ICP-MS TRACE ELEMENT ANALYSIS OF CALCIUM PHOSPHATE BONE SUBSTITUTE MATERIALS ACCORDING TO USP 232/233 GUIDELINES

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INTRODUCTION

Within the last years, a change in the elemental impurity testing of medical devices has been seen. Specifically, the definition of tolerable limits for metal impurities has shifted from a fixed concentration-based (e.g. < 50 ppm heavy metals) to a device-specific, release-based approach (maximum tolerable *daily* exposure) as seen within United State Pharmacopeia (USP) chapters <232> (product-specific risk analysis) and <233> (test validation) as well as ISO 10993-18:2020 (biological assessment of medical devices). These standards all refer to the recommendations of the *International Council for Harmonization (ICH Q3D).* Bone substitute materials (BSM) made of β-tricalcium phosphate and hydroxyapatite must fulfil the requirements of ASTM F1088-18 and ISO 13175-3:2012. Whereas ISO 13175-3:2012 is expected to change to release-based limits in a future revised version, ASTM F1088-18 currently already is referring to USP <233>. RMS Foundation has faced a number of new challenges during the validation of this method using *inductively coupled plasma mass spectrometry (ICP-MS)* since the element threshold concentrations drop significantly when more implant material is resorbed in a shorter amount of time (consequence of the product-specific risk analysis).

METHOD VALIDATION

USP 232: Release-based risk assessment

Example of worst case BSM resorption, based on product-specific risk analysis : 2.857 g/d

(conversion of release- to conc.-based limits see Tab. 1)

USP 233: Validation of quantitative procedures

- Calibration with individual target element concentrations of *0, 0.5 J* and *2 J.*
- Show accuracy, precision (repeatability and intermediate) and specificity
- Analytical method: ICP-AES or ICP-MS

J is defined as the concentration of the element(s) at the *Target Limit*, appropriately diluted to the working range of the instrument.

Consequences:

1. Target concentrations *J* can get very low for certain elements (e.g. 0.08 µg/L for Cd) but still have to be measured reliably by the analytical method (ICP-MS).
2. Each element is calibrated in a different range (0, 0.5 *J* and 2 *J*) → High risk of class 3 elements (high *J* limits) interfering on masses of class 2 and class 1 elements (small *J* limits).
3. Preparing calibration curves by using multi-element standards is very efficient. However, possible interatomic interferences on a specific mass may lead to false calibration values and therefore, to possible false-negative results for the sample measurement.

Target element	Class[1)]	Release-based limits (µg/day)	Corresponding conc. limits (µg/g)	Target limit *J* (µg /L)
Cd	1	2	0.7	0.08
Pb	1	5	1.7	0.20
As	1	15	5.2	0.60
Hg	1	3	1.0	0.12
Co	2A	5	1.7	0.20
V	2A	10	3.5	0.40
Ni	2A	20	7.0	0.80
Tl	2B	8	2.8	0.32
Au	2B	100	34.8	4.02
Pd	2B	10	3.5	0.40
Ir	2B	10	3.5	0.40
Os	2B	10	3.5	0.40
Rh	2B	10	3.5	0.40
Ru	2B	10	3.5	0.40
Se	2B	80	27.8	3.22
Ag	2B	10	3.5	0.40
Pt	2B	10	3.5	0.40
Li	3	250	87.0	10.06
Sb	3	90	31.3	3.62
Ba	3	700	243.5	28.17
Mo	3	1500	521.7	60.37
Cu	3	300	104.3	12.07
Sn	3	600	208.7	24.15
Cr	3	1100	382.6	44.27

Table 1: Target limits *J* of 24 elements for BSM calculated based on a risk assessment according to USP 232. The concentration limit was calculated for each *Target element* based on a given release-based limit and the calculated max. daily intake of BSM (2.857 g/d).

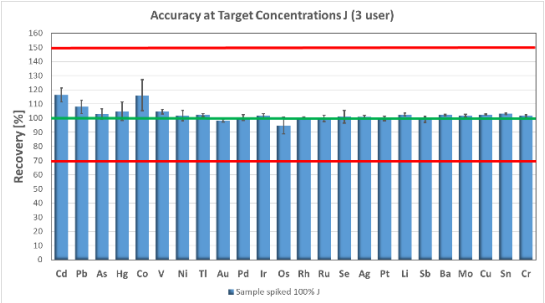

Figure 1: Recovery of the 24 elements obtained by 3 users on 3 different days (3 *J* spiked replicate measurements per user).

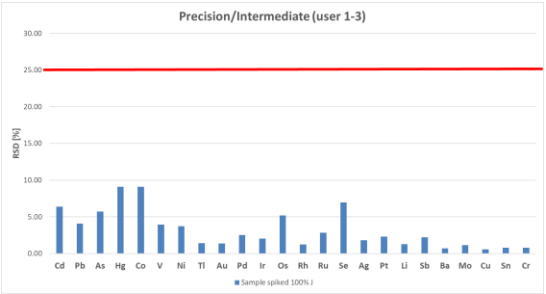

Figure 2: RSD% of the 24 elements obtained by 3 users on 3 different days (18 *J* spiked replicate measurements in total).

RESULTS

1. Fig. 1 and 2 show the mean recovery (accuracy) and %RSD (intermediate precision) values, obtained by 3 users, for each *Target Element*. All measured results were within the limits required by USP 233. The corresponding target concentrations based on the performed risk analysis for CaP bone substitute materials had a range as low as 0.08 µg/L for Cd up to 60.00 µg/L for Mo.
2. $^{95}Mo^{16}O^{+}$ is contributing to mass 111 (spectral interference in ICP-MS) where ^{111}Cd as a class 1 element is measured → high Mo content samples may lead to false positive Cd contents.
   Solution: Also measure ^{110}Cd on mass 110 (but consider interference of ^{110}Pd)
3. Cd and Mo must not be calibrated within the same multi-element standard due to the interference of $^{95}Mo^{16}O^{+}$ on mass 111.
   → Cd calibrated with a single element standard, all other 23 elements with a multi-element standard (no significant interferences observed within these 23 *Target Elements*).

DISCUSSION & CONCLUSIONS

- The resulting *Limits of detection (LODs)* were at least 3 times lower (LOD for Co: 0.066 µg/L) than the respective threshold limit (Co: 0.2 µg/L).
- The least sensitive analyte was copper with a validated LOD of 0.179 µg/L.
- In conclusion, the method meets the requirements of USP 232 and USP 233 when testing the elemental impurities present in calcium phosphate products according to a risk assessment assuming 2.875 g of CaPs dissolved in the body per day.

References

<232> Elemental Impurities – Limits, in: *United States Pharmacop. Natl. Formul. (USP 38-NF 33), United States Pharmacopeia Convention, 2012: pp. 245-248*

<233> Elemental Impurities – Procedures, in: *Second Suppl. to United States Pharmacop. Natl. Formul. (USP 38-NF 33), United States Pharmacopeia Convention, 2012: pp. 243-244*

International council for harmonization of technical requirements for pharmaceuticals for human use: *Guideline for elemental impurities Q3D(R1), 2019.*

ISO 10993-18:2020-01: *Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process.*