White paper:

Elemental impurities ICH Guidelines

The new ICH Guideline for Elemental Impurities (ICH Q3D) has been finalised, and will come into effect in Australia from June 2016 for new products containing new drug substance(s), and from December 2017 for new products containing existing drug substance(s).

This whitepaper addresses your commonly asked questions relating to these guidelines, including a risk-based control strategy, testing elemental inpurities and instrument selection.

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Complying with the new elemental impurities USP/ICH requirements

Recently, the United States Pharmacopeial Convention (USP), European Medicines Agency (EMA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) finalised guidelines for new permitted daily exposure (PDE) limits for elemental (inorganic) impurities in pharmaceuticals and dietary supplements. Refer to **Table 1** for the new PDE limits.

On the 17th of August 2015, the Australian TGA announced that the date for the **ICH Guideline for Elemental Impurities (ICH Q3D)** coming into effect in Australia, will align with implementation in the EU. That is, from June 2016 for new products containing new drug substance(s), and from December 2017 for new products containing existing drug substance(s). In Australia this guideline applies to registration applications for prescription medicines only.

The new PDE limits were determined according to the toxicity of the elements and the route of exposure, rather than method capability (as was the case for the old sulphide precipitate test in USP‹231›).

Existing wet chemical and colorimetric heavy metal quantification tests, such as **European Pharmacopeial Convention (Ph. Eur.) Heavy Metals chapter 2.4.8** and **USP‹231›**, have been replaced with methods that use modern instruments to quantify specific elements in drug products and ingredients.

The routes of exposure covered in the guidelines are:

- oral dosage
- parenteral
- inhalation.

The ICH training materials include instructions on how to apply ICH Q3D concepts to other routes of administration.

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Table 1. The PDE limits for elemental impurities in drug products, according to their route of administration and for dietary supplements. Elements shaded green should be considered in product risk assessment. All elements listed should be included in risk assessment if naturally present or intentionally added.

ICH/USP Class	Element	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalational PDE (µg/day)	Final dosage form of dietary supplements (µg/day)
Class 1	Cd - Cadmium	5	2	2	5
	Pb - Lead	5	5	5	10
	As - Arsenic (inorganic)	15	15	2	15
10	Hg - Mercury (inorganic)	30	3	1	15 (total) 2 (Methylmercury)
Class 2A	Co - Cobalt	50	5	3	
	V - Vanadium	100	10	1	
	Ni - Nickel	200	20	5	
Class 2B	Tl - Thallium	8	8	8	
	Au - Gold	100	100	1	
	Pd - Palladium	100	10	1	
	Ir - Iridium	100	10	1	
	Os - Osmium	100	10	1	
	Rh - Rhodium	100	10	1	
	Ru - Ruthenium	100	10	1	
	Se - Selenium	150	80	130	
	Ag - Silver	150	10	7	
	Pt - Platinum	100	10	1	
Class 3	Li - Lithium	550	250	25	
	Sb - Antimony	1200	90	20	
	Ba - Barium	1400	700	300	
	Mo - Molybdenum	3000	1500	10	
	Cu - Copper	3000	300	30	
	Sn - Tin	6000	600	60	
	Cr - Chromium	11000	1100	3	

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When will the new regulations come into effect?

ICH Q3D has now reached Step 5 (implementation) and has been in effect since June 2016 for new marketing authorisation applications, and will come into effect from December 2017 for existing authorised medicinal products.

Other jurisdictions will have different dates, depending on if/when the country's regulatory body has adopted the guidelines.

The new USP General Chapters **USP‹232› 'Elemental Impurities – Limits'**, **USP‹233› 'Elemental Impurities – Procedures'** and **USP‹2232› 'Elemental Contaminants in Dietary Supplements'** are due to be implemented in January 2018. They cover all drug products and dietary supplements (new and existing).

Which drug products are covered?

Some specific drug products are included/excluded from the elemental impurities limits, as listed below.

Table 2: Inclusions and exclusions

Included	Excluded
Purified proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates) Drug products containing synthetically produced polypeptides, polynucleotides, and oligosaccharides. All other drug products not specifically excluded	Herbal products (but covered by USP 2322 of they are dietary supplements) Radiopharmaceuticals Vaccines Cell metabolites DNA products Allergenic extracts Cells Whole blood Cellular blood components or blood derivatives including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation Elements intentionally included for therapeutic benefit Gene-based products Cell therapy products Tissue engineering (advanced therapy medicinal products) Drugs in clinical research phase

Note: There are special considerations for bio-technologically derived products. Refer to ICH Q3D.

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Risk-based control strategy

Both ICH Q3D and USP ‹233› recommend implementing a **risk-based control strategy** for elemental impurities. The **ICH Q9 'Quality Risk Management' guideline** and **Q11 'Development and Manufacture of Drug Substances'** guideline can be used for this process.

By applying the Quality by Design (QbD) principles, you should have detailed knowledge of the product and its manufacturing process, and therefore be able to identify likely sources of elemental impurities that could find their way into the product during manufacture.

Elemental impurities in drug products may arise from several sources, as shown in the figure below.

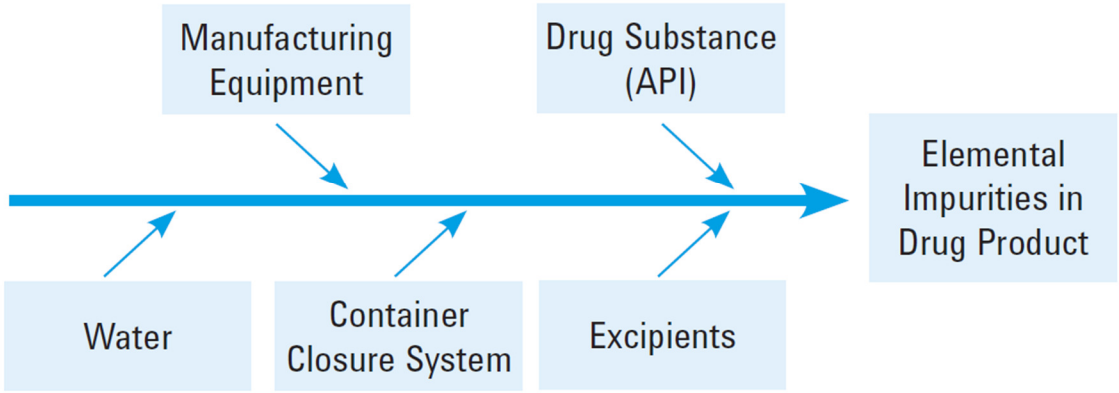

Figure 1: Sources of elemental impurities

Elemental impurities may be introduced via APIs or excipients, or they may be introduced during the manufacturing process e.g. catalysts that were added intentionally in synthesis or from with processing equipment or container/closure systems.

Your first step should be to undertake a risk assessment for each product that must comply with ICH Q3D or USP ‹232›. The results of the risk assessment and any control strategies you subsequently put in place , should be documented and available for viewing by auditors.

The ICH Q3D training materials, available from the ICH website, include good examples of a risk assessment for elemental impurities (refer to the case studies).

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A control strategy should be put in place if the risk assessment identifies a source of elemental impurities that is **more than 30% of the PDE limit** for that drug product. For example, if the risk assessment identifies that an excipient may contain more than 30% of the permitted daily exposure for Cd in an oral product, then a control such as an incoming material specification should be put into place for the excipient.

Controls can include:

- parameters and attributes related to drug substance and drug product materials and components
- facility and equipment operating conditions
- in-process controls
- finished product specifications and the associated methods and frequency of monitoring and control.

The control strategy needs to be maintained across the product lifecycle. It should be documented and evidence of its implementation maintained.

Tip: As part of your risk assessment you'll most likely need to request information and data from suppliers. Give them plenty of notice about forthcoming requests and work with your procurement department to consolidate requests so that suppliers aren't getting multiple requests for the same information from different product teams in your company.

Testing for elemental impurities

As part of a risk assessment, or as a control strategy, you may need to implement testing for elemental impurities. The ICH Q3D guidelines require that pharmacopoeial procedures or suitable alternative procedures be used.

The new **USP‹233› procedure 'Elemental Impurities – Procedures'** recommends the use of modern instrumental techniques e.g. Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) or ICP-Mass Spectrometry (ICP-MS).

Alternative procedures may be used, provided they can be demonstrated to meet the performance requirements defined in the methods. USP‹233› also recommends the use of closed vessel sample digestion for solid samples, to ensure the quantitative recovery of all the regulated analytes, including volatile elements, such as mercury.

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Outsource or in-house testing?

If you have previously been performing only the colorimetric heavy metals testing as per European Pharmacopeial Convention (Ph. Eur.) Heavy Metals chapter 2.4.8 and USP‹231›, and do not currently have an ICP-OES or ICP-MS instrument, then the decision to do elemental impurity testing in-house, or outsourcing it to an independent laboratory, will depend on several factors:

- the number of samples that need to be analysed
- how quickly you need the results
- the expertise of your laboratory technicians
- capital cost and cost of ownership.

In Australia, a TGA-certified laboratory will charge between $500-$1000 per sample to test for all of regulated 24 elements. If you compare this to the estimated per sample operating costs calculated by Robert Thomas in this Chromatography Today article of A$0.40 for ICP-OES analysis and A$0.90 for ICP-MS (10 elements per sample and with lots of assumptions about the instrument operation), then doing the testing in-house suddenly seems attractive.

But factor in the capital costs of buying the instrument (about A$60-80K for an ICP-OES and $80-100K+ for an ICP-MS) **PLUS** the costs of the sample preparation equipment, the validation of the testing, and the salary of the experienced and skilled technician you'll need to do the work. If you are producing only a few batches of product per week, then the cost of buying and operating an ICP instrument is prohibitive and it would be more cost-effective to send it out to a contract lab who can batch up your samples with the others they receive, and run the analysis more efficiently.

The turnaround time needed for test results is another factor to consider. An external lab will typically take 5-7 days to report the results. If you can't release a batch of product until you have the results, or production is being held up because they are waiting for the results from a raw material, then having in-house testing capabilities may be necessary. In-house, it will around take 2-3 hours of sample preparation and another 0.5-1 hours to calibrate the instrument and run a sample. This means same-day results versus having to wait a week for the results from an external lab.

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Sample preparation

There are four objectives for the sample preparation step of elemental impurities testing:

- put the sample into solution (if it is not already in solution)
- stabilise the sample-containing solution, especially if low concentrations of an analyte element are present
- make the analyte concentration fall within the working range of the instrument through dilution or pre-concentration or spiking
- ensure that the sample-containing solution can be nebulized in a reproducible manner.

The USP‹233› procedure specifies four different sample preparation options:

- Neat: Used for liquids or alternative procedures that allow the examination of unsolvated samples.
- Direct aqueous solution: Used when the sample is soluble in an aqueous solvent.
- Direct organic solution: Used where the sample is soluble in an organic solvent.
- Indirect solution: Used when a material is not directly soluble in aqueous or organic solvent.

The option you use will depend upon the characteristics of your samples and the instrument technique you are using. It's worthwhile noting that if your samples are not soluble in aqueous or organic solvents, then you'll need to use closed vessel digestion, which requires more equipment and expertise.

Which instrument to buy? ICP-MS vs ICP-OES?

If you have decided to have elemental impurities analysis capabilities in-house, then you'll need to decide which type of instrument to buy: ICP-OES or ICP-MS.

Note that you can use any technique as long as it has been validated and meets the acceptance criteria listed in USP‹233›. If you need to quantify only one (or a low number) element in your product that has high PDE limits, then you may be able to do your testing with a Flame AA instrument.

The key performance differentiators between ICP-OES and ICP-MS include:

Detection limits

The first place to start is with the instrument sensitivity you'll need for your samples. ICP-MS has much better detection limits (DLs) than ICP-OES – around 3 orders of magnitude lower for most elements. This may be partly offset by the fact that ICP-OES can tolerate samples with dissolved solids levels around 10 x higher than ICP-MS, so samples may not need to be diluted as much prior to analysis.

ICP-OES DLs may be sufficient for analysis of ingredients such as bulk raw materials (fillers, binders, and so on) and for oral medicines, where the PDE limits are higher. ICP-MS instruments achieve detection limits in the low parts per trillion range, easily low enough to permit accurate determination of all required elements in all dosage forms, including drugs

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intended for parenteral or inhalation administration, where the PDE levels are typically an order of magnitude lower than for oral medicines. If your facility is producing a range of products, ICP-MS offers the flexibility to achieve the required limits for all regulated elements in all sample types.

Dilution levels applied during sample preparation must also be considered. If you have only small quantities of samples available, such as for some APIs, a large dilution may be needed to give sufficient sample volume for analysis. Similarly, samples that contain high levels of dissolved solids, or that contain analyte concentrations beyond the working range of the instrument, must be diluted prior to analysis. The lower detection limits of ICP-MS allow greater flexibility to choose a dilution level appropriate to the material and the sample preparation procedure. It should be noted that diluting samples introduces an additional step in the sample preparation procedure and potential for error, however it can be automated with the right equipment selection.

To determine the detection limits you'll need, calculate the 'worse case' J value (refer to the adjacent section) for your products for the elements you've identified as being potential impurities. If you don't know the dilution factor you'll need to apply then perhaps send samples to an external lab and ask them to do the sample preparation to determine this. Once you know the lowest concentrations of each element that you'll need to measure, you can compare this to the Instrument Detection Limits (IDLs) supplied by the instrument manufacturers (or, even better, they may be able to provide Method Detection Limits (MDLs) using your samples or samples with a similar matrix and analyte concentrations).

Typically, ICP-OES is used when detection down to parts-per-million levels are required, whereas ICP-MS can detect down to parts-per-billion or even trillion levels. If you calculate the ratio of the J-value to the instrument's detection limit i.e. J/IDL, you'll be able to determine if the analysis for that element can be performed with good accuracy and precision. Ratio values above a value of 1 are desirable – the higher the value the more reliable the result.

Ability to handle dissolved solids

ICP-OES can handle much higher levels of dissolved solids in samples than ICP-MS. Some ICP-OES instruments can handle ~25% total dissolved solids (TDS), more than 10 x higher than ICP-MS systems.

As an ICP-MS can detect much lower concentrations of elements, it means that samples with high levels of dissolved solids can still be analysed via ICP-MS by simply diluting the sample to reduce the level of solids. This does introduce an extra step, however, and one that can introduce errors. If your samples are likely to have high levels of solids e.g. calcium carbonate and you don't need the sensitivity of ICP-MS (because your risk assessment identified only elements with higher PDEs as being possible contaminants), then an ICP-OES may be the better choice for your facility.

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Measuring different forms of an element

For some elements, bioavailability and toxicity is highly dependent on their chemical form i.e. oxidation state, organometallic complex, and so on (often called 'species'). Of the analytes listed in the ICH/USP regulations, arsenic and mercury are a particular concern, and both must be considered in your risk assessment. For these two elements, the PDE limit refers to the inorganic form, because inorganic arsenic is the most toxic form, and inorganic mercury is considered the most likely form to be present in pharmaceutical materials.

Measurement of the different forms of an element is called **Speciation Analysis**. It is performed using a chromatographic technique, such as liquid chromatography (to separate the species of the element), coupled to an elemental analysis technique (to quantify each species), such as an ICP-MS. Note that USP‹2322› for dietary supplements includes methods for speciation testing for mercury and arsenic which require simpler apparatus.

In the case that the concentration of arsenic (total of all forms) exceeds the target concentration, USP‹232› suggests that a speciation analysis is performed to allow independent quantification of the inorganic arsenic. If the inorganic arsenice is found to be below the limit, the material would be considered compliant, even if the total arsenic concentration exceeds the limit.

You will need to perform speciation analysis of mercury if your samples are likely to contain the more toxic methyl mercury species, normally derived from marine material such as fish, seaweed, etc. Otherwise, compliance with the regulations is established by determination of the total level of mercury, which is most likely to be in the inorganic mercuric (2+) form.

If your risk assessment has identified mercury and/or arsenic as potential contaminants AND testing has shown that the concentration of all forms of arsenic or mercury is higher than the regulated levels, then you will need to do a speciation analysis to identify the concentrations of each different form of the element in your sample. If you have to do this regularly, as part of your control strategy, then having a completely automated system is recommended.

Speed of analysis

ICP-OES is a very fast technique, providing around twice the sample throughput of ICP-MS (which typically takes about 5 minutes per sample). If you have lots i.e. hundreds of samples per week, then an ICP-OES will analyse them quicker and cheaper.

Cost of ownership

As described in the Chromatography Today article, the cost to analyse a sample via ICP-MS is roughly double that of ICP-OES. The initial capital cost is about 30% more for an ICP-MS and the maintenance costs are also higher.

The ICP-MS detector will need replacing about once a year (depending on how much you use it) for A$2,000. The sample introduction consumables e.g. cones, cost another $1,000-$2,000 and to replace a vacuum pump (which only last for a period of time as the pumps are on all the time) is $20,000-$30,000.

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The ICP-OES is cheaper to run, with the only ongoing costs being replacement of the sample introduction components e.g. torch, which are relatively cheap.

Both techniques use similar amounts of argon, although the ICP-MS may also use other gases such as helium for interference control.

Ease of use

The basics of the two techniques are similar – create a calibration using known standards and then run the samples. The design of the software controlling the instrument will largely determine how difficult this process is, so it's worthwhile asking for a demonstration (where you get to drive the software).

ICP-MS is a more complex technique, with the instrument needing to be tuned with a tuning solution prior to analysis. You'll also need to understand polyatomic interferences and how to avoid/reduce them. This is where it gets complex and requires a higher level of skill compared to ICP-OES. The method will likely be determined by your product development team and passed through to the Production QC lab, so paying for some help from the instrument company may be worthwhile when developing the method if you don't have experienced ICP-MS technicians on staff.

Conclusion

The choice between outsourcing elemental impurities testing or purchasing an ICP-MS or ICP-OES depends on your analytical needs, budget and the skill level of your analysts. A comprehensive risk assessment and the use of controls may remove the need for any ongoing testing.

If you decide to have in-house capabilities for elemental impurity testing you should carefully consider your analytical needs, both now and in the future. This will determine which elemental analysis technique you should invest in.

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Using the J-value to help with instrument selection

The maximum level of elemental impurities in finished drug products is expressed as a maximum PDE. This limit takes into account the concentration of the element present in the drug products, and the maximum recommended daily dose for the drug.

For materials that require digestion or dilution in a solvent prior to analysis, the PDE limit (in µg/day) must be converted to a concentration limit (in µg/L) as measured in the prepared sample, after correcting for the dilution factor required to bring the analyte(s) within the analytical range of the instrument used.

The target concentration value in the prepared sample, referred to as the "J-value", defines the maximum permitted concentration limit for the analyte in that sample, where:

$$J = \frac{PDE}{Total\ Dil. \times Max.\ Daily\ Dose}$$

The J value is a useful number to have when selecting an instrument. You'll need to calculate the J value for your samples (which depends on the maximum daily dose of the final drug product and the dilution you apply during sample preparation) and then compare the J value to the detection limits for the instrument for each element you need to test for.

As you can see in the examples below, both techniques will easily meet the required sensitivity for the examples used, with the ICP-MS exceeding requirements by many orders of magnitude.

One of the questions to ask if you decide to purchase an ICP-MS, is the dynamic range of the instrument – what are the minimum and maximum concentrations of an element can it handle? If the dynamic range is limited then you'll find yourself having to dilute samples to bring them into the range of the instrument. Some instruments offer a dynamic range of 10-11 orders of magnitude, being able to measure elements at concentrations ranging from 0.001 µg/L to 0.1 µg/L.

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Example 1: Oral dosage drug

Element	Oral Dose PDE (µg/day*)	J-value at 250x Dilution (µg/L)	J-value at 1000x Dilution (µg/L)	ICP-OES IDLs (µg/L)	ICP-MS IDLs (µg/L)
Cd - Cadmium	5	20	5	0.1	0.0001
Pb - Lead	5	20	5	2.2	0.0002
As - Arsenic (inorganic)	15	60	15	3.7	0.005
Hg - Mercury (inorganic)	30	120	30	1.0	0.001

Calculated J values of Class 1 elements Cd, Pb, As and Hg in an oral dosage product, assuming a 1 g/day dosage and a dilution factor of 250 x (e.g. 0.2 g in 50 mL) and 1000 x (e.g. 0.1 g in 100 mL). Typical instrumental detection limits (IDLs) are shown for comparison – this is the minimum concentration of the element the instrument can measure.

* Values apply to oral dose drugs with a daily dose of ↖ 10 g.

Example 2: Inhalation administered drug- insoluble in water or organic solvents

For those samples that are not soluble in water or organic solvents, a closed vessel digestion procedure is typically used (as described in USP‹233›). This requires the analyst to pre-digest 0.5 g of primary sample in 5 mL of freshly prepared concentrated acid prior to adding another 10 mL of concentrated acid, followed by digestion. If the resultant solution is directly analysed (without further dilution) the dilution factor is 30. If the solution is further diluted with another 100 mL of acid the dilution factor is 230.

If we consider an example of an ingredient for a drug that is administered via inhalation (with a recommended maximum daily dose of 100 mg (0.1 g)) the J value calculation results in:

Element	Inhalation Dose PDE (µg/day)	J-value at 30x Dilution (µg/L)	J-value at 230x Dilution (µg/L)	ICP-OES IDLs (µg/L)	ICP-MS IDLs (µg/L)
Cd - Cadmium	2	667	87	0.1	0.0001
Pb - Lead	5	1660	217	2.2	0.0002
As - Arsenic (inorganic)	2	667	87	3.7	0.005
Hg - Mercury (inorganic)	1	333	44	1.0	0.001

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References

ICH Guideline for Elemental Impurities (ICH Q3D)

European Pharmacopeial Convention (Ph. Eur.) Heavy Metals chapter 2.4.8

USP ‹231› Heavy Metals and Affected Monographs and General Chapters

USP‹232› Elemental Impurities – Limits

USP‹233› Elemental Impurities – Procedures

USP‹2232› Elemental Contaminants in Dietary Supplements

ICH Q9 Quality Risk Management

Q11 Development and Manufacture of Drug Substances

Sources

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