Elemental impurities testing to ICH Q3D: Practical challenges

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Introduction

The ICH Q3D Guideline on Elemental Impurities has been adopted by the European and US Pharmacopoeias , meaning that they currently need to be assessed in all new marketed products within Europe and by end of 2017 will need to be assessed in all new and existing products in Europe and the US.

ICH Q3D adopts a risk based approach, providing toxicity data and Permitted Daily Exposure (PDE) concentrations for 24 elements, although additional elements may need to be included after considering the therapeutic use of the product, dosage form and manufacturing process.

No elemental impurity should be present at >30% of the PDE within the final product.

The PDE may be determined by assuming a 10g daily dose (Option1) or by considering the maximum daily dose of either the final product (Option 3) or individual components (Options 2a, 2b).

Existing data may be insufficient to assess the risk of an elemental impurity exceeding the 30% PDE control level and this has led to some companies screening their product portfolios. Others have completed the risk assessment and targeted analysis of only those elemental impurities identified as being of concern.

Due to the range of analytes, concentrations and types of materials that need to be assessed, microwave digestion followed by ICP-MS measurement has become the method of choice where testing is undertaken.

This poster gives an overview of some of the analytical challenges that may be encountered.

ICH Q3D PDE limits

*Assess if used during process

Impurity	Class	Oral PDE, µg/day	Parenteral PDE, µg/day	Inhaled PDE, µg/day	Risk Assessment Required?
Cd	1	5	2	2	Yes
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	If used during process
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	Not oral
Sb*	3	1200	90	20	
Ba*	3	1400	700	300	Inhaled only
Mo*	3	3000	1500	10	
Cu*	3	3000	300	30	Not oral
Sn*	3	6000	600	60	Inhaled only
Cr*	3	11000	1100	3	

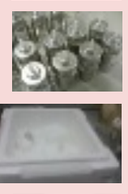
Sample preparation

Materials tested include APIs, excipients and final products within the drug delivery system. Some common issues that occur during preparation are:

Tablet coatings: difficult to homogenise.

Metered-dose Inhalers: contain propellant.

Excipients: waxes, liquids and other substances that are not compatible with microwave digestion.



Digestion

Total digestion is preferred but not always achievable. Residues, precipitates and undigested material may remain after digestion. Spiking the sample matrix with an element mix demonstrates recovery. If the sample does not fully digest at >180ºC at pressure with HNO_3, HCl and H_2O_2, but recoveries are achieved, is full digestion required?

Analysis

ICP-MS has the sensitivity and linear range required to cover the concentrations encountered. The table shows examples of Class 1 and 2A limits based on ICH Q3D Option 1 and Option 3.

	30% PDE Concentrations (µg/g)					
	Oral		Parenteral		Inhaled	
	Option 1 10g	Option 3 50mg	Option 1 10g	Option 3 50mg	Option 1 10g	Option 3 50mg
Cd	0.15	30	0.06	12	0.06	12
Pb	0.15	30	0.15	30	0.15	30
As	0.45	90	0.45	90	0.06	12
Hg	0.9	180	0.09	18	0.03	6
Co	1.5	300	0.15	30	0.09	18
V	3	600	0.3	60	0.03	6
Ni	6	1200	0.6	120	0.15	30

Inhaled and Parenteral Dosage forms are the most challenging in terms of quantitation limits and the use of a reaction / collision cell for low mass elements is essential in order to reduce isobaric interferences.

Conversely, for low dose oral products, elements such as Cr may be required to be measured in the wt.% range and large dilutions may be needed to bring spike concentrations down to suitable levels.

Additional challenges

Osmium tetroxide formation in the presence of the HNO_3 (used during digestion) can lead to over-recovery depending on the sample matrix. The use of modifiers during, or subsequent to, digestion may mitigate this, but no single solution exists for each product type. For example, a simple dilution with HCl instead of H_2O has improved Os recoveries in Product A, but has no effect in Product B.

Digesting Os separately is one solution, but given that Ag may also need a separate preparation avoiding HCl, may not be practical or cost effective.

Initial Digestion with HNO_3, HCl, H_2O_2 at 180°C		
Average recovery %	Product A	Product B
Dilution with H_2O	466	216
Dilution with HCl	104	206

Case study

Requirement was for a screening method for 24 elements for an excipient to be used in oral doses. Option 1 was required giving 30% PDEs between 150ng/g and 330µg/g. Preparation:~0.2g of material digested in HNO_3, HCl, H_2O_2 at 180ºC with further dilution with H_2O to equivalent of 100mL. Elements determined by collision cell quadrupole ICP-MS. Self-validating Limit Test with multiple spikes at 30% PDE used to demonstrate specificity, recovery and repeatability. Linearity, LOD and LOQ determined using matrix matched multi element standards and reagent blanks.

Units µg/g	LOD	LOQ	30% PDE Conc	Spike recovery range (%)	Spike %RSD		LOD	LOQ	30% PDE Conc	Spike recovery range (%)	Spike %RSD
Cd	0.005	0.014	0.150	132.6 – 137.6	1.95	Rh	0.0009	0.0025	3.00	104.1 – 106.7	1.25
Pb	0.008	0.012	0.150	107.4 - 119.9	5.52	Ru	0.050	0.152	3.00	105.2 – 108.2	1.58
As	0.016	0.022	0.450	77.3 – 83.2	3.68	Se	0.090	0.140	4.50	83.4 – 85.6	1.51
Hg	0.004	0.014	0.900	109.0 – 114.2	2.34	Ag	0.0007	0.0015	4.50	105.1 – 106.7	0.804
Co	0.001	0.003	1.50	81.4 – 83.0	1.06	Pt	0.019	0.047	3.00	104.4 – 107.2	1.33
V	0.185	0.237	3.00	104.6 – 104.6	2.19	Li	0.014	0.030	16.5	94.6 – 95.6	0.526
Ni	0.173	0.556	6.00	78.6 – 80.5	1.24	Sb	0.178	0.431	36.0	116.6 – 119.5	1.23
Tl	0.067	0.166	0.240	92.6 – 98.8	3.44	Ba	0.379	0.450	42.0	104.1 – 104.7	0.308
Au	0.165	0.507	3.00	108.3 - 116.4	3.76	Mo	0.005	0.013	90.0	105.3 – 107.3	0.981
Pd	0.005	0.012	3.00	118.9 – 128.7	3.96	Cu	0.481	1.46	90.0	79.4 – 80.3	0.565
Ir	0.007	0.019	3.00	102.4 – 107.0	2.42	Sn	0.013	0.038	180	102.5 – 105.9	1.64
Os	0.005	0.013	3.00	304.8 – 367.2	9.39	Cr	0.180	0.552	330	97.8 – 99.6	0.919

Osmium recovery accepted due to extremely low sample concentrations. All other recoveries within pre-defined acceptance limits. No elemental impurities seen at levels of concern.

Conclusion

Initially it was thought that every marketed product would required full testing for ICH Q3D elemental impurities. However, the risk based nature of ICH Q3D means that many elements can be eliminated from consideration if sufficient data are available.

Screening can fill the knowledge gap and allow an informed risk assessment to be completed prior to committing to full quantitative validation.

Published and anecdotal data, along with LGC's experience in testing a significant number of products, suggests that within EMA and FDA regulated areas, Elemental Impurities are rarely seen at levels that require control measures. This means that screening alone may be sufficient to satisfy the ICH Q3D requirements.