FAQ Pre-clinical characterization of Hydroxyapatite bone graft substitutes

according to the European Medical Device Regulation (MDR)

The European **Medical Device Regulation (MDR)** lays down regulatory rules for market access of medical devices for human use. In Annex II section 6.1, the framework requires physical and chemical characterizations of the device as well as proof of conformity with product specifications.

For synthetic bone substitutes made from Hydroxyapatite (HAp) granules or preforms, specifications for physical and chemical properties can be found in **ISO 13175-3**. This standard lists a series of analyses and specifies limits for the tested properties that a product must meet for conformity with the standard.

by Nicola Döbelin, PhD
Team Leader Bioceramics
nicola.doebelin@rms-foundation.ch

Q *Which pre-clinical physical / chemical characterizations must be performed?*

A ISO 13175-3 requires the following analyses:

- Identification and quantification of trace elements, specifically of heavy metal ions
- Qualitative and quantitative determination of crystalline phases
- Description of form and shape
- Quantification of the total porosity and pore size of micro- and macro-pores
- Determination of dissolution and pH change in solution
- Determination of the compressive strength

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/IEC 17025:2017**.

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

A The physical / chemical characterizations are part of the assessment of the safety for human use. Therefore, it is important to perform the analyses on **final products in their final packaging after sterilization**. This guarantees that interactions between the product and the packaging, as well as alterations of the product during sterilization are taken into account.

Analyses performed on semi-finished, unpackaged, or non-sterilized products have a high risk of being rejected by the regulatory authorities.

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

* For compressive strength testing, ISO 13175-3 requires at least 10 specimens regardless of the sampling plan.

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 material is required for the analyses?

A These are the material requirements for each analysis and sampling plan:

Analysis	Method	Gold	Economic	Minimum
Trace elements	ICP-MS	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
Form and shape	* Laser diffraction or sieving ** Dimensions	9 x 5.0 g * 9 blocks **	6 x 5.0 g * 6 blocks **	3 x 5.0 g * 3 blocks **
Total porosity	* From tapping density ** From apparent density	9 x 2.5 cm^3 * 9 blocks **	6 x 2.5 cm^3 * 6 blocks **	3 x 2.5 cm^3 * 3 blocks **
Micro- and macro-porosity	Electron microscopy	9 x 0.2 g	6 x 0.2 g	3 x 0.2 g
Dissolution and pH change	Ca, pH electrodes	9 x 0.3 g	6 x 0.3 g	3 x 0.3 g
Mechanical strength	* Not available ** Compressive strength	min. 30 blocks **	min. 20 blocks **	min. 10 blocks **

* for granular samples, ** for preform samples

Q How much do the analyses cost?

A The costs vary depending on the nature of the product and the selected sampling plan. 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.