

**EVALUATION OF AUTOMATIC CLASS III DESIGNATION (DE NOVO) FOR
BIO-SEAL LUNG BIOPSY TRACT PLUG SYSTEM**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Absorbable lung biopsy plug. A pre-formed (polymerized) absorbable lung biopsy plug is intended to provide accuracy in marking a biopsy location for visualization during surgical resection and closure of pleural punctures associated with percutaneous, transthoracic needle lung biopsies. Upon, deployment into the biopsy tract, the plug expands to fill the biopsy void and remains in place until resorbed.

NEW REGULATION NUMBER: 21 CFR.878.4755

CLASSIFICATION: II

PRODUCT CODE: OMT

BACKGROUND

DEVICE NAME: Bio-Seal Lung Biopsy Tract Plug System

510(K): K082438

DATE OF 510(K) NSE DECISION: MARCH 19, 2009

DATE OF DE NOVO PETITION: APRIL 16, 2009

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PETITIONER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The Bio-Seal Lung Biopsy Tract Plug System is indicated to provide accuracy in marking a biopsy location for visualization during surgical resection and to plug pleural punctures associated with percutaneous, transthoracic needle lung biopsies to significantly reduce the risk of pneumothoraces (air leaks).

LIMITATIONS

The sale, distribution, and use of the Bio-Seal Lung Biopsy Tract Plug System is restricted to prescription use only.

Limitations on device use are also achieved through the following statements included in the Instructions for Use:

The device is intended to seal pleural punctures associated only with percutaneous, transthoracic needle lung biopsies.

It can only be used with a compatible 19 gauge coaxial introducer needle with a translucent yellow cannula hub manufactured by Angiotech.

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

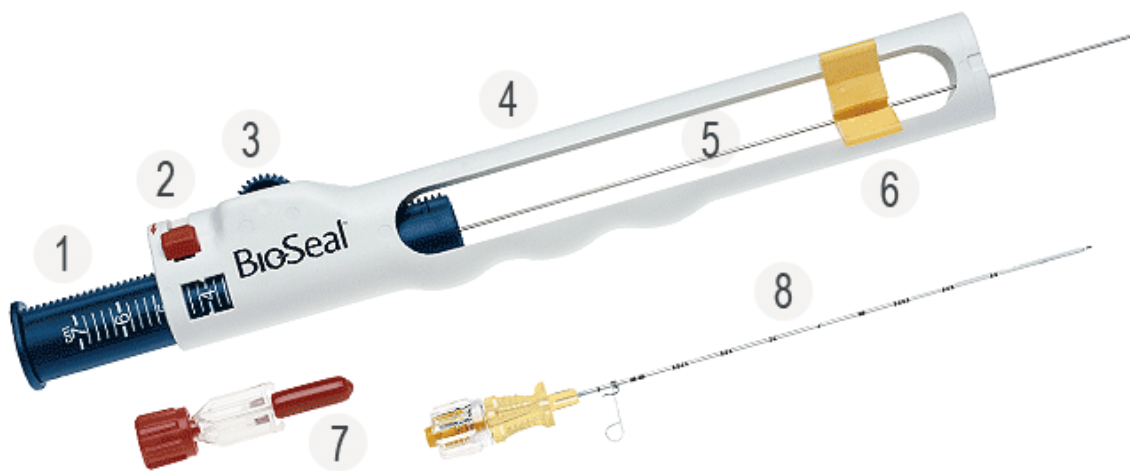
DEVICE DESCRIPTION

The Angiotech Bio-Seal Lung Biopsy Tract Plug System is comprised of (1) a pre-formed hydrogel plug and (2) a delivery system, which together are designed for use in conjunction with Fine Needle Aspiration (FNA) biopsy of the lung. During lung biopsy, a 19 gauge coaxial needle is placed at the site to be biopsied, under fluoroscopic guidance. The stylet is removed and a 20 or 22 gauge FNA biopsy needle or biopsy instrument is inserted to obtain the tissue sample. When the FNA biopsy needle or biopsy instrument is removed, the Bio-Seal Lung Biopsy Tract Plug is deployed using the Bio-Seal delivery system through the coaxial needle into the biopsy tract. Upon deployment into the biopsy tract, the hydrogel plug absorbs extracellular fluid and expands to fill the void of the biopsy tract and remains in place for months to mark the biopsy site.

The pre-formed hydrogel Bio-Seal plug was previously cleared as a lung biopsy site marker device under K041331. No changes have been made to the design of the implantable plug since its clearance in K041331. However, the indications for use are different; the device is now indicated to plug pleural punctures associated with percutaneous, transthoracic needle lung biopsies to significantly reduce the risk of pneumothoraces (air leaks) in addition to use as a biopsy site marker.

The delivery device has been modified for the Angiotech Bio-Seal Lung Biopsy Tract Plug System to improve manufacturability and ergonomics. The delivery device is provided sterile (by ethylene oxide), single use only and included in the package with the Bio-Seal plug. The delivery device uses a thumb wheel to position the correct depth of the plunger for deploying the Bio-Seal plug through the adapter and into the biopsy tract. A picture of the delivery system is provided in Figure 1 below.

Figure 1- Angiotech Bio-Seal Lung Biopsy Tract Plug System



- 1 - Depth Markings in 2mm increments
- 2 - Depth Locking Mechanism
- 3 - Depth Adjustment Thumb Wheel
- 4 - Easy Grip Handle
- 5 - Plunger Stylet
- 6 - Removable Stabilization Clip
- 7 - Bio-Seal Co-axial Adapter: houses the Bio-Seal Plug and connects to the co-axial introducer for placement of the plug into the biopsy tract.
- 8 - 19G Introducer Needle

The Bio-Seal Plugs are made of resorbable polyethylene glycol (PEG) hydrogel. The hydrogel material expands with exposure to fluid, thus sealing the cavity created by the biopsy procedure to prevent air leaks and marks the biopsy location for visualization during surgical resection. The Bio-Seal Plug is an expandable solid cylinder, [dimensions prior to insertion are 2.5 cm (0.984 inches) in length with a 0.084 cm (0.033 inches) outer diameter], composed of desiccated hydrogel (polymerized PEG).

The Bio-Seal Plugs are contained in the delivery system adapter. During use, the adapter is mated to the coaxial needle, and the delivery system, which is pre-set with the desired plunger depth, is placed on top of the adapter. The plunger is depressed, delivering the Bio-Seal Plug to the desired depth. The desired depth is determined by an appropriate imaging technique. The adapter was modified so that it only mates with the compatible 19 gauge coaxial introducer needle with a translucent yellow cannula hub manufactured by Angiotech.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The implantable Bio-Seal Plug is identical to the plug cleared within K041331 and according to the manufacturer has not changed in formulation, manufacturing or sterilization method.

Materials characterization of the Bio-Seal Plug is cross-referenced from K041331 and P990028. High-performance liquid chromatography and nuclear magnetic resonance spectroscopy (performed under K041331) showed no new species in the chemical composition of the polymerized plug and polymerized FocalSeal-L (P990028).

The Bio-Seal Plug is a hydrogel that degrades via hydrolysis. Results from rat studies with polymerized FocalSeal-L suggest that the material is essentially resorbed at 20 months and that 35% of the material was present at 6 months. Based upon these results the material theoretically degrades at body temperature in vivo within 20 months. In vitro studies performed at 37°C demonstrate theoretical degradation at body temperature in vivo within 15-18 months with approximately two-thirds degradation complete within 6-9 months.

The Bio-Seal Plug has been tested and results are acceptable for cytotoxicity, sensitization, intracutaneous reactivity, hemolysis, pyrogenicity, genotoxicity, mutagenicity, chromosomal aberrations, chronic toxicity, and implantation, which is appropriate for a permanent tissue implant contacting device.

However, material modifications were made to the delivery system which necessitated further testing. The modified patient-contacting components are the Housing, Stylet, and Adapter (which holds the Bio-Seal Plug). These components were evaluated for cytotoxicity, irritation, systemic toxicity (acute), hemolysis, delayed hypersensitivity, materials-mediated pyrogenicity and limulus amoebocyte lysate (LAL). All modified components were shown to be biocompatible per ISO 10993-1:2009 with respect to their intended use.

SHELF LIFE/STERILITY

The Bio-Seal Lung Biopsy Tract Plug System is sterilized via exposure to the ethylene oxide (EO) gas sterilization process to ensure a Sterility Assurance Level (SAL) of 10^{-6} . This process was appropriately validated in conformance with consensus standard ISO 11135:1994, Medical devices – Validation and routine control of ethylene oxide sterilization and updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA, issued on August 30, 2002.

The foil with Tyvek header packaging for the Bio-Seal Tract Plug System has not changed from the packaging that was used for the Bio-Seal Plug in K041331. However, the packaging has been redesigned to account for an additional Bio-Seal Tract Plug and

inclusion of the delivery device within the package. Due to these changes, a relative resistance study was conducted and passed. The purpose of the study was to evaluate more fully the EO resistance characteristics using the company's sterilization parameters including a) providing a new process challenge device, b) evaluating the normal device bioburden and c) providing new product resistance data that would include the Bio-Seal Lung Biopsy Tract Plug and associated delivery system.

Shelf life/stability testing was performed to establish the shelf life of the Bio-Seal Lung Biopsy Tract Plug System, including the delivery system and adapter. Testing supported the requested shelf life of three (3) years. Accelerated (storage at 55°C and greater than 70% relative humidity per ASTM F1980) and real time (storage at ambient conditions) aging testing was performed using sterilized Bio-Seal Lung Biopsy Tract Plug Systems to support the three year shelf life. The Bio-Seal Lung Biopsy Tract Plug System was visually, dimensionally and functionally assessed over the duration of the requested shelf life. Functional testing (please see the Performance Testing-Bench section below for further detail) included:

- The plug must deploy
- The plug must protrude from the simulated lung tissue
- Time for full deployment

Ten (10) samples were tested following accelerated aging and ten (10) samples were tested following real time aging. Two (2) samples at each time point of 1, 1.5, 2, 2.5, and 3 years were tested. All samples successfully passed testing and the pre-specified acceptance criteria. The Bio-Seal dimensions were within specification and there was no premature plug expansion during aging. The plugs all deployed after the 60 second hold time requirement identified in the protocol, and all the plugs protruded from the simulated tissue used in testing. Fifteen (15) Bio-Seal plugs were tested for hydration rate by exposing them to saline solution and measuring their diameter every 15 seconds (from 0 to 90 seconds). All plugs that were hydrated expanded beyond the pre-specified dimension.

PERFORMANCE TESTING – BENCH

Bench testing of the Bio-Seal Plug, adapter, and delivery system is cross-referenced from K041331:

- Critical dimension testing of the plug was performed. The outer diameter (OD) is critical as it is designed to fit into the housing assembly and coaxial needle during deployment and the plug should be wide enough to expand predictably. The length is critical as its positioning post-deployment depends upon its precise length. The distance of the plug from the skin surface depends upon the plug length, plunger length, and markings on the delivery system. The plug is intended to be implanted to a distance of 0.5 cm outside the pleural surface. (b)(4) sterile plugs were dimensionally inspected for OD and length and were found to be within acceptable tolerances.

- The rate of OD change (hydration rate) of the plug was observed over time. Hydration rates were used to estimate the amount of time the physician has to deploy the plug in worst-case conditions in the presence of excessive body fluid or blood. (b)(4) pre-sterilized and (b)(4) post-sterilized plugs were tested by submersion in dyed saline for (b)(4) and (b)(4). (b)(4) plugs were removed at each time point for measurement. Time lapsed photographs and scanning were used for dimensional analysis. The time needed to reach a predetermined diameter where the plug would no longer fit the internal diameter (ID) of the coaxial needle was also measured. Test results demonstrated that sterilization did not adversely affect the hydration rate. Post-sterilization, the plugs were able to expand to prespecified dimensions within (b)(4) and (b)(4).
- The plug is provided in a housing adapter assembly which has two end caps. Without the caps, the subassembly is referred to the Main Luer assembly. The length of this assembly is a critical dimension that serves as an alignment tool for the plug to enter the coaxial needle. The Main Luer assemblies were inspected for this critical length, and all (b)(4) tested assemblies were found to be within acceptable tolerances.
- The nylon tube inside the Main Luer assembly protects the plug and directs the plunger stylet as it advances the plug through the housing assembly and through the coaxial needle. The plunger stylet will bend at approximately (b)(4) of force (as determined during design characterization testing). The nylon tube should be able to withstand at least this amount of force without dislodging. The adhesive bond strength of the nylon tubing to the male-to-male adapter of the Main Luer assembly was pull tested to this specification. (b)(4) assemblies were measured to have a bond strength greater than or equal to (b)(4).
- Dimensional inspection was performed on the critical lengths and ID of the delivery system. The support column length is critical to assure proper mating with the coaxial needle. The ID of the support column is also critical for proper mating with the Main Luer assembly. The plunger stylet length must not protrude beyond the coaxial needle for a given depth setting at the time of the delivery, so overall length is a critical dimension, as is the first laser mark, which serves as a datum for all other markings. Finally the plunger stylet is assembled into a plunger adaptor. The plunger must seat completely within the hole of the adapter. Therefore, (b)(4) are used to verify this dimension. (b)(4) delivery systems each were tested. The support column length, ID, plunger length, and first laser mark were all within acceptable measurements. All (b)(4) measurements of minimum and maximum depths were passed.

To verify modifications made to the delivery system, functional testing using sterilized delivery systems was performed to determine if the plug deployed, the ease of plug

deployment, the time to deploy the plug, and the degree to which the plug protruded from a simulated skin to pleura thickness. Although acceptance criteria for testing only included that the plug deployed and it protruded from the simulated lung tissue, ease of deployment, time for full deployment and plug protrusion in centimeters were also recorded:

- Ease of deployment was observed to determine how easily the plug deployed through the coaxial introducer needle and was rated on a scale of (b)(4). Although not ideal, a rating of (b)(4) would be considered acceptable if the plug deployed correctly.
- During testing, a hold time of (b)(4) was implemented prior to deployment to simulate a worst case field condition. The time for full deployment is measured from the time the adapter is attached to the coaxial introducer needle and ends when the coaxial introducer needle is withdrawn from the testing medium and includes the (b)(4) hold time. The directions for use require plug deployment within (b)(4) of attachment to the coaxial introducer needle; the (b)(4) that was tested provides a (b)(4) for actual deployment times.
- The plug protrusion criterion is recorded to verify that the plug protrudes from the pleura of the simulated lung tissue.

All (b)(4) devices deployed the plug as intended with an average ease of plug deployment rating at (b)(4), an average deployment time of (b)(4), and an average plug protrusion above the simulated pleura of (b)(4).

PERFORMANCE TESTING - ANIMAL

Multiple non-clinical acute animal tests were previously conducted between June 2001 and April 2003, and cross-referenced from K041331. This testing is directly applicable to the Bio-Seal Plug, which is unmodified from K041331. The modified delivery system was evaluated through bench testing (discussed above) and clinical testing (discussed below).

Research and development acute studies included demonstrating expansion characteristics of a prototype plug under inflation, air leakage in the presence of blood, varying depth placements of the plug, physician preference, and techniques for maneuvering the marker, photographic documentation of placement and extension beyond pleura, and feedback for physician training.

To test for local tissue reaction to the Bio-Seal Plug, chronic testing was conducted in swine sacrificed at 7 days and 14 days. Reported inflammatory response was minimal, comparable to absorbable sutures. Additionally, a chronic GLP animal study was performed on swine sacrificed at 90 days and 180 days for histological evaluation.

Results showed minimal inflammation to the prototype plug, which was comparable to the absorbable sutures. The benefits to the patient are that for up to 6 months, there is minimal active inflammation in lung tissue when tested in an *in vivo* model.

SUMMARY OF CLINICAL INFORMATION

A multi-centered (15 US centers), randomized (1:1, block size 10, stratified by site and history of smoking), controlled trial was conducted under (b)(4) in patients receiving lung biopsies. The purpose of the trial was to demonstrate safety and effectiveness of the Bio-Seal Plug in reducing pneumothorax rates post lung biopsy. Patients were randomized to either receive or not receive a Bio-Seal Plug after a lung biopsy per standard hospital protocol.

The primary effectiveness endpoint was the incidence rate of pneumothorax during the first 30 days post lung biopsy, measured by chest x-rays at 0-60 minutes after procedure, 24 hours after discharge and 30 days post discharge. A blinded, independent reader analyzed the x-rays, whose opinion was used in evaluating the primary endpoint.

The sample size calculation was based upon an assumption of a 30% pneumothorax rate for the control group and 15% for the treatment group, alpha 0.05(2-sided) and 80% power, which yielded 134 patients per arm. After accounting for patients who might be disqualified after enrollment, a total of 330 patients were to be enrolled in the study.

A total of 339 (170 – Bio-Seal, 169 – Control) patients were enrolled and randomized in the trial (intent-to-treat population). A total of 287 (150 – Bio-Seal, 137 – Control) patients completed the study per the protocol (per protocol). The results of the trial show both statistically and clinically significant differences in the rates of pneumothoraces after transthoracic needle biopsies of lung for both the intent-to-treat (ITT) and per protocol (PP) populations, per the pre-specified analyses. For the ITT population, treatment success (no pneumothoraces to 30 days) was 75% with the device and 57% without the device (control) (p=0.0008). For the PP population, treatment success was 85% with the device and 69% without (p=0.0022). Use of the device was also associated with improvement in all the secondary endpoints:

- time to ambulation
- time to hospital discharge
- number of additional chest x-rays needed
- incidence of chest tube placement
- incidence of hospital admissions for pneumothorax

However, statistical analyses of these secondary endpoints were not provided and the study was not powered to detect statistically significant changes in these secondary endpoints. Analyses including imputation of missing data for the ITT population using the last observation carried forward method showed similar results. This method seems clinically reasonable. The major reasons for missing data were patient scheduling and resectional surgery before the 30 day chest radiograph.

Safety was assessed through review of the adverse events for the control and Bio-Seal groups and was comparable for non-procedure related events. The incidence of device or procedure-related

events were higher in the control group than the Bio-Seal group (44% versus 25%, PP). There were 7 device-related events that were noted on the case report forms (CRFs) that were not reported as adverse events. These events related to device malfunction and resulted in the device not being used in 5 of the 7 cases. The events did not result in clinical harm. Three deaths occurred during the study (2 Control, 1 Bio-Seal) and were unrelated to the device or the procedure. The adverse events are summarized in Table 1:

Table 1 - Summary of Adverse Events

AE Category	Bio-Seal N = 170		Control N = 169	
	Number of Events	Number (%) of Patients	Number of Events	Number (%) of Patients
Any Device AE	61	43 (25%)	96	74 (44%)
AE other than pneumothorax	23	6 (4%)	30	8 (5%)
Non-device AE	53	31 (18%)	59	36 (21%)
<i>Adverse Events that were more common in Bio-Seal than Control and greater than 1%</i>				
Coughing with Blood	5	3 (2%)	2	2 (1%)
Infections	3	3 (2%)	2	2 (1%)

The study results clinically support the intended use for the Bio-Seal device.

LABELING

Labeling has been provided which includes instructions for use and an appropriate prescription statement as required by 21 CFR 801.109(b). The labeling:

- includes directions for determining the depth of plug placement and directions for deploying the plug and for removing both the deployment device and coaxial needle.
- includes data on effectiveness of the device from a randomized, controlled trial comparing the pneumothorax rates of a treatment group to the control group.
- includes a list of the anticipated adverse events.
- identifies warning statements to mitigate potential risks in the clinical setting. These include:
 - The Bio-Seal Lung Biopsy Tract Plug System can only be used with a compatible 19 gauge coaxial introducer needle with a translucent yellow cannula hub manufactured by Angiotech.
 - This instrument should only be used by a physician familiar with the possible side effects, typical findings, limitations, indications and contraindications of lung biopsies.
 - Physician judgment is required when considering biopsy on patients with bleeding disorders, receiving anti-coagulant medications, or with bullous emphysema at or near the biopsy site.

Both the second and third warning above require the physician be familiar with lung biopsy procedures. Further, a physician must use judgment regarding the risks associated with performing lung biopsies on patients who may be prone to bleeding. Patients with bullous emphysema were excluded from the IDE safety and effectiveness trial so the effectiveness of the hydrogel plug in this patient population is unknown.

RISKS TO HEALTH

Table 2 identifies the risks to health associated with use of absorbable lung biopsy plugs and the measures to mitigate these risks.

Table 2 – Identified Risks and Mitigation Measures

Identified Risks	Mitigation Method
Inability to deploy plug	Design and Material Characterization Bench Testing In Vivo Evaluation Labeling
Delayed plug expansion	Design and Material Characterization Bench Testing In Vivo Evaluation Labeling
Leakage around plug	Design and Material Characterization Bench Testing In Vivo Evaluation Labeling
Plug migration (whole plug and/or fragments)	Design and Material Characterization Bench Testing In Vivo Evaluation Labeling
Procedural complications	In Vivo Evaluation Labeling
Adverse Tissue Reaction	Biocompatibility In Vivo Evaluation
Infection	Biocompatibility Sterility Shelf Life Testing
Use error	Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the Bio-Seal Lung Biopsy Tract Plug System is subject to the following special controls:

1. The design characteristics of the device must ensure that the geometry and material composition are consistent with the intended use.
2. Performance testing must demonstrate deployment as indicated in the accompanying labeling, including the indicated introducer needles, and demonstrate expansion and resorption characteristics in a clinically relevant environment.
3. In vivo evaluation should demonstrate performance characteristics of the device including the ability of the plug to not prematurely resorb or migrate and the rate of pneumothorax.
4. Sterility testing must demonstrate the sterility of the device and the effects of the sterilization process on the physical characteristics of the plug. Shelf-life testing must demonstrate the shelf-life of the device including the physical characteristics of the plug.
5. The device must be demonstrated to be biocompatible.
6. Labeling must bear all information required for the safe and effective use of the device. Labeling must include a detailed summary of the device-related and procedure-related complications pertinent to the use of the device and appropriate warnings. Labeling must include identification of compatible introducer needles.

In addition, this is a prescription device and must comply with 21 CFR 801.109.

BENEFIT/RISK DETERMINATION

The risks of pneumothorax and bleeding with Bio-Seal use are the same as for percutaneous, transthoracic lung biopsy procedures performed without the device and are consistent with the incidence of these risks associated with fine needle aspiration (FNA) reported in the literature. Risks related to biocompatibility issues with a hydrogel plug are low. Major hemorrhage, hemoptysis, air embolism, neoplastic seeding of the needle tract, pericardial tamponade, lung torsion and empyema are rare complications that have been reported in the literature. The consequences associated with these rare adverse outcomes include longer length of stay and higher rates of respiratory failure. However, they do not seem to be evident in either the treatment or control group of the trial conducted.

In a randomized controlled trial of the Bio-Seal Plug versus controls in patients undergoing percutaneous, transthoracic needle biopsies of the lung, there were both statistically and clinically significant differences in the rates of pneumothoraces after transthoracic needle biopsies of lung in favor of the Bio-Seal Plug. For the intent-to-treat (ITT) population, treatment success (no pneumothoraces to 30 days) was 75% with the device and 57% without the device

(control) ($p=0.0008$). For the per protocol (PP) population, treatment success was 85% with the device and 69% without ($p=0.0022$).

In conclusion, given the available information, the data support that for the intended use [to plug pleural punctures associated with percutaneous, transthoracic needle lung biopsies to significantly reduce the risk of pneumothoraces], the probable benefits outweigh the probable risks. The risks can be mitigated by the use of general and special controls.

CONCLUSION

The de novo petition for the Bio-Seal Lung Biopsy Tract Plug System is granted and the device is classified under the following:

Product Code: OMT
Device Type: Absorbable lung biopsy plug
Class: II
Regulation: 21 CFR 878.4755