FAQ

Pre-clinical characterization of hydroxyapatite and β-TCP-based bone graft substitutes

according to FDA guidance document «Dental Bone Grafting Material Devices»

The document entitled «Dental Bone Grafting Material Devices - 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 and physical properties.

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

A The guidance document recommends the following analyses specified in FDA-recognized standards:

- Elemental analysis for Ca and P
- Phase quantification
- Elemental impurities / heavy metals

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

In addition, the following information is recommended to be included:

Chemical composition:

- complete chemical composition, summing to 100% by mass, including all additives and the Chemical Abstracts Service (CAS®) registry number of all components.
- description of the composition, including an elemental analysis, identifying the trace impurities.

Physical properties :

- magnified photographs, e.g., SEM micrographs, of the device showing particle size, shape, and porosity
- a plot of the resorption of your device versus time showing the time for total clearance or integration under a representative model
- healing time, i.e., the earliest time at which implant loading may be successfully attempted[2]
- phase purity, i.e., the relative mass percentages of crystalline and amorphous phases (%)
- calcium to phosphorous ratio (Ca/P)
- volumetric porosity (% void space)
- particle size distribution plot (µ)
- sintering temperature(s) (°C)
- compressive strength (MPa)
- elastic modulus (GPa)
- shear modulus (GPa)
- pH
- water solubility @ 20°C (µg/mm^3).

[1] Issued April 28, 2005
[2] Not part of physical / chemical bench testing

Q Can RMS Foundation perform these characterizations?

A We offer all bench test 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 except the shear and elastic modulus measurements are validated and accredited according to **ISO 17025**.

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

A We recommend to perform the characterization on final, sterilized devices in their final packaging. 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
Complete chemical composition (functional groups)	FTIR	9 x 0.2 g	6 x 0.2 g	3 x 0.2 g
Elemental analysis (Ca and P, trace impurities)	ICP-MS [1]	9 x 0.2 g	6 x 0.2 g	3 x 0.2 g
Crystalline / amorphous phase fractions, Ca/P ratio	XRD	9 x 2.0 g	6 x 2.0 g	3 x 2.0 g
→ *For products in the form of granules*				
Photographs of particle shape and size (incl. distribution plot)	Microscopy-based morphology analysis	9 x 0.2 g	6 x 0.2 g	3 x 0.2 g
Volumetric porosity	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*				
Volumetric porosity	Calc. from mass, volume and theoretical bulk density	9 blocks	6 blocks	3 blocks
Mechanical properties	Stress – strain curve	9 blocks	6 blocks	3 blocks
Resorption plot, pH	Dissolution test [3]	6 x 0.15 g (for any sampling plan, defined in standard)		
Water solubility	Solubility product [4]	6 x 0.4 g (for any sampling plan, defined in standard)		

[1] compliant with ASTM F1088 / USP <232> & <233> or ASTM F1185 / ASTM F1581 / ISO 13175-3, [2] according to ISO 23145-1, [3] ASTM F1926, [4] ISO 13779-6

Glossary:
FTIR: Fourier-transform infrared spectroscopy
ICP-MS: Inductively coupled plasma-mass spectrometry
XRD: X-ray diffraction
TOC: Total organic carbon
TIC: Total inorganic carbon