as official from December 2014 under step 4 version. EMEA released a comment by stating that new marketing authorization for new product should comply with ICH/CHMP guideline effective from June 2016; where a control of an elemental impurity is warranted, an elemental specific method is requested by the guideline. Therefore, a non-specific compendial test for heavy metals will not be accepted. USFDA published the final Q3D Elemental impurities guidance on September 2015. Color comparison of test will be replaced by instrumental techniques like Atomic absorption spectroscopy (AAS), Graphite furnace atomic absorption spectroscopy (GFAAS), Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

Keywords: Elemental impurities; Specification; Testing procedure; Heavy metals; ICH; USP; ICP-OES; ICP-MS

Introduction

Impurities in pharmaceutical substances can be classified into three groups; Organic impurities, Residual solvents and inorganic impurities. Inorganic impurities can result from the manufacturing process. They are normally known and identified and include; Reagents, ligands and catalysts, heavy metals or other residual metals and inorganic salts [1-2]. If any is added intentionally, it should be considered in the risk assessment [3-4]. While some elemental impurities though intentionally not added, may be present in some drug substances and excipients. The possibility for inclusion of these elements in the drug product should be reflected in the risk assessment. The contribution of elemental impurities arise from manufacturing equipment may be limited, and the subset of elemental impurities should be considered in the risk assessment will depend on the manufacturing equipment used in the production of the drug product [5].

Elemental impurities are classified into three categories [6] based on their toxicity (PDE) and occurrence in the drug product. Class 1 includes As, Pb, Hg and Cd. Elements that are categorized in Class 2 are further divided in sub-classes 2A and 2B. The class 2A elements are: Co, Ni and V. The elemental impurities in class 2B include: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl. The elements comes under Class 3 are relatively low toxicities by the oral route of administration but may require consideration in the risk assessment for inhalation and Parenteral routes. The elements in this class include: Ba, Cr, Cu, Li, Mo, Sb, and Sn. Some elemental impurities for which PDEs have not been established due to their low inherent toxicity and differences in

regional regulations are not addressed in this guideline which includes Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn.

The current heavy metals [7-18] limit test as stated in pharmacopeias EP 2.4.8 and USP 231 method has been the main reference for more than hundred years; the method has basically a limit of 10 ppm. The basic reaction is between metal impurities and thioacetamide to form sulfides. The intensity of the colored sulfide precipitate is compared with a lead reference standard. The test is less sensitive, non-specific and does not provide adequate recovery of the elements being tested. The test is difficult to conduct, time consuming and it is not able to detect some toxic elements.

Generally, most elemental analysis has been performed by Atomic absorption spectroscopy (AAS) [19-29] or Optical emission spectroscopy (OES). Sub-ppb level elements were measured by graphite furnace atomic absorption spectroscopy (GFAAS) [30-35] but this is a high sensitive single-element technique. Inductively coupled plasma optical emission spectroscopy (ICP-OES) [36-40] is a less sensitive (ppm to ppb) and able to detect simultaneous multi-elements. Inductively coupled plasma mass spectrometry (ICP-MS) [41-46] is a highly sensitive and multi-element technique.

Potential sources and identification of elemental impurities: Residual impurities from intentionally added reagents and catalysts, water or excipients used in the process, manufacturing equipment and container closure system are the main potential sources of elemental impurities.

Intentionally added elements should be considered for risk assessment. They are usually known, controlling and analyzing these impurities are easily defined. Elements that are not intentionally added should be addressed in risk assessment. Based on the knowledge of manufacturing equipment composition, process knowledge and

equipment selection, potential impurities that can be originated from manufacturing equipment can be identified and controlled. When compare to drug product drug substances are more potential to leach or remove elemental impurities from equipment. Based on scientific

knowledge on interaction of container closure system with drug product they can be easily identified and controlled. There is higher probability of leaching for liquids and semi solids from container closure system. Figure 1 denotes source of elemental impurities.

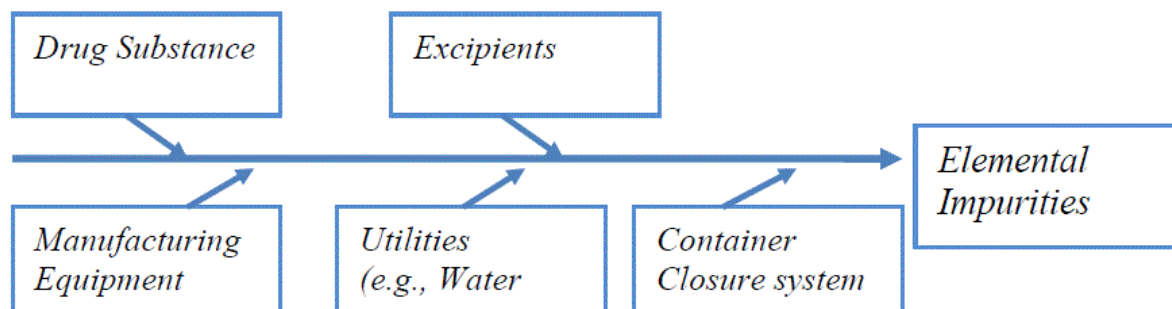


Figure 1: Fishbone diagram of elemental impurities sources.

Classification of elemental impurities

The metals that will respond to the USP <231> heavy metal test are As, Hg, Pb, Cd, Sb, Bi, Sn, Cu, Ag and Mo. EP 2.4.8 added extra 5 elements to that of USP those are Au, Pt, Pd, V and Ru.

Classification as per European Medicines Agency (EMA)

Metal residues are placed in three classes as per EMA guideline. Metals of significant toxicities includes human carcinogens are placed in Class 1. The metals that are currently included in Class 1 are further subdivided into three subclasses called class 1A, 1B and 1C. Platinum and palladium comes under Class 1A. Ir, Os, Rh and Ru elements are placed in Class 1B. Class 1C elements are Mo, Ni, Cr and V. Metals of low safety concern are placed in Class 2 and which includes Cu and Mn. Class 3 group includes metals with no significant toxicity, elements comes under this category are Fe and Zn. Figure 2 indicates classification of elements as per EMA.

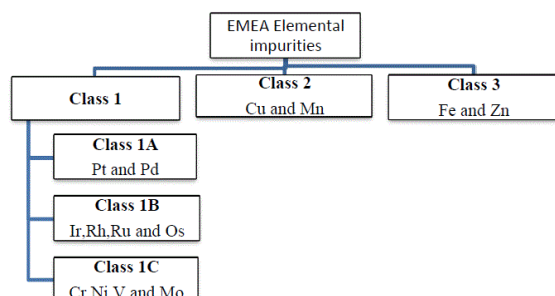


Figure 2: EMA classification of elemental impurities.

probability of occurrence in the drug product Class 2 elements are further divided in to Class 2A and Class 2B. Class Elements that are high probability occurrence are Class 2A elements than Class 2B elements. Class 2A elements should be considered for risk assessment whereas Class 2B elements need not be considered during risk assessment. Class 3 elements are relatively low toxic elements but may require consideration of risk assessment for inhalations and parenteral routes. Class 4 elements are low inherent toxic elements and daily exposure limits for them are not established.

The elements under Class 1 are As, Pb, Hg and Cd. Elements in Class 2A are CO, Ni and V. Class 2B elements are Au, Ag, Pt, Pd, Os, Ir, Rh, Ru, Tl and Se. Elements under class 3 are Li, sb, Ba, Mo, Cu, Sn and Cr. Class 4 elements are Li, B, Ca, Fe, K, Mg, Mn, Na, W and Zn. Figure 3 represents classification of elemental impurities.

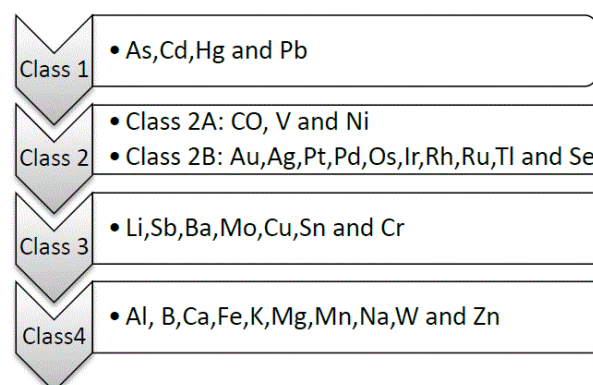


Figure 3: ICH classification of elemental impurities.

Classification as per International Conference on Harmonization (ICH)

Based on the toxicity and likelihood occurrence, elements are placed in to three classes in ICH Q3D guideline. Class 1 elements are human toxicants and should be evaluated during risk assessment. Considering

Limits of elemental impurities

The general limit for heavy metals in the United States Pharmacopeia (USP) and European Pharmacopeia (EP) is 10 ppm or 20 ppm. The developed test color solution varies for different metals.

There are chances of under-reporting and over-reporting when compared against lead standard solution.

Limits of elemental impurities as per EMEA: Taking into account the route of administration limits are proposed for each class of metals.

Table 1 provides information on permitted daily exposure and concentration limits for residues of the metals. Table 1 represents classification, exposure and concentration limits of elements.

Classification	Oral Exposure		Parenteral Exposure		Inhalation Exposure
	PDE (µg/day)	Concentration	PDE (µg/day)	Concentration	PDE (µg/day)
		(ppm)		(ppm)	
Class 1A:	100	10	10	1	70
Pt and Pd					
Class 1B:					
Ir, Rh, Ru and Os					
Class 1C:	100	10	10	1	-
Mo, Ni, Cr and V	250	25	25	2.5	Ni:100
					Cr:10
Class 2:	2500	250	250	25	-
Cu and Mn					
Class 3:	13000	1300	1300	130	-
Fe and Zn					

Table 1: Class, exposure and concentration limits of elemental impurities as per EMEA.

Limits of elemental impurities as per United States of Pharmacopeia (USP)

inhalation. Table 2 represent exposure and concentration limits of elements.

Based on chronic exposure limits of elemental impurities are proposed for three routes of administration; oral, Parenteral and

Element	Oral Exposure		Parenteral Exposure		Inhalation Exposure	
	PDE (µg/day)	Concentration (ppm)	PDE (µg/day)	Concentration (ppm)	PDE (µg/day)	Concentration (ppm)
Cadmium	25	2.5	2.5	0.25	1.5	0.15
Lead	5	0.5	5	0.5	5	0.50
Arsenic	1.5	0.15	1.5	0.15	1.5	0.15
Mercury	15	1.5	1.5	0.15	1.5	0.15
Iridium	100	10	10	1.0	1.5	0.15
Osmium	100	10	10	1.0	1.5	0.15
Palladium	100	10	10	1.0	1.5	0.15
Platinum	100	10	10	1.0	1.5	0.15
Rhodium	100	10	10	1.0	1.5	0.15
Ruthenium	100	10	10	1.0	1.5	0.15
Chromium	-	-	-	-	25	2.5

Molybdenum	100	10	10	1.0	10	1.0
Nickel	500	50	50	5	1.5	0.15
Vanadium	100	10	10	1.0	30	3.0
Copper	1000	100	100	10	100	10

Table 2: Exposure and concentration limits of elemental impurities as per USP.

Limits of elemental impurities as per International Conference on Harmonization (ICH)

PDE values of elemental impurities were established, according to the procedures for setting exposure limits in pharmaceuticals, and the method adopted by International Programme for Chemical Safety (IPCS) for Assessing Human Health Risk of Chemicals. Assuming

daily intake of drug product 10 g or less common permissible target elemental concentration for each component in the drug is calculated as per the below given expression. Table 3 represent exposure and concentration limits of elements.

$$\text{Concentration } (\mu\text{g/g}) = \frac{\text{PDE } (\mu\text{g/day})}{\text{Max daily dosage (g/day)}}$$

Metal	Class	Oral Exposure		Parenteral Exposure		Inhalation Exposure	
		PDE (μg/day)	Concentration (ppm)	PDE (μg/day)	Concentration (ppm)	PDE (μg/day)	Concentration (ppm)
Cd	I	5	0.5	2	0.2	2	0.2
Pb	I	5	0.5	5	0.5	5	0.5
As	I	15	1.5	15	1.5	2	0.2
Hg	I	30	3.0	3	0.3	1	0.1
Co	2A	50	5.0	5	0.5	3	0.3
V	2A	100	10	10	1	1	0.1
Ni	2A	200	20	20	2	5	0.5
Tl	2B	8	0.8	8	0.8	8	0.8
Au	2B	100	10	100	10	1	0.1
Pd	2B	100	10	10	1	1	0.1
Ir	2B	100	10	10	1	1	0.1
Os	2B	100	10	10	1	1	0.1
Rh	2B	100	10	10	1	1	0.1
Ru	2B	100	10	10	1	1	0.1
Se	2B	150	15	80	8	130	13
Ag	2B	150	15	10	1	7	0.7
Pt	2B	100	10	10	1	1	0.1
Li	3	550	55	250	25	25	2.5
Sb	3	1200	120	90	9	20	2
Ba	3	1400	140	700	70	300	30
Mo	3	3000	300	1500	150	10	1
Cu	3	3000	300	300	30	30	3
Sn	3	6000	600	600	60	60	6

Cr	3	11000	1100	1100	110	3	0.3
----	---	-------	------	------	-----	---	-----

Table 3: Exposure and concentration limits of elemental impurities as per ICH.

Harmonized limits for elemental impurities

In order to have a common approach among all regulatory authorities. The current USP <231> heavy metal test will be replaced with USP <232> elemental impurities with ICH Q3D specification. USFDA published the final ICH Q3D Elemental impurities guidance on September 2015. EMEA proposed a recommendation on implementation of elemental impurities by stating that new marketing authorization for new product should comply with ICH/CHMP guideline effective from June 2016.

This International Conference on Harmonization (ICH) guidance on elemental impurities provides a unified standard for the European Union, Japan, and the United states.

Procedures for Elemental Impurities

Color comparison test

Comparing color of the test sample with colored lead standard Solution has been in use for many years as recommended by United

States of pharmacopeia, European pharmacopeia and Japan pharmacopeia. The reaction is mainly based on the metal impurities present in the sample and thioacetamide to form sulfide ion. The colored sulfide precipitate is compared with lead standard solution. The test is less sensitive, non-specific and does not provide adequate recovery of the elements being tested. The test is difficult to conduct, time consuming and it is not able to detect some toxic elements and need to be replaced by modern analytical methods. Figure 4 shows an image of color comparison test.

Atomic Absorption Spectrometry (AAS)

The source of atoms generation in AAS is Air/Acetylene or Nitrous oxide/Acetylene flame. When a hollow cathode lamp passed on to the cloud of atoms, the selected metals to monitor absorbs the light from the lamp and the concentration is measured by a detector. Most of the elements reach excitation temperature under the source with a maximum temperature of 2600°C.

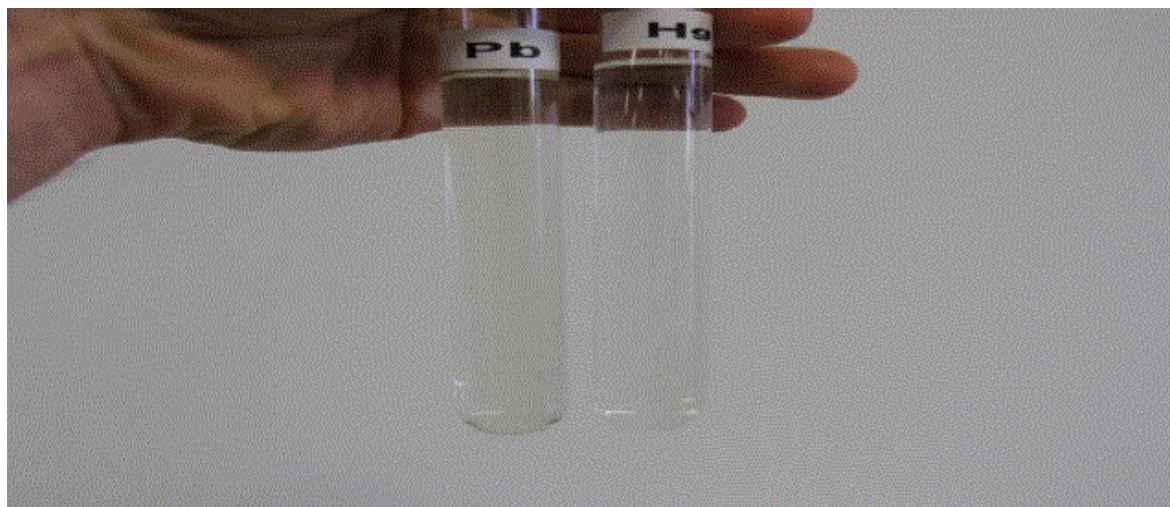


Figure 4: Testing of heavy metals against lead standard solution.

For a few elements like V, Zr, Mo and B, the temperature is not sufficient to breakdown as results sensitivity is reduced. Moderate detection limits, element limitation and only few elements for determination are some limitation of Atomic absorption spectroscopy. A schematic diagram of Atomic absorption spectrometer is shown in Figure 5.

Graphite furnace atomic absorption Spectrometry (GFAAS) is technically same as AAS but flame source is replaced with electrically heated graphite tube and which can be heated up to 3000°C. Detection limits are increased by 1000 times when compared to AAS. However refractory element performance, only few elements for determination and slow speed are some limitations.

Inductively coupled plasma atomic emission spectrometry (Icp-Aes or Icp)

The source in ICP emits temperature as high as 10,000°C where all elements including refractory elements atomizes with higher efficiency as a result lower levels of elements can be determined precisely. There are two variants in ICP, radial and axial. Axial viewing increases the path length and reduces the plasma background signal, resulting in lower detection limits. ICP is a multi-element technique, under the source of plasma sample dissociate into its atoms and ions. At excitation level they emit light at characteristic wave length. The concentration of particular element in the sample can be measured from intensity of emitted light with a detector. The detection limits in

ICP are moderate to low. A schematic diagram of Inductively Coupled Plasma Atomic Emission Spectrometry is shown in Figure 6.

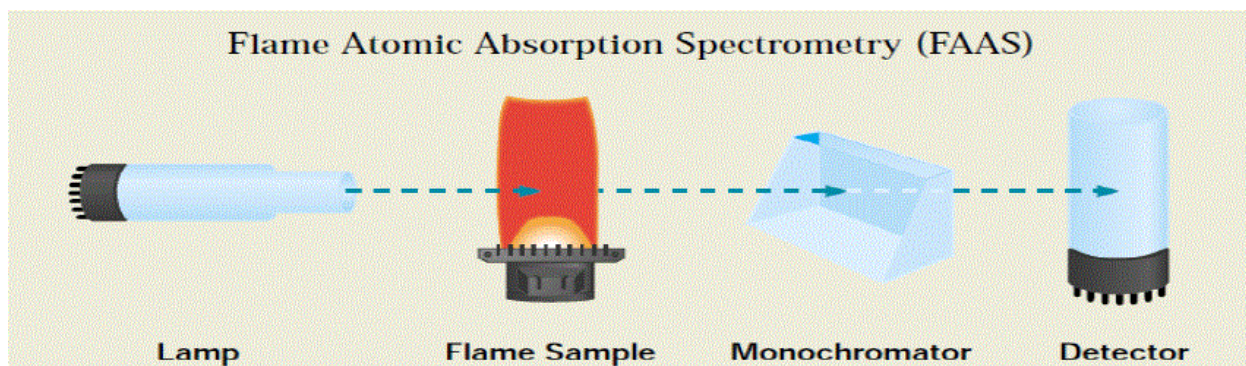


Figure 5: Schematic diagram of AAS spectrometer.

Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

The same source is used to dissociate sample into atoms and ions as mentioned in ICP. It is a multi-element technique. The basic difference

between ICP-AES and ICP-MS is, ions are directly detected in MS rather than emission of light as in the case of ICP-AES. The ions are separated by quadrupole based on mass-to-charge ratio.

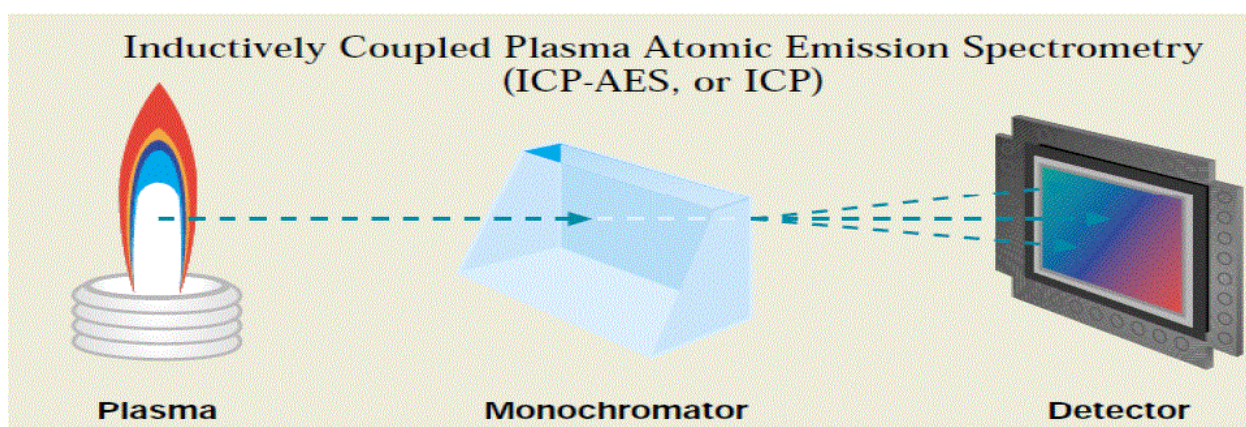


Figure 6: Schematic diagram of ICP-AES spectrometer.

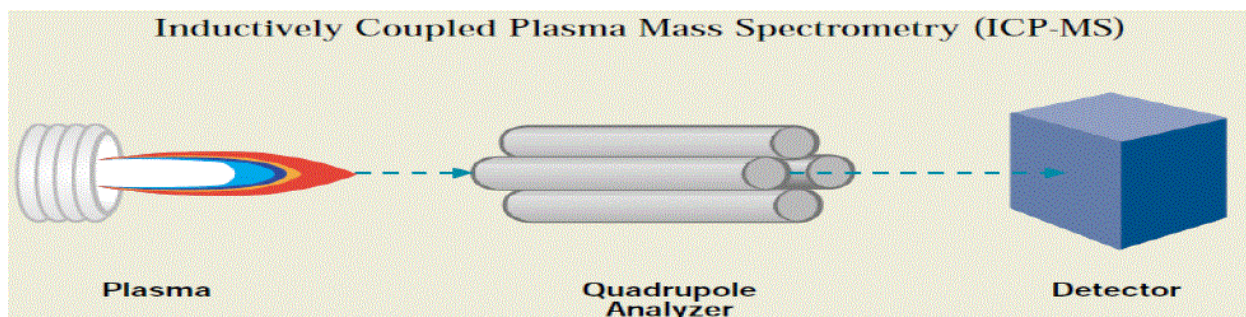


Figure 7: Schematic diagram of ICP-MS spectrometer.

Best detection limits are available for most of the elements as the number of ions produced is high. Though some spectral interference is seen but they are defined and limited. A schematic diagram of

Inductively Coupled Plasma Mass Spectrometry is shown in Figure 7. Simplified comparison of AAS, GFAAS, ICP and ICP-MS is given in Table 4.

	ICP-MS	ICP-OES	Flame AAS	GFAAS
Detection Limits	Excellent for most elements	Very good for most elements	Very good for some elements	Excellent for some elements
Sample throughput	All elements <1 min	1-60 elements/Min	15 sec/element	4 min/element
Dynamic range	108	106	103	102
Precision				
Short Term	0.5-2%	0.1-2%	0.1-1%	0.5-5%
Long Term	2-4%	1-5%	1-2%	1-10%
Isotopes	Yes	No	No	No
Interferences				
Spectral	Few	Many	Very few	Very few
Chemical	Some	Very few	Many	Very few
Physical	Some	Very few	Some	Very few
Semi quantitative	Yes	Yes	No	No
Method Development	Difficult	Moderate	Easy	Moderate
Capital cost	Very High	High	Medium-High	Low

Table 4: Simplified comparison of AAS, GFAAS, ICP and ICP-MS.

Summary and Recommendations

Heavy metal procedure to report elemental impurities has been in use for many years. It is not specific and less sensitive. Common specification limit of 10-20 ppm for all metals may be a concern. To have a common approach among all the authorities, ICH Q3D proposed Guideline for elemental impurities under step 4 version. USP published elemental impurities-limits in USP 39-NF 34 and which is official from May 1, 2016. EMEA declared that the guideline will be in force for new marketing authorization applications effective from June 2016. In September 2015 USFDA published Q3d Elemental impurities under the guidance for industry. Color comparison test with lead reference solution will be replaced with instrumental technique. ICP-AES and ICP-MS detect multi-elements at a time with higher sensitivity.

Conflict of Interests

The author declares no conflict of interests.

References

- ICH (2006) Q3A (R2): Impurities in new drug substances.
- Schicher H (1983) Contamination of natural products with pesticides and heavy metals. In: BreimerDD, Speiser P (eds.) *Topics in Pharmaceuticals Sciences*. Elsevier Science, Amsterdam, p: 417.
- US EPA (2004) Boron and Compounds. *Integrated Risk Management System (IRIS)*.
- Blake K (1995) Harmonization of the USP, EP and JP heavy metal testing procedures. *Pharm Forum*, pp: 1638-1640.
- USFDA (2015) Guidance for industry. Impurities in new drug substances: Q3D Elemental impurities.
- ICH (2014) Q3D (R2) Impurities in new drug substances: Current Step 4 version.
- AOAC (Association of Official Analytical Chemists) (1998) Wet digestion for non-volatile metals. In: *AOAC official methods of analysis* (16th edn.).
- Haider S, Naithani V, Barthwal J, Kakkar P (2004) Heavy metal content in some therapeutically important medicinal plants. *Bulletin of Environmental Contamination and Toxicology* 72: 119-127.
- ATSDR (Agency for Toxic Substances and Disease Registry) (2007) *Toxicological Profile for Lead*. Agency for Toxic Substances and Disease Registry: U.S. Department of Health and Human services, Public Health Service Atlanta, GA, USA.
- Mudipalli A (2007) Lead hepatotoxicity and potential health effects. *Indian Journal of Medical Research* 126: 518-527.
- Huff J, Lunn RM, Waalkes MP, Tomatis L, Infante PF (2007) Cadmium induced cancers in animals and in humans. *International Journal of Occupational and Environmental Health* 13: 202-212.
- Prozialeck WC, Edwards JR, Nebert DW, Woods JM, Barchowsky A, et al. (2008) The vascular system as a target of metal toxicity. *Toxicological Sciences* 102: 207-218.
- Jiang SY, Sun H, Wu XC, Zhou Y, Ma XJ, et al. (2006) Analysis and quality assessment standard of heavy metals and arsenic in Rhizoma et Radix notopterygii from different localities. *Zhongguo Zhong Yao Za Zhi* 31: 978-980.
- Chuang IC, Chen KS, Huang YL, Lee PN, Lin TH (2000) Determination of trace elements in some natural drugs by atomic absorption spectrometry. *Biological Trace Element Research* 76: 235- 244.
- FDA (U.S. Food and Drug Administration) (1999) U.S. Department of Health and Human Services 21 CFR: 556.60.
- FDA US Food and Drug Administration (1984) Action Level for Methyl mercury in Fish. *Federal Register* 49.
- WHO (World Health Organization) (1989) Evaluation of certain food additives and contaminants. Thirty-third report of the joint FAO/WHO expert committee on food additives. WHO technical report series number 776. WHO, Geneva, Switzerland.
- WHO (World Health Organization) (1997) Guideline for drinking water quality recommendations (2nd edn.) WHO, Geneva, Switzerland.

19. Walsh A (1955) The application of atomic absorption spectra to chemical analysis. *Spectrochim Acta* 7: 108-117.
20. L'vov BV (1984) Twenty-five years of furnace atomic absorption spectroscopy. *Spectrochim Acta Part B* 39: 149-157.
21. Becker-Ross H, Florek S, Heitmann U, Weisse R (1996) Influence of the spectral bandwidth of the spectrometer on the sensitivity using continuum source AAS. *Fresenius J Anal Chem* 355: 300-303.
22. Harnly JM (1986) Multielement atomic absorption with a continuum source. *Anal Chem* 58: 933A-943A.
23. Matousek JP, Brodie KG (1973) Direct Determination of Lead Airborne Particulates by Nonflame Atomic Absorption. *Anal Chem Acta* 45: 1606.
24. Runnels JH, Merryfield R, Fisher HB (1975) A Method for Improving Detection Limits for Some Elements with the Graphite Furnace Atomizer. *Anal Chem* 47: 1258.
25. Aggett J, Sprott AJ (1974) Non-flame Atomization in Atomic Absorption Spectrometry. *Anal Chim Acta* 72: 49.
26. Maessen FJM, Posma FD (1974) Fundamental Aspects of Flameless Atomic Absorption Using the Mini Massmann Carbon Rod Atomizer. *Anal Chem* 46: 1439.
27. Van Den Broek WM, De Galan L, Matousek JP (1978) Gas Temperature inside Graphite Furnaces used for Atomic Absorption Spectrometry. *Anal Chem Acta* 100: 121.
28. Brodie KG, Matousek JP (1974) Determination of Cadmium in Air by Non-Flame Atomic Absorption Spectrometry. *Anal Chem Acta* 69: 200.
29. Rousselet F, Thuillier F, Prog (1978) AAS Determination of Metallic Elements in Pharmaceutical Products. In: *Anal Atom Spectr* 1: 353.
30. Ediger RD (1975) Atomic Absorption Analysis with the Graphite Furnace using Matrix Modification. *Atomic Absorption Newsletter* 14: 127.
31. Guevremont R (1980) Organic Matrix Modifiers for Direct Graphite Furnace Atomic Absorption Determination of Cadmium in Sea Water. *Anal Chem* 52: 1574.
32. Sturgeon RE, Siv KWM, Gardner GJ, Berman SS (1986) Carbon-oxygen Reactions in Graphite Furnace Atomic Absorption Spectrometry. *Anal Chem* 58: 42.
33. Holcombe J, Rayson G (1983) Analyte Distribution and Reactions within a Graphite Furnace Atomizer. *Prog Analyt Atom Spectros* 6: 225.
34. Chang S, Chakrabarti C (1985) Factors Affecting Atomization in Graphite Furnace Atomic Absorption Spectrometry. *Prog Analyt Atom Spectros* 8: 83.
35. Niskavaara H, Virtasalo J, Lajunen (1985) Determination of Antimony in Geochemical Samples by Graphite Furnace AAS using Different Matrix Modifiers. *Spectrochim Acta* 408: 1219.
36. Boss CB, Fredeen KG (1997) Concept Instrumentation and Techniques in Inductively Coupled Plasma Optical Emission Spectrometry (2nd edn.) Perkin-Elmer, Norwalk, CT.
37. Fassel VA (1986) Analytical Inductively Coupled Plasma Spectroscopies-Past, Present, and Future. *Fresenius Z Anal Chem* 324: 511-518.
38. Carey JM, Caruso JA (1992) Electrothermal Vaporization for Sample Introduction in Plasma Source Spectrometry. *Crit Rev Anal Chem* 23: 397-439.
39. Ramsey MH, Thompson M (1985) Correlated Variance in Simultaneous Inductively Coupled Plasma Atomic-emission Spectrometry: Its Causes and Correction by a Parameter-related Internal Standard Method. *Analyst* 110: 519-530.
40. Dickenson GW, Fassel VA (1969) Emission Spectrometric Detection of Elements at Nanogram per Milliliter Levels Using Induction Coupled Plasma Excitation. *Anal Chem* 41: 1021-1024.
41. Montaser A (1998) Inductively Coupled Plasma Mass Spectrometry, WileyVCH, New York.
42. Taylor HE (2001) Inductively Coupled Plasma Mass Spectrometry, Academic Press, San Diego.
43. Thomas R (2003) A Beginner's Guide to ICP-M. *Spectroscopy magazine*.
44. Baranov VI, Tanner S (1999) A dynamic reaction cell for ICP-MS. Part 1: The rf-field energy contribution in thermodynamics of ion-molecule reaction. *Journal of Analytical Atomic Spectrometry* 14: 1133-1142.
45. Tanner S, Baranov V (1999) A dynamic reaction cell for ICP-MS. Part 2: Reduction of interferences produced within the cell. *J Am Soc Mass Spec* 10: 1083-1094.
46. http://www.horiba.com/fileadmin/uploads/Scientific/Downloads/OpticalSchool_CN/TN/ICP/ICP-OES_ICP-MS_and_AAS_Techniques_Compared.pdf