

## REGENESORB Biocomposite Material Frequently Asked Questions

### 1. What is REGENESORB?

REGENESORB is an advanced biocomposite material with a unique formulation of proven materials, engineered to meet the demanding biomechanical specifications of our newest, open architecture implants. In pre-clinical studies, REGENESORB material was completely replaced by bone within 24 months<sup>i</sup>.

### 2. What are the ingredients that make up REGENESORB? How long has each been around and studied?

REGENESORB is a proprietary formulation of the following well-studied biocompatible materials:

65% Poly L-lactic co-glycolic acid (PLGA)	Member of a class of polymers that is one of the earliest and most frequently used bioabsorbable materials, starting originally with their use in the early 1970's <sup>ii</sup>
20% Calcium sulfate	One of the oldest bone graft substitutes with its first reported use dating back to 1892 <sup>iii</sup> . Contemporary commercial use of calcium sulfate as a bone void filler began in 1996. <sup>iv</sup>
15% Beta-Tricalcium phosphate ( $\beta$ -TCP)	Member of the larger family of calcium orthophosphates with its first successful repair of a bony defect described in 1920 <sup>v</sup> and incorporation into commercialized products in the 1970's <sup>ii</sup>

### 3. Is REGENESORB safe?

REGENESORB is a third-generation biocomposite material. During its development, Smith & Nephew scientists and engineers closely examined previous generations of biocomposites to understand their strengths and weaknesses. Using this knowledge, they designed a new and unique material tailored to the needs of orthopedic surgeons.

REGENESORB is composed entirely of materials that have individually been proven biocompatible and safe in clinical trials and over decades of clinical use<sup>ii,iii,v</sup>. The safety of REGENESORB itself has been confirmed in extensive

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biocompatibility testing and evaluation in pre-clinical models. For example, REGENESORB was evaluated in four pre-clinical animal studies with no reported adverse events, and no evidence of giant cell reactions or cyst formation in any of the 82 total animals implanted<sup>i,vi,vii,viii</sup>.

#### 4. How long does it take for the REGENESORB material to be absorbed?

In pre-clinical studies, REGENESORB material was completely replaced by bone within 24 months<sup>i</sup>.

#### 5. What makes REGENESORB different from other biocomposite materials? Why was calcium sulfate included in the formulation of REGENESORB material?

REGENESORB contains PLGA, a biocompatible polymer that has been used safely for decades in a wide variety of medical devices<sup>ii</sup>. In the body, PLGA has been proven to degrade faster than competing polymers such as PLLA<sup>ix</sup>. Products made from polymers like PLLA can require up to four years to fully degrade, and even then, they are not replaced by bone.

Like many biocomposite materials, REGENESORB contains  $\beta$ -TCP, an osteoconductive material that mimics the mineral phase of bone, facilitates adhesion of osteoblasts, and supports bone integration and ingrowth<sup>x,xi</sup>.  $\beta$ -TCP has been shown to absorb and support sustained bone formation over an 18 month period<sup>xii</sup>, which is well aligned with degradation rate of PLGA.

***Unlike other biocomposite materials, REGENESORB also contains 20% calcium sulfate.*** In addition to having a similar compressive strength to cancellous bone<sup>xiii</sup>, calcium sulfate has a 4-12 week absorption rate<sup>xii</sup>, indicating this osteoconductive filler stimulates early bone regrowth. It has also been associated with increased levels of local growth factors (e.g. BMP-2)<sup>xiv</sup>, suggesting it provides an additional mechanism of action – biochemical – to complement the scaffolding mechanism that  $\beta$ -TCP has been shown to provide for enhancing bone formation<sup>x</sup>.

With its unique formulation of proven materials, REGENESORB material has been shown to be replaced by bone within 24 months in pre-clinical studies<sup>i</sup>, aligned with the standard healing times of many orthopedic fixation procedures and surgical repairs.

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## 6. Why did Smith & Nephew create a new biocomposite material?

Older generations of polymers and biocomposite materials did not meet the standards required to meet the demanding biomechanical specifications of our latest open architecture implants. Consequently, Smith & Nephew started a development program to create a material that could be a foundation on which a family of advanced biocomposite implants could be built. Our primary objective was to create a material that maintained fixation strength through the healing process and that was completely replaced by bone within 24 months. REGENESORB was the result<sup>i</sup>.

REGENESORB is the first biocomposite material released by our Advanced Healing Technologies group, a team specifically focused on introducing orthobiologic solutions to improve patient outcomes in areas of unmet clinical need. REGENESORB material's unique formulation was developed through exhaustive testing to identify a combination of proven materials that could meet our stringent criteria. To complement  $\beta$ -TCP, which has individually been shown to absorb and provide enhanced bone formation over 18 months<sup>xii</sup>, REGENESORB also contains calcium sulfate, which has individually been shown to work in the early phases<sup>xiii</sup> (4-12 weeks) of bone formation and is associated with increased levels of local growth factors<sup>xiv</sup>.

In pre-clinical testing, REGENESORB material was absorbed and replaced by bone within 24 months. When implemented in the HEALICOIL<sup>®</sup> design, REGENESORB has fixation strength comparable to permanent implants made from PEEK.

## 7. Should patients with sulfur allergies be contraindicated for the HEALICOIL REGENESORB Suture Anchor (which contains calcium sulfate)?

Per the Instructions for Use, contraindications include known hypersensitivity to the implant material. Where material sensitivity is suspected, appropriate tests should be conducted and sensitivity ruled out prior to implantation.

**8. Is REGENESORB material visible on imaging (X-Ray, CT, MRI)? Does it cause MRI scatter?**

REGENESORB material is visible on X-ray and CT, but to a lesser extent than bone itself. It is also visible on MRI; however, there is no MRI scatter associated with REGENESORB material.

**9. I used CALAXO<sup>®</sup> in the past, and had some complications. Is REGENESORB like CALAXO?**

No. REGENESORB is a unique formulation of proven materials, each of which has a long history of clinical use. REGENESORB has an entirely different composition than CALAXO, including a different base polymer and different set of bioactive fillers.

<b>CALAXO</b>	<b>REGENESORB</b>
65% <u>PDLG</u>	65% <u>PLGA</u>
35% Calcium <u>Carbonate</u>	20% Calcium <u>Sulfate</u>
	15% <u>β-TCP</u>

The REGENESORB material has been tested in 4 pre-clinical (sheep) studies, including two long-term (18-24 months) and two shorter-term (12 weeks) implantation studies. A total of 82 animals were implanted with REGENESORB material with no adverse events observed<sup>iv,i,vii,viii</sup>.

*(Only if prompted on CALAXO absorption timeframe)*

In pre-clinical studies, REGENESORB has been shown to absorb and be replaced by bone within 24 months, due to the crystallinity and absorption profile of each of its individual components – PLGA, calcium sulfate, and β-TCP – all of which have a long history of clinical use.

*(Only if prompted on swelling)*

The HEALICOIL<sup>®</sup> REGENESORB Suture Anchor undergoes a special heat treating process after molding that minimizes implant deformation during sterilization and shipping.

**10. One of my primary concerns when using biocomposite implants is patient bone health. I don't want to have to worry about complications such as anchor failure or cyst formation. Why should I choose REGENESORB?**

REGENESORB is an advanced biocomposite material with a unique formulation of materials that have individually proven safe and effective in decades of clinical use. In bench-top testing, the REGENESORB material has proven strong and durable. In addition, REGENESORB was evaluated in four pre-clinical studies with a total of 82 animals implanted and no reported adverse events and no evidence of giant cell reactions or cyst formation.

**11. Your pre-clinical data look good, but when do you plan to have human data?**

There is currently a 60-patient clinical trial in progress in Japan to look at REGENESORB in an OSTEORAPTOR<sup>®</sup> implant design. When this study ends we will have human data on our new biocomposite material.

Human clinical trials evaluating Smith & Nephew HEALICOIL<sup>®</sup> suture anchors and other implants made from the new REGENESORB material are being planned. As these results become available, we will provide them in white papers and clinical publications. In all of the pre-clinical studies performed to date, no adverse events have been reported.

**12. Is there any intellectual property around the REGENESORB material?**

Yes, it is covered under an issued patent.

## HEALICOIL<sup>◊</sup> REGENESORB Suture Anchor Frequently Asked Questions

### 13. Where are the HEALICOIL REGENESORB Suture Anchors manufactured?

HEALICOIL REGENESORB Suture Anchors are manufactured at the Smith & Nephew facility in Mansfield, MA.

### 14. Is the HEALICOIL REGENESORB Suture Anchor cleared by the FDA?

Yes, it has been cleared under 510(k) K123393.

### 15. What is the shelf life for the HEALICOIL REGENESORB Suture Anchor?

The shelf life for HEALICOIL REGENESORB Suture Anchors is 3 years.

### 16. What testing has been done on the HEALICOIL REGENESORB Suture Anchor with respect to performance? Is it strong and durable?

REGENESORB is a unique formulation of proven materials that have individually been well studied<sup>ii,iii,v</sup>. In extensive bench top mechanical testing, the HEALICOIL REGENESORB Suture Anchor was shown to have superior (40% better) pullout strength in poor quality bone and superior (up to 7 times better) insertion strength in hard bone compared to competitive biocomposite implants<sup>xv</sup>. In addition, the HEALICOIL REGENESORB Suture Anchor provides the benefits of an absorbable implant with comparable fixation strength to non-absorbable PEEK implants.

### 17. With the HEALICOIL design having far less material, do I need to worry about REGENESORB absorbing too quickly in anchor designs like HEALICOIL that have far less material?

REGENESORB material has been tested in 2 long-term implantation studies including

- 24 month study testing REGENESORB in a 9x10 mm interference screw design<sup>i</sup>
- 18 month study testing REGENESORB in a 2.3 mm instability suture anchor design<sup>vi</sup>

The results of both pre-clinical studies confirmed that REGENESORB material is absorbed and replaced by bone within 24 months and that its absorption profile is independent of implant design, density, or open surface area.

In extensive bench top testing, the HEALICOIL<sup>®</sup> REGENESORB Suture Anchor was found to have superior pullout strength in poor quality bone and superior insertion strength in hard bone compared to competitive biocomposite implants<sup>xv</sup>. Bench top degradation testing also confirmed that the HEALICOIL REGENESORB Suture Anchor maintained clinically required fixation strength over time throughout the healing period<sup>xvi</sup>.

**18. How is the structural integrity of the HEALICOIL REGENESORB anchor impacted given that calcium sulfate has individually been shown to have an absorption rate of 4-12 weeks? Does it weaken over that period of time?**

REGENESORB material consists of 3 components – PLGA,  $\beta$ -TCP, and Calcium sulfate – of which the largest contributor is PLGA (65%). PLGA is the component predominantly responsible for providing overall structural integrity to the implant.

Bench testing in simulated, worst case (poor quality) bone verifies that the initial fixation strength of the HEALICOIL REGENESORB Suture Anchor is maintained throughout the healing period (12 weeks) and is sustained out to 26 weeks<sup>xvi</sup>, desirable for withstanding typical shoulder loading forces and supporting the range of motion necessary for physical therapy and rehabilitation.

**19. Can the threaded dilators that are recommended for use with HEALICOIL REGENESORB Suture Anchors be used for HEALICOIL PK Suture Anchors as well?**

Please refer to the Instructions for Use for HEALICOIL PK Suture Anchors for the appropriate hole preparation devices to be used.

**20. For certain bone conditions, is it ok to undersize the threaded dilator for the 5.5 mm HEALICOIL REGENESORB Suture Anchor, i.e. use the 4.75 mm threaded dilator for to prepare the hole for the 5.5 mm HEALICOIL REGENESORB Suture Anchor?**

Per the Instructions for Use, the same size (in this case, 5.5 mm) threaded dilator should be used.

**21. Can alternative Smith & Nephew hole preparation devices be used with the HEALICOIL<sup>®</sup> REGENESORB Suture Anchors other than the corresponding HEALICOIL REGENESORB threaded dilators?**

Per the Instructions for Use, only the HEALICOIL REGENESORB threaded dilators should be used with the HEALICOIL REGENESORB Suture Anchors.

**22. Do the HEALICOIL REGENESORB Suture Anchors require special storage conditions (e.g. cold packs)?**

No, the HEALICOIL REGENESORB Suture Anchors may be stored at standard ambient temperatures. Refer to the device packaging and labeling for specific storage specifications.

**23. What is the overall length of the HEALICOIL REGENESORB Suture Anchor?**

The length for the HEALICOIL REGENESORB suture anchor is roughly 18.5mm.

**24. Is the length of the HEALICOIL REGENESORB Suture Anchor different from HEALICOIL PK Suture Anchor? If so, how/why?**

While the HEALICOIL REGENESORB Suture Anchor shares a distinctive open-architecture design similar to that of the HEALICOIL PK Suture Anchor, its design has been slightly optimized to account for the properties of the REGENESORB material. One of these design changes includes a minor difference in overall anchor length, with the HEALICOIL REGENESORB Suture Anchor being roughly 1 mm shorter than the HEALICOIL PK Suture Anchor.

**25. How many threads are on the HEALICOIL REGENESORB Suture Anchor? Is it the same number of threads as on the HEALICOIL PK Suture Anchor?**

Both the HEALICOIL PK and HEALICOIL REGENESORB Suture Anchors have 8 threads viewable along the anchor body. However, the HEALICOIL REGENESORB Suture Anchor has a dual-lead thread design, as opposed to the single-lead thread design of HEALICOIL PK Suture Anchor, allowing for faster insertion since fewer turns are required to seat the implant.

**26. What are the outer diameters for each size of the HEALICOIL REGENESORB Suture Anchor? (Is it truly 4.75 mm and 5.5 mm)?**

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The nominal outer diameters for the HEALICOIL REGENESORB Suture Anchors are 4.75 mm and 5.5 mm.

**27. Why is the smaller HEALICOIL<sup>®</sup> REGENESORB Suture Anchor 4.75 mm in diameter and not 4.5 mm like the HEALICOIL PK Suture Anchor?**

While the HEALICOIL REGENESORB Suture Anchor shares a distinctive open-architecture design similar to that of the HEALICOIL PK Suture Anchor, its design has been slightly optimized to account for the properties of the REGENESORB material. One of these design changes includes a minor increase to the outer diameter for the smaller of the two sizes offered – a difference equivalent to the thickness of roughly 2-3 strands of human hair.

**28. Why does the inserter for the HEALICOIL REGENESORB Suture Anchor appear different from that of the HEALICOIL PK Suture Anchor, i.e. why doesn't it run completely past the implant?**

While the HEALICOIL REGENESORB Suture Anchor shares a distinctive open-architecture design similar to that of the HEALICOIL PK Suture Anchor, its design has been slightly optimized to account for the properties of the REGENESORB material. One of these design changes includes a minor change to the inserter/implant interface. The inserter for the HEALICOIL REGENESORB Suture Anchor still engages nearly 100% the anchor's length, minimizing stress and providing predictable insertion into hard bone by distributing torque along the entire length of the anchor.

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<sup>i</sup> *In vivo* animal testing has demonstrated that the composite material is bioabsorbable and is replaced by bone. Implants (9x10 mm) were implanted in ovine cancellous bone and compared to an empty defect (9x10 mm) at 6, 12, 18, and 24 months (n=6). Micro-CT analysis demonstrated that by 24 months, bone in-growth into this material (289.5 mm<sup>3</sup>) was significantly greater (p<0.05) than bone in-growth into an empty defect (170.2mm<sup>3</sup>) and reaches a bone volume not statistically different from intact bone (188.2 mm<sup>3</sup>). **Results of in vivo simulation have not been shown to quantitatively predict clinical performance.** Data on file at Smith & Nephew in report 15000897.

<sup>ii</sup> Suchenski M, McCarthy MB, Chowanec D, Hansen D, KcKinnon W, Apostolakos J, Arciero R and Mazzocca AD. Material Properties and Composition of Soft-Tissue Fixation. *Arthroscopy* (2010) 26(6): 821-831.

<sup>iii</sup> Peltier LF, Bickel EY, Lillo R and Thein MS. The use of plaster of paris to fill defects in bone. *Ann Surg* (1957) 146(1):61-69.

<sup>iv</sup> Hak DJ. The Use of Osteoconductive Bone Graft Substitutes in Orthopaedic Trauma. *J Am Acad Orthop Surg* 2007;15:525-536

<sup>v</sup> Albee FH, Studies in Bone Growth, Triple Calcium Phosphate as a Stimulus to Osteogenesis. *Ann Surg* 7 (1920), 32–36.

<sup>vi</sup> Data on file at Smith & Nephew in report 15001194

<sup>vii</sup> Data on file at Smith & Nephew in report 15000921

<sup>viii</sup> Data on file at Smith & Nephew in report 15000919

<sup>ix</sup> Chih-Chu Chang. 1995. Section IV:44, “Biodegradable Polymeric Biomaterials.” In *The Biomedical Engineering Handbook*. Bronzino JD ed. Hartford: CRC Press.

<sup>x</sup> Ogoose et al. Histological assessment in grafts of highly purified beta-tricalcium phosphate in human bones. *Biomaterials* (2006), 27(8): 1542–1549.

<sup>xi</sup> Bonfield, W., Chapter 16, “Design of Bioactive Ceramic-Polymer Composites” in *An Introduction to Bioceramics*. Editors: L.L. Hench.

<sup>xii</sup> Costantino PD, Friedman CD. Synthetic Bone Graft Substitutes. *Craniofacial Skeletal Augmentation and Replacement* (1994) 27(5):1037-1074.

<sup>xiii</sup> Pietrzak WS, Ronk R: Calcium sulfate bone void filler: A review and a look ahead. *J Craniofac Surg* 2000;11:327-333.

<sup>xiv</sup> Walsh WR, Morberg P, Yu Y, Yang JL Hagard W, Sheath PC, Svehla M and Bruce WJM. Response of a Calcium Sulfate Bone Graft Substitute in a Confined Cancellous Defect. *Clin. Orthop. and Rel. Res.* (2003) 406:228-236.

<sup>xv</sup> Data on file at Smith & Nephew in report # 15002036

<sup>xvi</sup> Data on file at Smith & Nephew in report # 15001609