

**DE NOVO CLASSIFICATION REQUEST FOR
SPACEOAR SYSTEM**

DECISION SUMMARY

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Absorbable perirectal spacer. An absorbable perirectal spacer is composed of biodegradable material that temporarily positions the anterior rectal wall away from the prostate during radiotherapy for prostate cancer with the intent to reduce the radiation dose delivered to the anterior rectum. The absorbable spacer maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

NEW REGULATION NUMBER: 21 CFR 892.5725

CLASSIFICATION: II

PRODUCT CODE: OVB

BACKGROUND

DEVICE NAME: SPACEOAR SYSTEM

SUBMISSION NUMBER: DEN140030

DATE OF DE NOVO: OCTOBER 1, 2014

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REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum. The SpaceOAR System is composed of biodegradable material and maintains space for the entire

course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

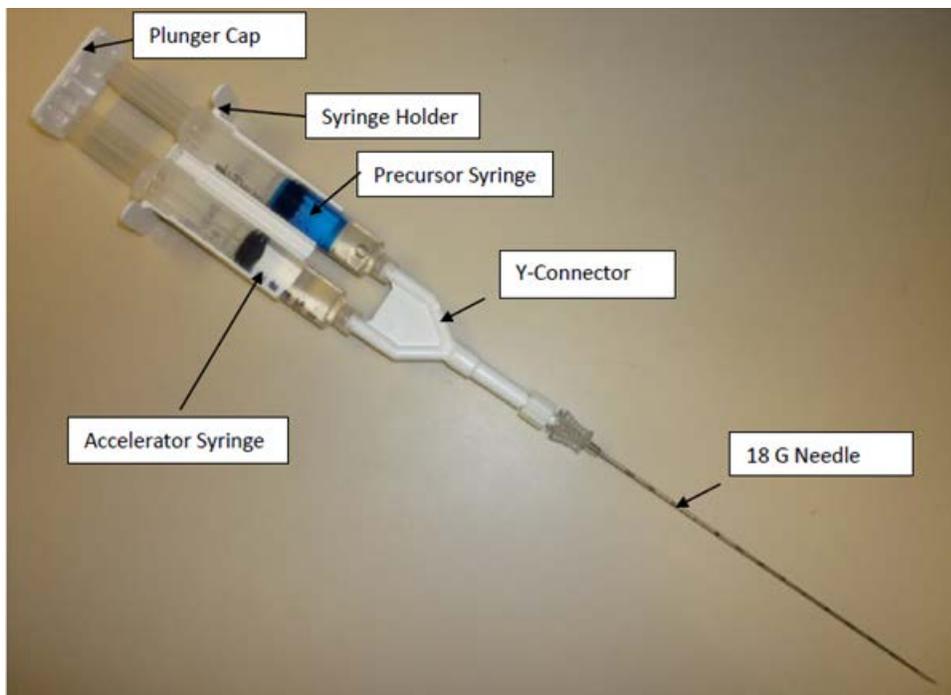
LIMITATIONS

The SpaceOAR System is restricted as a prescription device regulated under 21 CFR 801.109.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

SpaceOAR System is a polyethylene glycol (PEG) hydrogel that upon injection creates a space that temporarily positions the anterior rectal wall away from the prostate during radiotherapy for prostate cancer with the intent to reduce the radiation dose delivered to the anterior rectum. The SpaceOAR System consists of components for the preparation of a synthetic, absorbable hydrogel spacer and a delivery mechanism provided in a sterile, single use package. Once assembled as shown in the figure above, the Y-connector allows for hydrogel injection via an 18 gauge needle. The spacer is formed by mixing two solutions, the Precursor and the Accelerator. The Precursor solution is formed through the mixing of the Diluent solution (Trilysine buffer solution) with the PEG powder. The Accelerator solution is a salt buffer solution.



PRINCIPLE OF OPERATION

When mixed together, the solutions cross link to form a soft hydrogel. The mixing of the solutions is accomplished as the materials pass through a static mixer in the Y-connector prior to passing through the 18g injection needle. The in situ formed hydrogel spacer creates a temporary space between the prostate and rectum during radiation therapy. The hydrogel spacer maintains space for approximately 3 months and is then gradually liquefies via hydrolysis; it is absorbed and cleared via renal filtration in approximately 6 months of implantation, a sufficient time to support the intended use.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The chemical composition of SpaceOAR System is similar to DuraSeal Xact Sealant, a Polyethylene Glycol (PEG) based hydrogel which was FDA approved (PMA P080013) in 2009 as a spinal dural sealant. The SpaceOAR hydrogel (b)(4) and degradation are both a function of temperature and pH. At (b)(4) the (b)(4)

As the hydrogel is not enzymatically degraded, a uniform hydrolysis rate is expected due to physiologically controlled temperature and pH which does not vary substantially from patient to patient. The chemical characteristics were validated in the bench testing mentioned below.

SpaceOAR hydrogel is an implant device contacting tissue/bone with permanent contact (>30 days). The SpaceOAR delivery system is classified as a short-term tissue external communicating device (< 24 hrs).

Biocompatibility testing has been performed to evaluate both the hydrogel and the non-patient contacting components of the device. Additional studies have evaluated the SpaceOAR delivery system (i.e., 18g stainless steel needle, syringe holder, Y-connector, plunger cap). Biocompatibility testing was performed consistent with ISO 10993-1, Federal Good Laboratory Practices Regulations (21 CFR §58) and FDA's Blue Book memorandum G95-1 "Use of ISO 10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing".

The biocompatibility testing of the hydrogel includes potential systemic toxicity and local tissue responses at different time points with and without irradiation exposure. The delivery system was tested for cytotoxicity, sensitization, and irritation.

Based on the overall biocompatibility evaluations, the systemic toxicity risks associated with the intended use of the hydrogel are considerably low and acceptable. Testing results demonstrate that SpaceOAR System product is non-cytotoxic, non-irritating, non-sensitizing, non-mutagenic, and elicits no acute or sub-acute systemic toxicity.

SHELF LIFE/STERILITY

SpaceOAR System devices were tested for functionality following irradiation at (b)(4) and storage at (b)(4) relative humidity for (b)(4). Additionally, the hydrogel components (PEG Powder Vial, Diluent Syringe and Accelerator Syringe) were tested for functionality following irradiation at (b)(4) and storage at (b)(4) relative humidity for (b)(4). Finally, SpaceOAR delivery system plastic components (delivery system components, tray, and pouch) were tested for functionality following irradiation at (b)(4) (worst-case), ship testing and storage at (b)(4) relative humidity for (b)(4). All testing supports a SpaceOAR System shelf life 24 months, as reflected in the labeling of the device.

Sterilization is performed via (b)(4), a contract sterilization facility located (b)(4) (b)(4) sterilization to a Sterility Assurance Level (SAL) of 1×10^{-6} was validated in accordance with ISO 11137-2 using (b)(4) with (b)(4).

PERFORMANCE TESTING – BENCH

A series of engineering/bench tests were performed on the SpaceOAR System components and materials (final, finished, sterilized devices). The bench tests (i.e., gel time, pot life, swelling, in vitro disappearance) were conducted to assess the functional performance of SpaceOAR System. These tests also assure the SpaceOAR hydrogel components are not adversely affected by the manufacturing or sterilization processes. The tests were performed on final manufactured product, often exposed to worst-case irradiation prior to testing to assess the key functional characteristics of the hydrogel.

PERFORMANCE TESTING – ANIMAL

Animal studies were performed to evaluate the in vivo performance and safety of the SpaceOAR hydrogel. Specifically, these studies were designed to:

- Demonstrate the safety and performance of SpaceOAR hydrogel when applied in a clinically relevant model;
- Demonstrate local and systemic compatibility, with no signs of toxicity;
- Demonstrate simple injection and hydrogel space maintenance through 13 weeks; and
- Demonstrate that hydrogel completely absorbs in vivo, that there is no effect on local tissue response due to irradiation, that the inflammatory response is acceptable and that the infection risk for this hydrogel should be low relative to other biomaterials.

The animal studies successfully demonstrate SpaceOAR System product specifications, specifically gel time, pot life, and swelling.

SUMMARY OF CLINICAL INFORMATION

A prospective, randomized, parallel arm, multicenter study was conducted. Men with a pathologically confirmed diagnosis of clinical stage T1 or T2 prostate cancer indicated for IG-IMRT (Image Guided Intensity Modulated Radiation Therapy) were included in the study. Following successful fiducial marker placement, two hundred twenty-two (222) subjects were randomized (2:1) to the Treatment group (149) or Control group (73) at 20 investigational sites in the United States. Subjects randomized to the treatment group underwent placement of 10mL SpaceOAR hydrogel. Subjects randomized to the Control group did not receive injection of the SpaceOAR hydrogel. Subjects began IMRT within 21 days following fiducial marker placement. The treatment planning studies, target volume definitions, and rectal contouring for each subject with or without hydrogel injection were performed using the identical technique and similar set-up.

The effectiveness goal of this study was to demonstrate that the proportion of subjects achieving a 25% reduction in rV70 for SpaceOAR treated subjects is greater than a minimally clinically acceptable success rate considered to be 70%. The primary safety objective was to demonstrate that SpaceOAR treated subjects who experienced a Grade 1 or greater safety endpoint event through the 6 Month Follow-Up assessment was lower than (i.e., superior to) that for the Control group.

Based on independent Core Lab measurements, 97.3% [95% CI: 93.2, 99.3] of SpaceOAR treated subjects achieved a $\geq 25\%$ reduction in rV70. Based on investigator measurements, 91.8% [95% CI: 86.2, 95.7] of SpaceOAR treated subjects in the MITT (modified intent to Treat) Population achieving a reduction of $\geq 25\%$ in rV70. Both results from independent Core Lab and investigator show statistically significant results ($p < 0.0001$) that at least 70% of the subjects achieve a reduction of at least 25% in rectal V70. The primary effectiveness objective was achieved.

The primary safety endpoint is the proportion of subjects with grade 1 or greater rectal adverse events or procedure adverse events in the 6 months following the index procedure. All adverse events were reviewed by an independent Clinical Events Committee (CEC). The evaluation of the safety data determined that the SpaceOAR procedure and hydrogel material were demonstrated to be well-tolerated. There were no unanticipated adverse device effects and no events attributed to the device based on independent review by a CEC. Furthermore, there were no differences between the SpaceOAR System and Control study groups in any of the pre-specified safety endpoints evaluated (i.e., the incidence of CTCAE Grade 1 or greater or Grade 2 or greater rectal or procedural events, changes from baseline in EPIC Urinary and Sexual domains, proportion of subjects requiring medication changes for mitigation of rectal or urinary symptoms or for procedure-related events). No subject in this study required a delay in radiation therapy that was associated with a procedure or device-related adverse event. There were no CTCAE Grade 3 or Grade 4 procedural or rectal events within the SpaceOAR treatment group and there were no serious procedure-related rectal events. In particular no incidences of true rectal perforations, rectal hemorrhaging or infections were associated with the administration or presence of the device. The majority of the procedural-events that were observed were mild and transient and typical for men undergoing a transperineal injection or fiducial marker placement. The event rates for the two groups were comparable with 34.0% for the SpaceOAR treatment group vs. 31.9% for the Control group ($p = 0.6862$).

Overall, the study results support that SpaceOAR increased the space between prostate and rectum and resulted in less radiation in the rectal area. The rate of Grade 1 or greater rectal adverse events or procedure adverse events through 6 months for the SpaceOAR group is similar to the Control group. Risk of a harmful event is low as there were no device-related serious or non-serious adverse events. The injection of the SpaceOAR hydrogel uses well established techniques.

LABELING

The labeling for the SpaceOAR system is consistent with the clinical data and covers the hazards, warnings, contraindications, and other clinically relevant information that may impact safe and effective use of the device. The labeling is sufficient and satisfies the requirements of 21 CFR Part 801, including the prescription device labeling requirements under 21 CFR 801.109. The following summarizes how the SpaceOAR labeling addresses certain labeling issues:

a. Detailed instructions for system preparations and detailed implant procedure instructions.

The instructions for system preparation and implant procedure for the SpaceOAR system include three main steps: 1. Preparing the Precursor Syringe, 2. Assembling the delivery components for injection, and 3. Positioning the needle and injection of SpaceOAR hydrogel. The Instructions for Use also include detailed sub-step instructions and photographic illustrations for each sub-step. The labeling also provides detailed instructions on how to enable and maintain ultrasound image guidance of the needle to prevent rectal wall penetration, how to properly advance the needle, verify needle position, dispense hydrogel and withdraw the needle.

b. Appropriate contraindications, warnings, and an expiration date that is supported by performance data as well as supporting the sterility.

The labeling includes warning information “SpaceOAR System must only be administered via an aseptic transperineal route. Do not administer transrectally.” The labeling also includes precautions on the implantation procedure “The SpaceOAR needle tip must be at the prostate midline during SpaceOAR hydrogel injection to avoid lateral hydrogel formation.”; “Use within 1 hour of preparing the Precursor solution. Discard entire system if not used within 1 hour.” and “SpaceOAR System injection should proceed uninterrupted, without stopping.”

The labeling provides warning information on the injection failures observed or experienced in the clinical study. The labeling includes a list of potential complications that may be associated with the use of SpaceOAR System: pain associated with SpaceOAR hydrogel or hydrogel injection; needle penetration of the bladder, prostate, rectal wall, rectum, or urethra; injection of SpaceOAR hydrogel into bladder, prostate, rectal wall, rectum, or urethra; local inflammatory reactions; infection; injection of air, fluid, or SpaceOAR hydrogel intravascularly; urinary retention; rectal mucosal damage, ulcers, necrosis; bleeding; constipation; and rectal urgency.

The labeling also provides instructions to mitigate potential risks. These include: “If the needle enters the rectal lumen at any time during the procedure, abandon the procedure to avoid infection.”; “The perirectal space may not open during hydrodissection, e.g., scar tissue. If the perirectal space does not open with saline do not inject SpaceOAR.”

The labeling also contains the statement: “The SpaceOAR System is provided sterile. Do not use if packaging or seal has been damaged or opened. Do not re-sterilize. Do not use if the PEG powder is not free flowing. All system components are intended for single-use only. SpaceOAR components cannot be re-used.”

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of absorbable peri-rectal spacer and the measures necessary to mitigate these risks.

Identified Risks	Required Mitigations
Device functional failure or the device is unable to maintain space stability during the course of radiation therapy	Special Controls (1)(i), (1)(ii), (1)(iv), and (1)(vi)
Prolonged or delayed procedure	Special Controls (1)(iii), (1)(iv), (2), and (3)
Needle penetration and/or spacer material injection into bloodstream, bladder, prostate, rectal wall, rectum or urethra	Special Controls (1)(iv), (2), and (3)
Incomplete absorption	Special Controls (1)(iii), (1)(iv), and (1)(vii)
Infection or local tissue inflammatory reactions	Special Controls (1)(iv), (1)(v), (1)(vi), (1)(vii), and (3)
Pain or discomfort associated with spacer	Special Controls (1)(iv) and (3)
Urine retention, bleeding, rectal mucosal damage, ulcers, necrosis, constipation, or rectal urgency	Special Controls (1)(iii), (1)(iv), (1)(vii), (2), and (3)

BENEFIT/RISK DETERMINATION

Summary of the Benefit(s)	The probability that a patient will experience benefit is high, as 97.3% of SpaceOAR System subjects achieved a clinically relevant reduction of > 25% of the rectal volume receiving at least 70Gy (i.e., rV70) (p<0.0001).
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<p>Summary of the Risk(s)</p>	<p>Risk of a harmful event is low as there were no device-related serious or non-serious adverse events. The device is present throughout the treatment period before being eliminated through hydrolysis.</p> <p>Potential complications that may be associated with the use of SpaceOAR System include, but are not limited to: pain associated with SpaceOAR hydrogel injection; pain or discomfort associated with SpaceOAR hydrogel; needle penetration and/or spacer material injection into the blood stream, the bladder, prostate, rectal wall, rectum, or urethra; local inflammatory reactions; infection; injection of air or fluid into the blood stream; urinary retention; rectal mucosal damage, ulcers, necrosis; bleeding; constipation; incomplete absorption; prolonged or delayed procedure; device functional failure or the device is unable to maintain space stability during the course of radiation therapy; and rectal urgency.</p>
<p>Summary of Other Factors</p>	<p>The current standard of care for treating prostate cancer does not include a spacer. SpaceOAR System was shown to be effective when compared to Control without increased risk. The rate of Grade 1 or greater rectal adverse events or procedure adverse events through the 6 Month Follow-Up for the SpaceOAR group (34.2%) was similar to the Control group (31.5%). Risks can be mitigated through special controls including demonstration of biocompatibility; sterility; shelf-life; perirectal space creation and maintenance for the duration of prostate radiotherapy, spacer stability and lack of migration, complete spacer absorption in the patient body (all those properties not altered by the therapeutic radiation level); and clear instructions in the labelling and user training regarding the safe and effective use of the device.</p>

<p>Conclusions Do the probable benefits outweigh the probable risks?</p>	
<p>The clinical results showed that the primary effectiveness hypothesis was met, i.e., the percent of SpaceOAR subjects with 25% reduction in dose in the rectal V70 region was > 70% with statistical significance. Overall, the study results support that SpaceOAR increased the space between prostate and rectum and resulted in less radiation in the rectal area. The rate of Grade 1 or greater rectal adverse events or procedure adverse events through 6 months for the SpaceOAR group is similar to the Control group.</p> <p>Risk of a harmful event is low as there were no device-related serious or non-serious adverse events. The injection of the SpaceOAR hydrogel uses well established techniques. The SpaceOAR System is comprised of the same PEG hydrogel technology as other previously approved devices used on other body sites (DuraSeal P040034, Matrix VSG PMA P040044, DuraSeal Xact Sealant P080013, ReSure Sealant P130004 and Bio-Seal DEN090007). Additionally, long term follow up from the European and US clinical trials and post market AE data on over 2600 SpaceOAR System since CE Mark approval in 2010 and Australian TGA approval in 2011 did not record any AE's or complications related to persistent hydrogel or to long-term safety issues associated with SpaceOAR hydrogel use. Moreover, for this low to moderate risk device, risks can be mitigated through the identified special controls, and this device is not life-supporting or life-sustaining.</p> <p>It is reasonable to conclude that the benefits of using the device outweigh the potential risk of injury when used as indicated in accordance with the instructions for use.</p>	

CONCLUSION

The request for de novo for the SPACEOAR SYSTEM is granted. FDA believes that special controls, along with the applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type. This device is classified under the following:

Product Code: OVB
Device Type: Absorbable perirectal spacer
Class: Class II (special controls)
Regulation: 21 CFR 892.5725

(a) *Identification.* An absorbable perirectal spacer is composed of biodegradable material that temporarily positions the anterior rectal wall away from the prostate during radiotherapy for prostate cancer with the intent to reduce the radiation dose delivered to the anterior rectum. The absorbable spacer maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time.

(b) *Classification.* Class II (special controls). An absorbable perirectal spacer must comply with the following special controls:

- (1) The premarket notification submission must include methodology and results of the following non-clinical and clinical performance testing. For all clinical investigations used to support premarket notification submissions for this type of device, line listings of the study data must be provided.
 - (i) Performance bench testing must demonstrate appropriate perirectal space creation and maintenance for the duration of prostate radiotherapy;
 - (ii) Performance bench testing must demonstrate that therapeutic radiation levels do not alter the performance of the device;
 - (iii) Performance in vivo testing must demonstrate appropriate deployment of spacer as indicated in the accompanying labeling, and demonstrate appropriate expansion and absorption characteristics in a clinically relevant environment;
 - (iv) Clinical study must demonstrate appropriate spacer stability and lack of migration for the entire course of radiotherapy, complete absorption, and lack of long term toxicity;
 - (v) Sterility testing must demonstrate the sterility of the device and the effects of the sterilization process on the physical characteristics of the spacer;
 - (vi) Shelf-life testing must demonstrate the stability of the physical characteristics of the spacer throughout the shelf-life as indicated in the accompanying labeling; and,
 - (vii) The device must be demonstrated to be biocompatible.
- (2) The risk management activities performed as part of the manufacturer's 21 CFR 820.30 design controls must document an appropriate end user initial training program which will be offered as part of efforts to mitigate the risk of failure to

correctly operate the device, including, but not limited to, documentation of an appropriate end user initial training program on the proper spacer deployment technique.

- (3) The device labeling must include the following:
- (i) A detailed summary of reported or observed complications related to the use of the device;
 - (ii) Appropriate warnings;
 - (iii) Detailed instructions for system preparations and detailed implant procedure instructions; and,
 - (iv) An expiration date that is supported by performance data as specified in subparagraph (b)(i)(vi).