RISK ASSESSMENT, IMPLEMENTATION AND VALIDATION OF ELEMENTAL IMPURITIES FOR ICH Q3D, USP <232><233> AND EP 5.20

AUTHOR: THOMAS DEVADDER, TEAM LEADER QC AAS/ICP/PARTICLES/TGA – LABORATORY SERVICES, SGS LIFE SCIENCE SERVICES

On December 16, 2014 the ICH Working Group published the elemental impurities guideline into the current version step 4. The aim of this control strategy is to track impurities that may contaminate pharmaceutical products and are potentially contributed by several sources. Additionally, the guideline also focuses on final drug product quality. To ensure that all components and all needed production steps required for a pharmaceutical product demonstrate regulatory compliance, risk assessment will become a priority for every pharmaceutical manufacturer. This approach of testing and documentation can become a major challenge, especially in the consideration of various potential sources such as excipients, water, APIs, container systems and manufacturing processes.

In the current version, ICH Q3D considers 24 elements in their specific toxicity class and their permitted daily exposure (PDE, µg/day). Based on a maximal daily intake of not more than 10g of a drug product, drug substance or excipients, ICH Q3D provides a table outlining permitted concentrations based on µg/g. However, when the assessment process shows a potential risk, then additional data will be required and testing for elemental impurities will become the next challenge. Based on the low PDE concentrations, and new specific and sensitive instrument technology, implementing these new guidelines will be on every pharmaceutical manufacturer and contract laboratories' minds.

IMPLEMENTING A STRATEGY

As a quality control contract analytical laboratory serving many multinational, as well as local pharmaceutical companies, SGS receives many client inquiries for elemental impurity testing for which the samples' background is unclear or uncertain. To provide valid information about elemental impurities in pharmaceutical products, we needed to implement a screening procedure to close the gap in risk assessment whenever additional data is required. Based on our previous experience with heavy metals determination, our lab focused on optimizing ICP-MS because of its selectivity and sensitivity. In order to prepare for the broad range of sample materials we will receive from clients, we considered three worst case scenarios for method development:

1. All target elements from ICH Q3D, EP 5.20 and USP 232
2. Worst case limit from ICH Q3D, EP 5.20 and USP 232
3. Worst case sample matrix, spiked with potential interferences (K, Na, Ca, Mg, Cl)

For the validation procedure, the European Pharmacopoeia (2.4.20) and United States Pharmacopoeia <233> advise parameters and acceptance criteria. We combined these requirements for a qualitative procedure and performed a validation by spiking experiments in Omega-3 fish oil. This sample matrix was considered because of its high carbon content and difficulty with digestion. Compared to other tests, sample preparation is also a critical step for analysis for elemental impurities using ICP-MS. In this case, the main goal is to reduce organic sample background by a closed-vessel microwave digestion to match the background of the sample in the calibration solution. Additionally, to demonstrate the applicability of our procedure to different sample materials, our objective was to verify the procedure on every new sample material in future routine screenings via a spiking experiment.

CHALLENGES

To move ICP-MS to the next level of multi-element testing, different categories of interferences must be controlled. Physical interferences due to viscosity, density, nebulisation effects and chemical interferences like contaminations and carry over effects are more likely to be present before the sample solution arrives in the plasma. For instance, spectral, isobare, and polyatomic interferences are expected in the plasma and vacuum chamber. Fortunately, most commercially available instruments today have a control strategy for spectral interferences incorporated into the daily setup procedure. However, based on the target elements and sample background, the challenge will come from specific isobare interferences and polyatomic argon species. Argon plasma gas, in the presence of oxygen, nitrogen, chlorine or hydrogen from reagents or sample in the

vacuum, can form polyatomic combinations that can become a potential source of false positive results.

Furthermore, Mercury is a metal that warrants special interest because of absorption effects on plastic surfaces in concentrations <10 µg/l. Consequently, sample stabilization with higher concentration of gold will be necessary to avoid analyte loss within sample- and pumping surfaces.

Additionally, Osmium is one of the mainly discussed target elements from the past. Although it is a rare element, it is also a target element within the requirements of ICH Q3D, EP 5.20 and USP<232>. The specific challenge with osmium is the enhanced nebulisation efficiency on the formed osmium-tetroxide after a closed vessel microwave digestion with nitric acid. The impact is a false positive signal, compared to the equivalent concentration without nitric acid by a factor of ~1 to 10. In order to control this chemical interference, the use of an appropriate complexing agent shows the fulfilled acceptance criteria for recovery in the spiking experiment.

Arsenic, vanadium, chromium and nickel are target elements with a low target limit and a low atomic mass which leads to high potential for polyatomic interferences from argon species. In these cases, the use of a reaction or collision cell in the ICP-MS becomes fundamental. Small amounts of a specific gas (e.g. NH3, H2, He) is added to the ion beam in order to destroy polyatomic argon species. Furthermore, a mass shift to a higher atomic mass can be another approach for certain target elements. For instance, in the case of arsenic and vanadium, oxygen will be added to the ion beam and the target element can be forced into a polyatomic combination and therefore to a different atomic mass.

VALIDATION

To combine the requirements of EP 5.20 and USP <233>, the scope of the validation aggregates the selectivity, linearity/range, accuracy, method precision, ruggedness/intermediate precision and limit of quantification. The individual worst case limit for every target element was considered as the 100% level. Table 1, on the following page, shows a summarized overview about the validation results.

For the selectivity of the method we compared the isotopic abundance in the spiked sample solution with the known abundance from the literature. This approach is only applicable for elements determined in standard mode and which have more than one isotope. The test for linearity was done by preparing five different concentration levels of a standard, including a blank solution covering the range up to 250% of the worst case limit. The precision and accuracy was demonstrated for all relevant elemental impurities measuring six individually spiked samples in the range of 10-200% of the individual worst case limit. In this validation, we defined the limit of quantification (LOQ) as the lowest concentration level that complies with the acceptance criteria from accuracy and repeatability. Finally, we defined the LOQ for most of the target elements at 10% of the worst case limit, except of nickel due to a lack of recovery and copper because of imprecision at the 10% level. By defining the sensitivity of the LOQ at less than 30% of the individual target limit, allows the risk assessment the control strategy to consider any additional testing on each batch of the pharmaceutical product.

ROUTINE SCREENING

After finalizing the validation, the next step was to apply the tests in the world of real sample material. In the first year we verified the procedure on 300 different sample materials via a spiking experiment.

Figure 1 shows a summarized overview about the collected experiences.
In most cases, whenever the sample material is one of a pure organic basis, a spiking experiment leads to satisfied verification criteria. Inorganic components from finished products, salts or inorganic excipients are likely to cause physical interferences, because they are still present after the sample preparation in the solution. In those cases, filtration of undigested residues of the sample solution needs to be performed. Tin and antimony are typical elements which show false negative results after the filtration step. Despite the added potential interferences from potassium, magnesium, sodium or calcium in the validation work, the concentration of these salts can overestimate the added concentration whenever a pure salt is the sample.

Typical false positive results are summarized in Figure 2

CRITICAL EXCIPIENTS

The main challenge with the determination of elemental impurities in inorganic sample material is achieving a clear sample solution and low levels of digested inorganic background. As far as the analytical threshold and the sensitivity of the ICP-MS allows a dilution of a sample solution, it is good practice to control elemental impurities in dissolvable inorganics. Nevertheless, several inorganic sample materials require more than a nitric acid digestion. Based on our experiences, the addition of hydrofluoric acid to the nitric acid will be the only way to force inorganic sample material like titanium dioxide or silicone components into a clear sample solution. The risk for the lab worker from the hydrofluoric acid must be considered. For an application with hydrofluoric acid, the use of glass within the digestion and ICP-MS sample introduction must be avoided.

CONCLUSION

In order to provide valid information on elemental impurities in pharmaceutical products, ICP-MS will become the standard technology. Potential interferences within the determination can be controlled within sample preparation and instrument settings. Furthermore, data generated from a generic, validated screening procedure, can close the gap within a risk assessment whenever additional data is required. Besides the challenging considerations that inorganic sample material is present, there is one question that should be discussed: How can the patient digest an impurity from a solid form that concentrated nitric acid can‘t?

TABLE 1: RESULTS OVERVIEW OF VALIDATION

ELEMENT	LIMIT	SELECTIVITY	LINEARITY	METHOD PRECISION	INTERMEDIATE PRECISION	ACCURACY / MEAN RECOVERY 70-150% FOR EACH SPIKING LEVEL					LOQ [LEVEL]
	[µg/g]	ISOTOPE RATIO: 0,8-1,2	CRITERIA: R≥0,998	RSD N=6 (100%): ≤20%	RSD N=12 (100%): ≤25%	10% LEVEL	20% LEVEL	50% LEVEL	100% LEVEL	200% LEVEL	TARGET: ≤50%
As	0.15	Reaction cell	0.99976	10.0%	7.1%	104.2%	98.8%	101.1%	98.5%	100.5%	10%
Cd	0.15	complies	0.99910	2.4%	2.2%	93.1%	97.1%	97.4%	99.4%	100.3%	10%
Hg	0.12	complies	0.99972	15.3%	16.6%	69.7%	78.5%	74.6%	84.3%	88.5%	10%
Pb	0.5	complies	0.99983	11.3%	12.6%	89.7%	95.7%	92.1%	76.8%	82.8%	10%
V	0.12	Reaction cell	0.99996	7.3%	5.5%	92.5%	93.3%	92.3%	93.7%	95.3%	10%
Cr	0.29	Reaction cell	0.99983	1.9%	2.6%	98.3%	92.7%	104.3%	102.6%	100.8%	10%
Ni	0.15	complies	0.99994	8.6%	6.5%	66.4%	110.3%	93.0%	95.0%	100.8%	20%
Cu	1.3	complies	0.99964	2.4%	1.7%	100.3% (RSD:32.7%)	92.5%	102.8%	102.4%	106.3%	20%
Mo	0.76	complies	0.99950	4.8%	3.4%	118.1%	113.5%	120.1%	111.2%	104.9%	10%
Ru	0.14	complies	0.99972	3.2%	3.5%	109.5%	110.7%	117.5%	110.0%	109.3%	10%
Rh	0.14	Mono Isotope	0.99993	2.1%	3.3%	106.4%	106.8%	114.0%	107.5%	106.7%	10%
Pd	0.1	complies	0.99976	2.3%	3.0%	75.0%	88.0%	103.7%	102.6%	103.7%	10%
Ir	0.14	complies	0.99994	9.8%	10.9%	76.2%	78.5%	74.6%	84.3%	88.5%	10%
Pt	0.14	complies	0.99807	12.3%	13.5%	79.8%	72.3%	78.5%	79.4%	84.4%	10%
Os	0.14	complies	0.99993	10.2%	9.5%	84.5%	82.5%	74.9%	84.4%	80.0%	10%
Fe	130	complies	1.00000	1.5%	1.3%	97.2%	98.6%	102.0%	99.8%	100.4%	10%
Zn	130	complies	0.99976	7.6%	5.7%	91.4%	93.2%	94.6%	98.0%	103.0%	10%
Mn	25	Mono Isotope	0.99986	1.0%	1.0%	107.6%	108.8%	113.8%	109.9%	110.8%	10%
Co	0.29	Mono Isotope	0.99991	1.3%	1.5%	106.2%	107.6%	114.2%	110.4%	111.1%	10%
Se	8.5	complies	0.99837	11.6%	9.4%	92.5%	93.1%	98.8%	97.3%	104.5%	10%
Ag	0.69	complies	0.99839	1.9%	12.5%	72.7%	86.2%	101.4%	106.0%	106.7%	10%
Sb	2.2	complies	0.99998	8.9%	8.6%	92.4%	90.0%	90.5%	92.3%	79.6%	10%
Tl	0.8	complies	0.99996	12.3%	11.1%	74.8%	76.3%	73.8%	81.7%	86.2%	10%
Ba	34	complies	0.99993	3.6%	2.5%	93.7%	95.7%	93.6%	98.8%	101.6%	10%
Li	2.5	complies	0.99996	2.9%	3.3%	106.8%	108.8%	113.9%	115.6%	116.7%	10%
Sn	6.4	complies	1.00000	3.1%	3.2%	95.3%	92.9%	97.4%	95.0%	81.4%	10%

FIGURE 1: OVERVIEW OF CONSIDERATIONS FOR POTENTIAL INTERFERENCES FOR ROUTINE SAMPLES

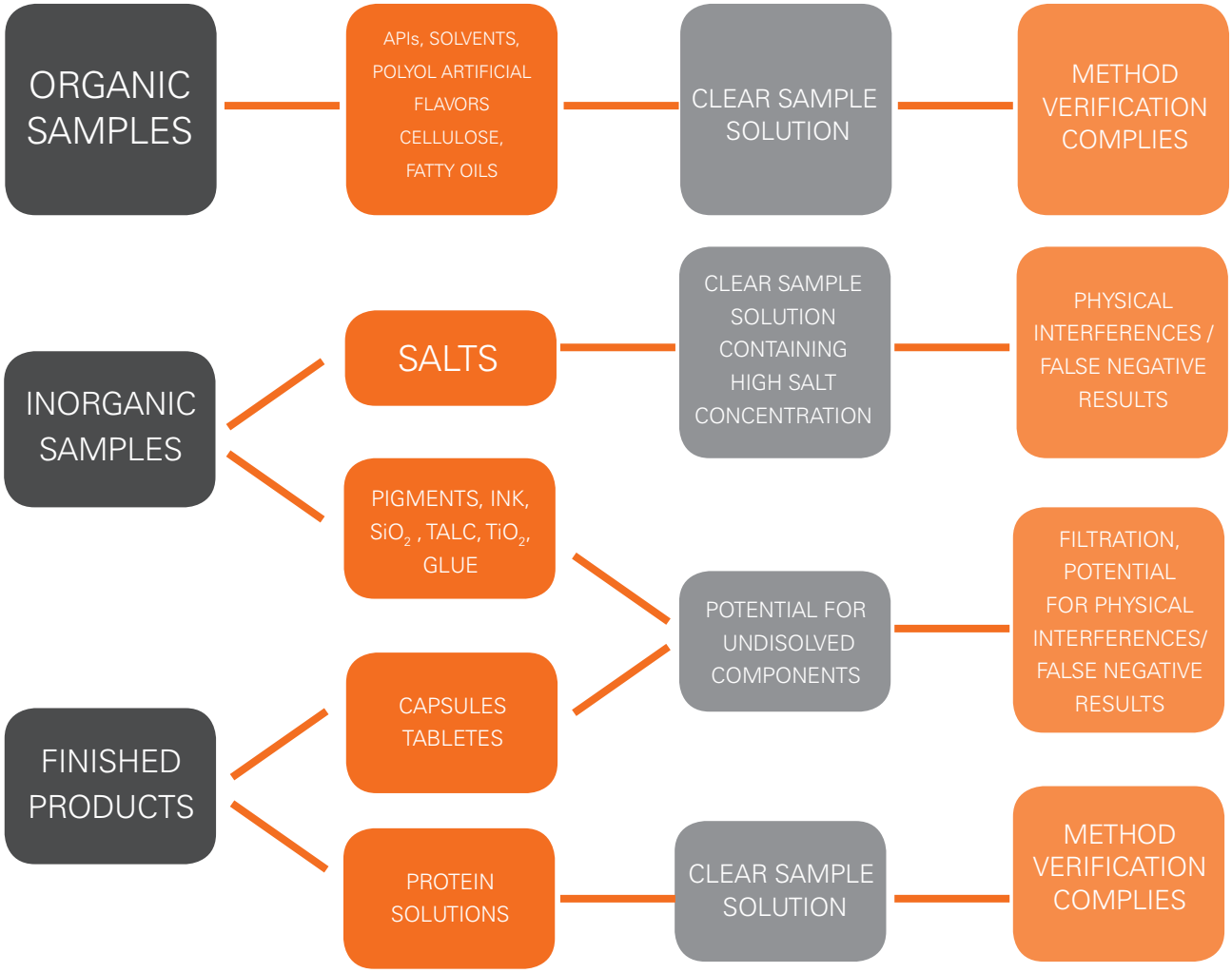
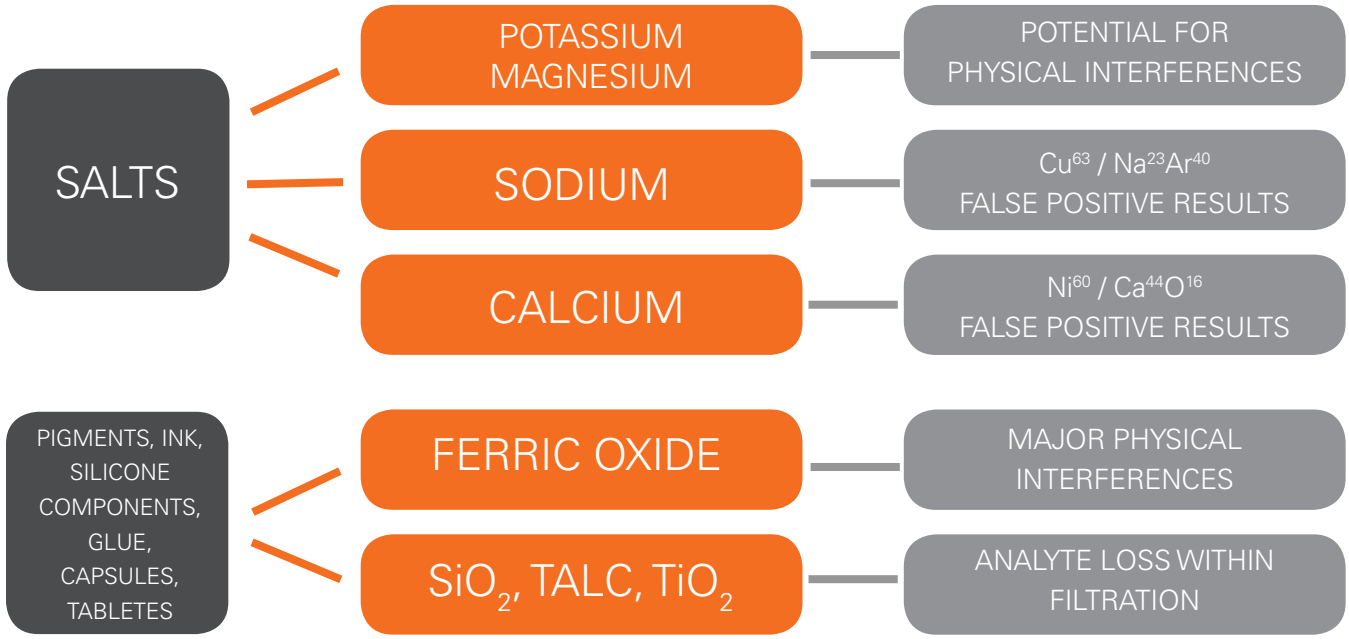


FIGURE 2: POTENTIAL INTERFERENCES FROM INORGANIC SAMPLE MATERIALS



REFERENCES

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceu-ticals for Human Use; ICH Harmonised Guideline; Guideline for Elemental Impurities Q3D Step 4; 16 December 2014, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf

USP<232> Elemental Impurities – Limits: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/2013-12-27_232_pf40-2.pdf

Council of Europe, European Pharmacopoeia News:
https://www.edqm.eu/en/The-European-Pharmacopoeia-revises-its-strategy-regarding-implementation-of-chapter-520-Metal-catalysts-or-Metal-reagent-residues-1583.html?mbID=128

To receive future articles on current trends and regulatory updates, subscribe to SGS' Life Science News at www.sgs.com/lss_subscribe

CONTACT INFORMATION

EUROPE

BELGIUM
+32 10 42 11 11
be.pharmaqc@sgs.com

FRANCE (PARIS)
+33 1 41 06 95 93
fr.pharmaqc@sgs.com

FRANCE (POITIERS)
+33 (0) 5 49 57 04 04
clinicalresearch@sgs.com

GERMANY (BERLIN)
+49 30 3460 7500
de.pharmaqc@sgs.com

GERMANY (TAUNUSSTEIN)
+49 6128 744 245
de.pharmaqc@sgs.com

ITALY (LIVORNO)
+39 0586 852591
it.pharmaqc@sgs.com

SWITZERLAND (GENEVA)
+41 22 794 8374
ch.biopharma@sgs.com

UK (WOKINGHAM)
+44 118 912 1190
uk.biopharma@sgs.com

UK (GLASGOW)
+44 141 952 00220
biosafety@sgs.com

ASIA

INDIA (CHENNAI)
+91 44 2254 2601
in.pharmaqc@sgs.com

INDIA (MUMBAI)
+91 22 6457 2540 45
in.pharmaqc@sgs.com

SINGAPORE
+65 677 53 034
sg.pharmaqc@sgs.com

CHINA
+86 21 6115 2197
cn.pharmaqc@sgs.com

NORTH AMERICA

CANADA
+ 1 905 364 3757
ca.pharmaqc@sgs.com

USA (CARSON, CA)
+1 310 885 3792
us.pharmaqc@sgs.com

USA (FAIRFIELD, NJ)
+1 973 244 2435
us.pharmaqc@sgs.com

USA (LINCOLNSHIRE, IL)
+1 847 821 8900
us.pharmaqc@sgs.com

USA (WEST CHESTER, PA)
+ 1 610 696 8210
us.biopharma@sgs.com

WWW.SGS.COM/LIFESCIENCE