Elemental Impurity Analysis in Pharmaceuticals

A method to identify the presence of heavy metals in pharmaceuticals was introduced in the United States Pharmacopoeia more than 100 years ago. Today pharmaceutical companies are still using essentially the same method, the USP <231> Heavy Metals Limit Test. This paper will give an overview of the current method limitations, considerations for the new methodology and the risk-based assessments being carried out by manufacturers.

The current colorimetric methodology was intended to control metals which form a sulfide precipitate, such as lead and copper, which are potential contaminants from water pipes, manufacturing equipment and processes. However, the risk factors for metal contamination have changed dramatically, for example with the use of metal catalysts, yet the standards for their control have changed little in more than 50 years. The method is no longer fit for purpose and most heavy metal limits currently in place have little basis in toxicology. To that end whilst IPEC (International Pharmaceutical Excipients Council) Americas, state that they are unaware of any known metal impurity issues impacting patient safety, they, along with pharmaceutical manufacturers and regulators, agree on the need to enhance and harmonise future testing. However, harmonisation of pharmacopoeia methods has a history of making slow progress and it is not surprising that this task has taken as long as it has in coming to what appears to be a conclusion when the Q3D Expert Working Group expects to reach Step 4 later this year following the publication at Step 2 of the ICH Q3D document in June 2013.

So why the need to change the method?

As previously mentioned the principal of the current method is the formation of coloured sulfide precipitates, to visually demonstrate the presence of metallic impurities. There are five key issues with the current procedures:

- **Specificity:** There is no comprehensive list of the elements common to the pharmacopoeia heavy metals limit tests. Whilst the method identifies that there is a heavy metal present, it does not identify which impurity or combination of impurities has been identified. As a simple limit test, it cannot identify trace elemental impurities in the presence of organometallic compounds where the metal component produces an insoluble metal sulfide.
- **Sensitivity:** The current method lacks the sensitivity to determine some of the listed elements to the required detection limits, even though it typically involves using up to 2g of substance for testing purposes. This sample requirement can make testing very costly for small scale production of early stage development batches.
- **Accuracy:** All results are based on a lead standard, while the colour and intensity of the different precipitates formed can vary considerably from that of lead sulfide. The test is also subjective, in that it relies on an analyst's opinion on whether the precipitate in the sample is lighter or darker than the prepared standard, which can be further complicated if the background is not a colourless solution.
- Some key elements form soluble sulfide salts, meaning they are not detected using this wet chemistry approach.
- The current method of ashing (@600°C) and acid dissolution is prone to sample loss, particularly the volatile elements such as mercury and selenium, and is also matrix dependent. The current limit test often appears to be applied with little thought to validation for the matrix concerned.

In addition to these limitations, with the published ICHQ3D Guidelines on Elemental Impurities comes the establishment of Permitted Daily Exposure (PDE) limits for each element of toxicological concern, determined using publicly available data. The elemental impurities have also been placed into categories that are intended to facilitate risk assessment as part of quality risk management (Table 1). This risk assessment process follows the principles employed in ICH Q3C: Residual Solvents, and means that a suitable and specific method can now be chosen and validated for the ongoing assessment of elements of concern in raw materials and/or finished products.

Table 1 – Elemental Impurity Classification

	Included Elemental Impurities	Include in Risk Assessment?
Class 1	As, Pb, Cd, Hg	Yes
Class 2A	V, Mo, Se, and Co	Yes
Class 2B	Ag, Au, Tl, Pd, Pt, Ir, Os, Rh, and Ru	Yes, only if intentionally added
Class 3	Sb, Ba, Li, Cr, Cu, Sn, Ni	Dependent upon route of administration
Class 4	B, Fe, Zn, K, Ca, Na, Mn, Mg, W, Al	No

Alternative methods

To overcome the inherent deficiencies of the current wet chemistry based procedure, all parties have been looking to employ modern instrumental techniques that identify and quantify individual elements.

The three major Pharmacopoeias, United States, European and Japanese, describe procedures based on analysis by ICP-OES (or ICP-AES) and ICP-MS. Whilst they do not rule out alternative techniques such as AAS, XRF, UV and IC, the standard method of reference will be ICP. The USP proposed the ICP route in 2005, when it first put forward the introduction of USP Chapters <232> Elemental Impurities Limits and <233> Elemental Impurities Procedures.

The Key benefits of ICP instruments, whether ICP-OES or ICP-MS, are:

- Ability to perform multi element analysis simultaneously
- Achieve the detection limits required
- Can be run unattended
- Physical matrix effects can be overcome using internal standards
- Large linear ranges

This means the issues of Specificity, Sensitivity and Accuracy of the current procedure are addressed. However, as with any instrumental technique, the analysis is only as good as the sample preparation technique involved. With this in mind, it is critical to have an understanding of the material to be analysed and the elemental impurities of interest in order to select the most appropriate sample preparation technique.

The proposed USP procedures, whilst stating that preparation techniques involving either neat, direct aqueous solution or direct organic solution are acceptable, also outlines a procedure using closed vessel digestion. This latter procedure can have a number of benefits:

- Enhanced digestion temperatures, reducing digestion duration whilst achieving higher digestion quality
- Reduced acid consumption resulting in reduced blank values and better matrix matching with standards
- No loss of volatile elements
- Reduced contamination risks

Considerations on Transitioning to ICP

Whilst there are obvious benefits from the use of modern instrumentation in replacing the well established wet chemistry limit test, there are a number of considerations. Firstly, there is the capital expenditure; an ICP-OES costs in the region of £50k and an ICP-MS £100k, with a closed vessel microwave digestion system £20k. Secondly, the cost of installation of the equipment, services and ongoing running costs. Thirdly, there is the training of staff in the new technique or, in some instances, the employment of another analyst with the relevant experience to operate the equipment and interpret the data. Finally, there are validation considerations. The USP and other Pharmacopoeias have produced some general outline procedures for Elemental Impurities Testing by ICP, the USP states:

By means of verification studies, analysts will confirm that the analytical procedures ..... are suitable for use on specified material

If alternative procedures are used then the USP requires that these are fully validated to USP <1225>. However, there is the proviso in USP <232> that says:

If, by validated processes and supply-chain control, manufacturers can demonstrate the absence of impurities, then further testing is not needed.

Developing and validating an ICP method for a new material, in theory, begins with identifying whether the procedure needs to be a limit test to show the absence of elemental impurities, or a quantitative procedure for one or more elements known to be present. From a practical point of view, given the large linear range of ICP instruments, it is often more efficient in terms of time and costs to move straight to the development of a method capable of quantifying any elemental impurities known to be present.

With such emphasis on validation requirements, for each material requiring elemental impurity testing, pharmaceutical manufacturers are looking carefully at the cost benefits or otherwise of investing in these techniques, especially with the added costs of any ongoing routine testing required.

Risk Assessment/Control Strategy

As previously mentioned, pharmaceutical manufacturers are applying the principles of quality risk management, with the risk assessment being based on scientific knowledge and principles as set out in the ICH Q9 guidance document.

This process can be described in four steps:

- **Identify:** Identify known and potential sources of elemental impurities that may be present in drug product
- **Analyse:** Determine the probability of observance of a particular elemental impurity in the product
- **Evaluate:** Compare the observed or predicted levels of elemental impurities with the established PDE
- **Control:** Document and implement a control strategy to limit elemental impurities in the product

The data on elemental impurity content for the components of a drug product can be derived from a number of sources. These include: published literature, data provided by reagent and/or excipient manufacturers and data previously generated on the product. However,

manufacturers have been finding that there is little or no substantive information on the levels of elemental impurities available for making this risk assessment. There are also materials where it will be difficult to obtain consistent data. For example: plant derived materials or natural products and inorganic minerals which may be grown or mined in differing parts of the world, where it may not be possible to set a reliable baseline of typical elemental impurities content. Whilst pharmaceutical manufacturers may push excipient suppliers to provide the data, rather than produce it for themselves, are there sufficient incentives for these suppliers to warrant investment in the equipment to obtain the required data?

With this lack of reliable data, some manufacturers have decided to generate the data themselves for their current product ranges, to assess if any particular product or dosage form gives rise to significant levels of elemental impurities, using a generic quantitative screening method for 30 common elements. In other cases, where manufacturers use a limited range of excipients, the approach has been to assess multiple batches of raw materials. This data can then be used for risk assessment and shared across product ranges.

ICH Q3D requires the manufacturer to measure the significance of the level of an observed elemental impurity relative to the PDE. A control threshold of 30% of PDE in the drug product has been established and is to be used to determine if additional controls may or may not be required.

Case Study

The results in Table 2 are part of an investigation recently carried out at Butterworth Laboratories Ltd into three formulations of the same product, with multiple batches for each formulation being prepared using closed vessel microwave digestion and analysed by ICP-MS.

The results obtained show that there may be concern over the levels of Lithium, Cadmium and Lead. The manufacturer now needs to evaluate these figures with respect to the PDE as they all exceed the 30% threshold. It should be borne in mind that the PDE figures are based on a 10g daily dosage of the formulation. The majority of drug products are not formulated for this dosage level and as such it may be that the levels determined are perfectly acceptable. If not, ongoing analytical strategies can be implemented to regularly monitor the levels in raw materials and/or the finished product.

Many manufacturers are outsourcing such testing to contract testing laboratories, who already have the equipment, trained staff and expertise in elemental impurities analysis by ICP for this risk assessment stage. Given the level of metals testing required by the pharmaceutical industry many have never invested in ICP technology up to this point and so do not have any in-house expertise. Unless they identify that there is a significant need for ongoing monitoring, it is likely that they will continue to use sub-contractors to perform this work if they cannot persuade the raw materials suppliers to provide the necessary data at source.

Table 2

		Recommended PDE µg/g, Based on 10g/day dosage	Mean Result µg/g				
			Chewable Tablet		Tablet	Extended Release Tablet	
Element	**Class**	**Oral**	**2mg**	**25mg**	**200mg**	**25mg**	**300mg**
Lithium	3	78	58.9	61.6	0	0	0
Vanadium	2A	12	1.7	1.7	0.1	0.6	0.1
Chromium	3	1100	2.6	1.1	0.1	0.1	0.1
Cobalt	2A	5	0.1	0.1	0	0.1	0
Nickel	3	60	0.5	0.8	0	0.4	0.2
Copper	3	130	0.6	0.4	0	0.1	0
Arsenic	1	1.5	0.2	0.3	0	0	0
Selenium	2A	17	0.2	0.1	0.2	0.1	0.1
Molybdenum	2A	18	0.1	0.1	0	0	0
Ruthenium	2B	100	0	0	0	0	0

Rhodium	2B	100	0	0	0	0	0
Palladium	2B	10	0	0	0	0	0
Silver	2B	17	0	0	0	0	0
Cadmium	1	0.5	0.4	0.2	0	0	0
Tin	3	640	0.3	0.2	0.3	0.1	0.1
Antimony	3	120	0	0	0	0	0
Barium	3	1300	9.2	4.3	0.8	0.9	1.2
Osmium*	2B	100	0	0	0	0	0
Iridium*	2B	100	0	0	0.1	0	0
Platinum	2B	100	0	0	0	0	0
Gold	2B	13	0	0	0	0	0
Mercury	1	4	0	0	0	0	0
Thallium	2B	0.8	0	0	0	0	0
Lead	1	0.5	2.2	1.1	0	0	0

Author Biographies

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David started his career at Messers Sandberg Testing Laboratories which specialises in testing samples for the construction industry. He moved to Butterworth in 1986 as an Analytical Chemist specialising in Elemental Microanalysis. David is currently Head of Analytical Operations having previously held the posts of Analytical Operations Manager and Senior Manager of Inorganic & General Chemistry.

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John started his career with Kodak Ltd at their Research Facilities in Wealdstone, Harrow, before moving into the pharmaceutical industry with Upjohn Ltd. He moved to Butterworth in 1987 as an Analytical Chemist and has occupied roles including Laboratory Manager, QA Manager and is currently Head of Business Operations. An active member of the RSC, John has spoken at RSC and MHRA Seminars on subjects relating to contract analytical chemistry.

References

ICH Q3d Draft Document: July 2013

ICH Q9 Finalised Guideline: November 2005

USP 36 – NF 31 Second Supplement <232> Elemental Impurities – Limits

USP 36 – NF 31 Second Supplement <233> Elemental Impurities – Procedures