FAQ Pre-clinical characterization of bone graft substitutes

according to FDA guidance document «Resorbable Calcium Salt Bone Void Filler Device»

The document entitled «Resorbable Calcium Salt Bone Void Filler Device - Class II Special Controls Guidance Document for Industry and FDA staff»[1] lays down recommendations for companies submitting a 510(k) premarket notification on how to provide reasonable assurance of the safety and effectiveness of their device. In particular, the document outlines how the device should be characterized in terms of chemical composition, physical properties and (bench) performance.

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Q *Which pre-clinical physical / chemical characterizations are recommended?*

A The guidance document lists the following analyses:

Chemical composition of device:

- identification of the device material(s), including all additives, along with their respective amounts
- identification of the crystalline and non-crystalline phases, phase purity, and the weight percentage of phases
- elemental analysis, identifying the cation to anion ratio (e.g., Ca/P, Ca/S) and all trace impurities
- diffraction patterns along with superimposed patterns of each phase as given for the relevant calcium salt[2]

→ recommended standards[3] for the material characteristics (elemental analysis for Ca and P, phase quantification, elemental impurities / heavy metals):

- ASTM F1185, «Standard Specification for Composition of Ceramic Hydroxylapatite for Surgical Implants»
- ASTM F1088, «Standard Specification for Composition of β-Tricalcium Phosphate for Surgical Implantation»

Physical properties of device:

- identification of the physical form of the device (e.g., granules, pre-formed block, or putty/paste intended to set ex-vivo or in-vivo)
- dimensional specifications
- irregularly shaped devices (other than irregularly shaped granules), device drawings or
- specification of device mass, volume and density
- specification of device porosity (e.g., total porous volume, pore diameter, interconnectedness).

Performance Testing – Bench[4]**:**

- pH testing
- dissolution/solubility testing compared to the predicate device

Q *Can RMS Foundation perform these characterizations?*

A Yes, we offer all these analyses as an attractive package, including a report with detailed descriptions of the test procedures, as well as statistical evaluation and critical assessment of the results. All test methods are validated and accredited according to **ISO 17025**.

[1] Issued June 2, 2003, [2] *Available from the International Center for Diffraction Data/Joint Committee on Powder Diffraction Standards (ICDD/JCPDS),* [3] *Not considered here: United States Pharmacopoeia (USP) National Formulary (NF) "Official Monograph for Calcium Sulfate",* [4] *Devices intended to set in-vivo: not covered here*

Q What kind of samples should be used for the characterization?

A The FDA recommends to perform the characterization – in particular performance testing – on **final, sterilized devices**. Moreover, products in their final packaging should be used. This guarantees that alterations of the product during sterilization, as well as interactions between the product and the packaging are taken into account.

Q How many samples should be tested?

A The results of the analyses must be **statistically robust**. This means that reliable mean values and standard deviations across several batches must be determined. Therefore, **multiple measurements are indispensable**. We recommend one of the following sampling plans:

Sampling plan	Batches	Samples per batch	Samples total
Gold	3	3	9
Economic	3	2	6
Minimum	3	1	3

The «**Gold**» plan allows to determine a robust mean value and standard deviation of the results. Outliers can be identified reliably.

The «**Economic**» plan fulfills minimum requirements to determine the mean value and standard deviation according to statistical best practice.

The «**Minimum**» plan allows to determine a mean value and standard deviation of the results, but the reliability of the statistics is low. A risk assessment based on this standard deviation is not recommended.

Q How much do the analyses cost?

A Please contact us by e-mail or phone to **request a quote**. You can help us by providing the following information in your inquiry:

- The type of product (form, composition)
- The sampling plan you wish to receive a quote for (we can provide multiple quotes)
- Indicate for which region you plan to register your product (EU/CH, USA, other) or whether the characterizations will be used for development purposes

Our experts can also advise you on the planning of the characterizations in a consulting project. Please contact us to request a non-binding quote.

Q *What analysis methods are recommended and how much material is required?*

A These are the recommended methods and the material requirements (both for the subject device and the predicate device, if applicable) for each analysis and sampling plan:

Analysis	Method	Gold	Economic	Minimum
Elemental analysis (Ca and P, trace elements)	ICP-MS [1]	9 x 0.2 g	6 x 0.2 g	3 x 0.2 g
Crystalline phases	XRD	9 x 1.0 g	6 x 1.0 g	3 x 1.0 g
Identification of device materials and additives (incl. non-cryst. phases)	FTIR	9 x 0.2 g	6 x 0.2 g	3 x 0.2 g
Cation / anion ratio				
Ca / P	ICP-MS	(same aliquots as above; ICP-MS)		
Ca / S	XRF	9 x 2.0 g	6 x 2.0 g	3 x 2.0 g
Ca / CO_3	ICP-MS / TIC	9 x 0.7 g	6 x 0.7 g	3 x 0.7 g
Physical properties				
→ *For products in the form of granules*				
Particle size	Sieving *	9 x 5.0 g	6 x 5.0 g	3 x 5.0 g
Density	Tapped bulk density [2]	9 x 2.5 cm^3	6 x 2.5 cm^3	3 x 2.5 cm^3
→ *For products in the form of (pre-formed) blocks*				
Mass	Weighing	9 blocks	6 blocks	3 blocks
Dimensions / volume	Dimension measurements			
Density	= mass / volume			
Porosity fraction	= density rel. to bulk dens.			
Pore diameter	SEM [3]	9 x 0.2 g	6 x 0.2 g	3 x 0.2 g
Pore interconnections	Impregnation test	9 blocks	6 blocks	3 blocks
pH, dissolution, solubility	Dissolution test [4]	6 x 0.15 g (for any sampling plan, defined in standard)		
	Solubility product [5]	6 x 0.4 g (for any sampling plan, defined in standard)		

[1] compliant with ASTM F1088 / USP <232> & <233> or ASTM F1185 / ISO 13175-3, [2] according to ISO 23145-1, [3] ISO 13383-1, [4] ASTM F1926, [5] ISO 13779-6,

* in case of limited sample availability, an image-based method for the determination of the particle size may be chosen

Glossary:
ICP-MS: Inductively coupled plasma-mass spectrometry
XRD: X-ray diffraction
FTIR: Fourier-transform infrared spectroscopy
CGHE: Carrier gas hot extraction
TIC: Total inorganic carbon
SEM: Scanning electron microscopy