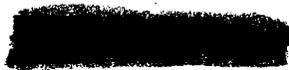


2009-4437b1-07

Amendment 2 to DuraSeal Spine Sealant System



October 20, 2008

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

Attn: George K. Ngatha
Division of General, Restorative & Neurological Devices

Subject: Amendment to DuraSeal™ Spine Sealant System, P080013

Dear Mr. Ngatha:

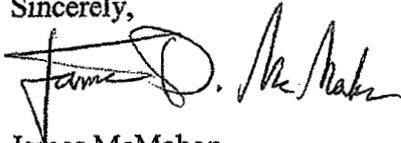
The purpose of this Amendment is to provide FDA with the response from Covidien to the DuraSeal Spine Sealant System PMA Major Deficiency Letter, dated August 15, 2008. Please find the FDA question followed by each response from Covidien.

Covidien believes that this Amendment fully addresses all of the remaining FDA questions that need to be resolved before the review of the PMA application can be completed. Covidien also believes the responses contained in this amendment and the previously reviewed data supporting the DuraSeal Sealant System PMA, P080013, do not raise any new issues or reveal any unanticipated safety or effectiveness issues that would require input from an FDA Advisory Panel. Therefore, Covidien does not believe a Panel meeting is necessary in the review of the DuraSeal Spine Sealant System PMA P080013.

We thank you in advance for your review of this Amendment and look forward to FDA's completion of this PMA application.

If you have any questions, please contact me at (781) 839-1787, FAX (781) 839-1787 or by email at James.McMahon@Covidien.com. In my absence, please contact Terry McGovern, Senior Director of Regulatory Affairs, at (781) 839-1738, FAX (781) 839-1763 or by email at Terry.McGovern@Covidien.com

Sincerely,

A handwritten signature in black ink, appearing to read "James D. McMahon". The signature is written in a cursive style with a large initial "J" and "M".

James McMahon
Manager, Regulatory Affairs

Attachment 1 – CSF Leak Rates (Published Literature)

Attachment 2 – The comprehensive analysis of the patients who leaked in both groups

Attachment 3 – The “standard of care” combinations used in control

Attachment 4 – Updated Instruction for Use

Attachment 5 – List of References

Encl: (3 copies)

FDA Question:

1. **Your clinical study was designed to assess whether the Spinal Sealant System, when used as an adjunct to sutured dural repair, was more effective than Standard of Care (SOC) methods in producing a watertight dural closure, the primary effectiveness endpoint, in patients undergoing an intentional durotomy during spinal surgery. This effectiveness was assessed intraoperatively. The treatment group achieved 100% success, at time of surgery as compared to 64.3% for the control group. Additionally, cerebrospinal fluid (CSF) leakage was determined for patients in each group out to 3 months and the incidence of postoperative leaks through day 90 was 7.8% in the sealant group vs. 5.4% in the control (p=0.748, Fisher's Exact test). The Kaplan-Meier estimates, which include the 5 incomplete subjects only for the length of time they were followed, were 8.4% sealant vs. 5.6% control (p=0.578).**

FDA considers the safety outcome of CSF leak (pseudomeningocele and incisional) and surgical site infection as the most critical clinical outcomes for this study. Given that there does not appear to be a correlation between intraoperative and postoperative CSF leakage, FDA has questions regarding the intraoperative CSF leak endpoint and its relationship to a clinical benefit (e.g., time in surgery, introduction of animal/non-animal materials, etc). Please explain why you believe the results of this study demonstrate a clinical benefit.

Sponsor Response:

We believe that the clinical benefit of DuraSeal Spine Sealant is two fold. First, while the overall rate of post operative dural leak was statistically similar between our groups, a post operative Dural leak was 2.5 times more likely in the subset of patients who failed to achieve the primary endpoint of an intraoperative seal. Second, with the establishment of non-inferiority of DuraSeal versus conventional standard of care methods through this clinical study, the synthetic nature of DuraSeal makes it an attractive alternative to standard of care methods that carry the small but real risk of viral transmission and immune reaction. These clinical benefits and others are presented below in detail. First, *the importance of intraoperative sealing is discussed.* Second, *the correlation between intraoperative sealing and a positive postoperative outcome is shown.* Third, *a comparison of the low post-op CSF leak rates found in literature using adjunctive therapies to the low rate of post-op CSF leaks in the study is presented.* Fourth, *the clinical benefit of a reduced risk of disease transmission is presented.* Fifth, *the clinical benefit of ease of application of the DuraSeal Sealant is presented.*

The DuraSeal Spine Sealant study was designed with intraoperative watertight closure as the primary effectiveness endpoint. Patients were randomized to either DuraSeal or to a "standard of care" control arm. The inclusion of a "standard of care arm" was determined to be necessary because both Covidien and the FDA believed

that control subjects should not receive sutured dural repair alone, due to the low expected success rate. Therefore, Covidien selected a "Standard of Care" comparator that was consistent with FDA's request in the IDE conditional approval letter (April 27, 2005), in which FDA stated that "based on the failure of sutures and autograft to achieve a watertight closure in any cases in the DuraSeal Intracranial IDE study (PMA 040034), allowing only additional sutures and autograft in the control group would likely result in a very low success rate for the 2nd intervention in that arm. Since intraoperative water-tight closure is the proposed primary effectiveness endpoint, FDA proposed that patients be randomized to either DuraSeal or to a "standard of care" control arm that included whatever the surgeon's standard of care treatment was. FDA stated "In the control arm, the final Valsalva maneuver should be conducted after all standard of care measures have been applied. Surgeons may opt to add additional devices that are not designed to provide an intraoperative watertight closure (such as gel-foam or Duragen) after the Valsalva maneuver is completed."

As a result, the Standard of Care (control) group in this study included devices designed to provide a watertight closure. Specifically, application of additional sutures, adhesive glues such as human fibrin or bovine, and/or soft tissue patch/graft.

Despite meticulous dural closure techniques, including the off-label use of bio-materials, true watertight closure has been an elusive target in spine surgery. Therefore, the need for an adjunctive measure to provide an intraoperative seal that has been proven safe and effective in providing a "watertight" sutured dural repair is needed.

IMPORTANCE OF INTRAOPERATIVE SEALING

Common effects of CSF leaks include vomiting, headaches, nausea, photophobia and tinnitus^(7, 9, and 10). More serious consequences of non-watertight primary closure may include formation of fistulas leading to possible meningitis, arachnoiditis or epidural abscess⁵. A fluid collection may also impede wound healing and lead to infection of the wound. Pseudomeningoceles may result in nerve deficits and possible nerve root entrapment^{3, 11}. Persistent CSF leak has also been associated with the development of cerebellar hemorrhage¹² (and intracranial subdural hematoma, presumably due to altered CSF dynamics resulting in caudally-directed movement of the spinal cord and brain, which in turn stretches fragile bridging veins with eventual rupture in the subdural space¹³). Treatment of CSF leaks varies depending on severity and presentation of symptoms. Some pseudomeningoceles resolve over time without surgical intervention, while other leaks require drainage or re-operation to repair the dura, in turn extending a patient's hospital stay. A retrospective review of costs of postoperative CSF leaks in 412 skull based procedures by Grotenhuis, et al¹⁴ found that CSF leaks incur significant costs. Of the 44 patients in the study with CSF leaks, they accounted for 21.7% of the total costs of the procedures. These studies highlight the significance of an intraoperative CSF leak endpoint as it relates to the potential benefits for reduced postoperative sequelae associated with CSF leaks. That is, the first line of defense against the complication of a CSF leak is to achieve a water-tight closure intraoperatively.

In 2005 when Confluent Surgical initially submitted the DuraSeal Spine IDE G050063 there were no FDA-approved products proven to be safe and effective for dural sealing in spine procedures. In current practice, watertight dural closure with sutures alone is not possible in many cases. Standard of care practices differ, but in general, neurosurgeons commonly use some type of adjunctive therapy to achieve an intraoperative watertight dural seal. Standard of care methods to achieve intraoperative watertight dural closure vary between surgeons based on the clinical circumstances of the case and the technique by which the surgeon trained but they generally use a variety of biomaterials off-label, including devices such as hemostatic agents (e.g., Gelfoam), fibrin glue sealant (e.g., Tisseel), bovine adhesive glue (e.g., BioGlue) and duraplasty materials (e.g., DuraGen) as dural sealants. The safety and efficacy of these products for dural sealing has not been proven.

Achieving watertight dural closure is considered standard of care in surgical practice because it reduces the likelihood of postoperative CSF leaks⁽¹⁻⁵⁾. The Atlas of Neurosurgical Techniques¹ proclaims, "a watertight closure is essential to reduce the likelihood of CSF leakage". Furthermore, the procedure for closing dural leaks is detailed in Campbell's Operative Orthopaedics⁶ where surgeons are taught that primary repair is essential and is in the best interest of the patient and the surgeon. If watertight closure is not achieved upon Valsalva, surgical practice dictates additional measures to assure dural closure prior to leaving the operating room to avoid postoperative complications of CSF leak.

The medical literature consists of multiple retrospective studies and case studies demonstrating the need for a watertight seal intraoperatively. To better understand the consequences of failure to achieve this endpoint, we conducted a literature review looking for correlation of outcomes in patients who suffered incidental durotomies and achieved or failed to achieve primary dural closure as defined in our protocol. A retrospective review by Camissa et al⁷ included a series of patients undergoing spinal surgery. Of 66 patients that experienced incidental durotomies, 60 were discovered and repaired intraoperatively. Of the remaining 6 patients who did not receive an intraoperative repair, 5 went on to develop a pseudomeningocele and one a cerebrospinal fluid leak. A review of 146 medical malpractice cases involving lumbar spine surgery found that incidental durotomies were associated with alleged complications and/or sequelae in all cases⁸.

The use of an intraoperative primary endpoint in the Spinal Sealant study is consistent with the endpoint used in the previous DuraSeal Cranial sealing study². Additionally the use of an intraoperative primary endpoint is consistent with the evaluation of other sealants that are indicated as adjuncts to sutured repair of tissues to provide leak (blood) free closure (e.g., P010022 for CoSeal Surgical Sealant, Cohesion Technologies approved December 14, 2001, BL 103980 and P010003 for BioGlue Surgical Adhesive, CryoLife, Inc. approved December 3, 2001). The selection of an intraoperative endpoint in these studies is related to the realization that a leak-free primary repair at the time of the initial treatment is the primary goal of the surgical closure.

CORRELATION BETWEEN INTRAOPERATIVE AND POSTERATIVE LEAKS

This DuraSeal Spine Sealant pivotal study was designed as a non-inferiority study. As measures of safety, it was expected that there would be no worsening of the postoperative outcomes in the DuraSeal Spine Sealant group as compared to the Control, including late CSF leaks, surgical site infections (SSI), and incidence of adverse events. The results of the study confirm that the rates of postoperative CSF leak were comparable between the treatment and control groups (7.8% vs. 5.4% respectively, $p=0.748$). The incidence of postoperative SSI was also comparable between the treatment and control groups (6.9% and 7.1% respectively, $p=1.00$) and as discussed below, both postoperative CSF leak and SSI rates observed in the treatment group are well within the published literature rates. Therefore, the results confirm that although there were postoperative CSF leaks that occurred in the DuraSeal arm, the rate of occurrence was similar to that observed for the control group and overall, there was no worsening of safety outcomes related to use of the DuraSeal Spinal Sealant.

A reliable sealant, such as the DuraSeal Spine Sealant, provides benefit to the patient by consistently providing this essential intraoperative watertight closure as evidenced by the results of the pivotal study. Specifically, in 102/102 (100%) patients treated with DuraSeal Spine, an intraoperative watertight dural closure was obtained, while

the same result was achieved in only 36/56 (64.3%) patients treated with Standard of Care Methods (control). To specifically address FDA's concern that there does not appear to be a correlation between intraoperative and postoperative CSF leakage, an additional analysis was performed with the total DuraSeal Spine study cohort evaluating the postoperative CSF leak rate based on the achievement of intraoperative sealing success regardless of treatment assignment. As shown in Table 1-1 below, the postoperative leak rate is 2.5 times greater in the group of patients deemed intraoperative primary endpoint failures versus those with successful intraoperative sealing. Although achievement of water tight closure intraoperatively does not guarantee with 100% certainty that the patient will not go on to experience a CSF leak postoperatively, this analysis shows that if watertight closure is achieved, the patient is less likely to experience a postoperative leak than a patient who does not achieve watertight closure.

Table 1-1: Patients with Post-Op leaks (DuraSeal and Control Patients combined)

	Patients with Intraoperative Failure (N=20)	Patients with Intraoperative Success (N=138)	p-value
Patients with Postoperative CSF Leak, n (%)	3 (15.0)	8 (5.8)	0.147

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Note: p-value was based on Fisher's Exact test

LOW POST-OP CSF LEAK RATE, CONSISTENT WITH OTHER ADJUNCTIVE THERAPIES

In a review of the literature, the rate of postoperative CSF leak (including pseudomeningocele) following surgery where intradural exploration is undertaken has been reported to be as high as 10.4% in surgery performed for the excision of intradural spinal tumors¹⁵, 17.6% for surgical management of tethered cord syndrome¹⁶ and approximately 13% for surgical correction of Chiari Malformation.¹⁷ A prospective review of 76 patients undergoing lumbar surgery reported 16% of patients experienced a postoperative CSF leak¹⁸. Even with meticulous attempts at a watertight seal, utilizing sutures augmented with fibrin glue, postoperative CSF leaks still occur in 5-10% of cases¹⁰. Shaffrey et al.², reviewed 134 patients in whom fibrin glue had been used as an adjunct in sealing a dural defect. In patients who had a primary tear repaired intraoperatively, there was an overall failure rate of 7%. Camissa et al.⁷, evaluated outcomes following direct dural suturing augmented with the use of a patch graft and/or fibrin sealant as necessary for repair of 67 incidental durotomies. In this series, postoperative complications that have been noted to be associated with CSF leaks occurred in 7 patients (i.e., severe headache-2 patients and deep wound infections-5 patients) for an overall failure rate of 10%. In a retrospective review performed by Hodges⁹ and colleagues, twenty incidental durotomies following spinal procedures were repaired intraoperatively with

dural stitches and fibrin glue. Of the twenty patients, 25% had symptoms related to the dural tear and one patient (5%) required revision surgery due to stitch loosening.

In the DuraSeal Spine Sealant study, the rate of postoperative leaks reported in the DuraSeal Spine and Control groups, 7.8% versus 5.4%, respectively, was well within the range found in the above discussed published literature. A comprehensive table of the literature review can be found in Attachment 1.

REDUCED RISK OF DISEASE TRANSMISSION

As described above, fibrin glue and other animal or human derived products are commonly used as off label adjuncts to sutures to achieve an intraoperative watertight dural closure. The use of the DuraSeal Spine sealant, as a synthetic material, will reduce the risk of disease transmission or immune reaction,

DuraSeal's 100% efficacy in this clinical study precluded the need for additional animal or human derived products to achieve the primary endpoint. In contrast, the 64% efficacy in the standard of care control group required the off-label use of products containing animal or human-derived materials, such as fibrin glue or DuraGen, to achieve a final water-tight dural closure in the operating room. While these agents have been proven safe, they are well-recognized by FDA to have unique risks of infection and immune reactions¹⁻⁴.

1. Citation 1. FDA Guidance for Industry. Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) – Small Entity Compliance Guide. August 2007.
2. Citation 2. FDA Guidance for FDA Reviews and Industry. Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices). November 16, 1998
3. Citation 3. FDA Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh. March 2, 1999.
4. Citation 4. FDA Guidance Document for Dura Substitute Devices; Guidance for Industry. November 9, 2000.

EASE OF APPLICATION

An important benefit of the DuraSeal Spine Sealant is the ease of assembly and ability to quickly stop intraoperative leaks. Although not statistically significant, there was also a reduction in the time-to-closure of three minutes in the Spinal Sealant group compared to the length of time required to close the dura of the control group.

Table 1-3 Time for Dural Closure

Parameter	Statistic	Spinal Sealant	Control	Mean Difference	p-value
Procedure Stop Time - Dural Closure Stop Time (min)	n	102	55	-2.9	0.510
	Mean (SD)	52.3 (28.51)	55.2 (22.65)		
	Median	46.0	50.0		
	Range(Min, Max)	(0,252)	(25,162)		

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 Note: p-value based on the t-test testing the difference between the means of the two treatments.

In the majority (91%) of cases (93/102), an intraoperative watertight closure was obtained following one application of the DuraSeal Spine Sealant, thus eliminating the need for additional applications / Valsalva maneuvers to confirm watertight dural closure. Additionally, in almost all DuraSeal Spine Sealant cases (98/102), surgeons rated their use of the device as “Easy” (n=41) or “Very Easy” (n=57). There were only 3 cases (3.9%) in which the surgeon felt the use of the Spinal Sealant was “Difficult”; however, in all 3 of these cases, a second kit was assembled and the sealant was applied with no additional issues. Most notably, in all subjects treated with the Spinal Sealant (102/102), the investigator was able to obtain a watertight dural closure after applying the Spinal Sealant only. That is, in no cases was there a need to apply any further adjunctive therapy (e.g., additional sutures, fibrin glue) to seal the dura, thus eliminating the additional time and cost of applying additional dural sealing products and associated lengthened surgery time

In conclusion, the DuraSeal Spine Sealant is a synthetic polymer that demonstrates a significant clinical benefit by eliminating the risks from material of animal or human origin, reducing surgical and closure time and most significantly, providing a watertight intraoperative dural seal. Further, the analysis presented in this Amendment supports the clinical precept that achievement of an intraoperative seal of dural leaks is associated with a reduced likelihood of postoperative CSF leaks. Covidien believes the DuraSeal Spine Sealant, as an adjunctive measure to provide a “watertight” intraoperative seal has been proven safe and effective and, provides a needed clinical benefit currently unmet by approved technologies.

FDA Question:

In addition, please provide the following information:

1a. A comprehensive analysis of the patients who leaked in both groups that should include the following:

- **type of procedure performed (ex. intradural tumor, spinal cord untethering, etc.), location of surgery (cervical vs. thoracic vs. lumbar), length of dural opening**

- **timing of treatment failure and whether the failure was a CSF leak through the skin or a pseudomeningocele; also, whether the treatment failure correlated with surgical site infection or meningitis (in the case of pseudomeningocele, whether or not the patient was symptomatic and/or required re-operation or drainage)**

- **other significant co-morbidities not listed in the study exclusion criteria that would limit wound healing or predispose to treatment failure (smoking, radiation treatment to surgical site, other)**

- **details on skin closure technique and immediate postoperative activity restrictions, if known (ex. running-locked nylon suture vs. interrupted stitch, etc.; bedrest duration post-op for lumbar cases)**

- **the “standard of care” technique or combination used in each control group case**

Sponsor Response:

Attachment 2 contains a comprehensive listing of all requested information on each of those subjects that experienced a postoperative CSF leak.

Attachment 3 contains the “standard of care” technique or combination used in each control group case

FDA Question:

1b. A Kaplan-Meier analysis for time to event for the CSF leaks in the patients of both groups

Sponsor Response:

Data is presented for CSF leaks within ninety days (90) post-procedure and time to first CSF leak in Table 1b-1 and Table 1b-2 below. In summary, there is no statistical difference between the Spinal Sealant group and the Control group with regard to the presence of CSF leaks. As shown in table 1b-2, there were five early leakers; defined as patients who incurred a postoperative CSF leak within 30 days and eight total patients incurred CSF leaks within 90 days. The estimated overall proportion of subjects experiencing postoperative leaks is not significant in either group.

Please find the Kaplan-Meier analysis in Table 1b-1 and 1b-2.

Table 1b-1: Endpoint CSF Leakage (Safety population)

Endpoint	Statistic	Spinal Sealant (N=102)	Control (N=56)	Difference (%)
Presence of endpoint CSF leak within 90 days post-procedure	n (%)	8(7.8)	3(5.4)	2.5
	p-value (1)	0.748		
Cumulative proportion of CSF leak within 90-days post-procedure	n (%)	8(8.4)	3(5.6)	2.8
	95% CI	(4.3, 16.3)	(1.8, 16.4)	(-5.6, 11.2)
	p-value (2)	0.578		

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Note: Cumulative proportion and 95% confidence interval are obtained using the Kaplan-Meier method.

(1) p-value is based on two-sided Fisher's Exact Test testing for a difference between treatments.

(2) p-value is based on the Log-Rank test for a difference between treatments.

Table 1b-2 Time to First Event of Late CSF Leakage Safety Population (Both Groups)

Days Following Procedure	Number With Event	Number Lost to Follow-up	Number Remaining	Estimated Proportion Without Event	Estimated Proportion With Event	95% CI for Proportion With Event
10	2	0	100	0.9804	0.0196	(0.0049,0.0761)
20	4	1	97	0.9607	0.0393	(0.0149,0.1014)
30	5	1	96	0.9508	0.0492	(0.0208,0.1142)
40	5	1	96	0.9508	0.0492	(0.0208,0.1142)
50	6	2	94	0.9408	0.0592	(0.0271,0.1271)
60	6	2	94	0.9408	0.0592	(0.0271,0.1271)
70	6	2	94	0.9408	0.0592	(0.0271,0.1271)
80	7	3	92	0.9307	0.0693	(0.0337,0.1400)
90	8	33	61	0.9156	0.0844	(0.0426,0.1633)

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 Note: Results are based on Kaplan Meier estimates.

FDA Question:

1c. Analysis of SOC early-leakers and their clinical outcomes as contrasted to DuraSeal intra-op successes, i.e., clinical outcomes and morbidity comparison of the two groups within the first 30 days, post-procedure.

Sponsor Response:

Per the question raised above, "SOC early leakers" was defined as patients in the Standard of Care cohort who incurred a postoperative CSF leak within 30 days. Per the results of the study and presented in Table 1c below, there was only 1 subject who experienced such a leak. Two attempts of additional sutures were attempted in this subject which were unsuccessful in obtaining a watertight closure. The investigator then applied fibrin glue. A pseudomeningocele developed 27 days postoperative requiring placement of a lumbar drain. Subject was also diagnosed with a deep surgical site infection and bacterial meningitis approximately 17 days prior to drainage of the pseudomeningocele. This was the only occurrence of bacterial meningitis in the study.

Table 1c: Clinical outcomes and morbidity comparison at 30 days (ITT population)

Parameter	Statistic	Spinal Sealant (N=102)	Control (N=15)
CSF Leak			
Yes	n (%)	5(4.9)	1(100.0)
No	n (%)	97(95.1)	0(0.0)
Type of Leakage			
Fistula	n (%)	3(2.9)	0(0.0)
Pseudomeningocele	n (%)	2(2.0)	1(100.0)
Surgical Site Infection			
Yes	n (%)	7(6.9)	1(100.0)
No	n (%)	95(93.1)	0(0.0)
Meningitis			
Yes	n (%)	0(0.0)	1(100.0)
No	n (%)	102(100.0)	0(0.0)

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 *Note: Only patients who were post-op CSF leak within 30 days (i.e., early leakers) will be included in the control group.

FDA Question:

1d. Your discussion of the clinical benefit of the device should address specifically the equivalent CSF leak rate over the 3 month follow-up time period, e.g., include consideration of the information requested above and also discuss possible benefits due to time required for harvesting autologous tissue for overlaying incisional sites, as well the lack of potential disease transmission from hemostatic agents derived from animal tissues.

Sponsor Response:

As discussed in question 1, the primary efficacy endpoint in the pivotal study was the percent success in obtaining a watertight closure following assigned treatment (DuraSeal Spinal Sealant or Control) where success is defined as: a watertight closure of the dural repair intraoperatively after assigned treatment, confirmed by Valsalva maneuver at 20-25 cm H₂O for 5-10 seconds. The surgeon was not able to achieve a watertight dural closure in 20/56 (35.7%) of Control subjects after employing the chosen "Standard of Care" method (i.e., devices designed to provide a watertight dural closure). Therefore, for patient safety reasons the surgeon continued to apply different methods to achieve a "watertight" seal before procedural closure.

The study was not designed to show a reduction (improvement) in the postoperative CSF leak rate. As measures of safety, it was expected that there would be no worsening of the postoperative outcomes in the DuraSeal Spine Sealant group as compared to the Control, including late CSF leaks, surgical site infections (SSI), and incidence of adverse events. The results of the study confirmed that the rates of postoperative CSF leak were comparable between the treatment and control groups (7.8% vs. 5.4% respectively, p=0.748). The incidence of postoperative SSI was also comparable between the treatment and control groups (6.9% and 7.1% respectively, p=1.00) and both postoperative CSF leak and SSI rates observed in the treatment group are well within the published literature rates. Furthermore, the rates of adverse events and serious adverse events were comparable between the two groups and there were no Unanticipated Adverse Device Effects. Therefore, the results confirm there was no worsening of safety outcomes related to use of the DuraSeal Spine Sealant.

The rate of postoperative CSF leak (including pseudomeningocele) is widely variable. The rate has been reported as high as 10.4% in surgery performed for the excision of intradural spinal tumors¹⁵, 17.6% for surgical management of tethered cord syndrome¹⁶, and approximately 13% for surgical correction of Chiari Malformation¹⁷. A prospective review of 76 patients undergoing lumbar surgery reported 16% of patients experienced a postoperative CSF leak¹⁸. Even with meticulous attempts at a watertight seal, utilizing sutures augmented with fibrin glue, postoperative CSF leaks still occur in 5-10% of cases¹⁰. Shaffrey et al¹⁹, reviewed 134 patients in whom fibrin glue had been used as an adjunct in sealing a dural defect. In patients who had a

primary tear repaired intraoperatively, there was an overall failure rate of 7%.² Camissa et al⁷, evaluated outcomes following direct dural suturing augmented with the use of a patch graft and/or fibrin sealant as necessary for repair of 67 incidental durotomies. In this series, CSF leak related postoperative complications occurred in 7 patients (i.e., severe headache-2 patients and deep wound infections-5 patients) for an overall failure rate of 10%. In a retrospective review performed by Hodges and colleagues, twenty incidental durotomies following spinal procedures were repaired intraoperatively with dural stitches and fibrin glue⁴. Of the twenty patients, 25% had symptoms related to the dural tear and one patient (5%) required revision surgery due to stitch loosening. The rates of postoperative leak in this study were therefore comparable to the rates found in the literature.

Finally, as noted in our response to the main Deficiency #1, DuraSeal Spine Sealant is a synthetic polymer that demonstrates a significant clinical benefit by eliminating the risks from material of animal or human origin, reducing surgical and closure time and most significantly, providing a watertight intraoperative dural seal thereby, reducing by 2.5x the likelihood of postoperative CSF leaks. Covidien believes the DuraSeal Spine Sealant, as an adjunctive measure to provide a "watertight" intraoperative seal has been proven safe and effective and, provides a needed clinical benefit currently unmet by approved technologies.

FDA Question:

2. In your PMA submission it is difficult to determine what SOC methods were employed and what decision pathway was followed. For example [REDACTED] failed because of 2 failed attempts with suture. The AE narrative describes the leak from the suture holes which would not be repaired with additional sutures. After being considered a failure the patient was successfully treated (for the primary intraoperative endpoint) with fibrin glue. In [REDACTED] you state that "due to the nature of the CSF leak, the investigator felt that adding additional sutures to the dural incision would provide no benefit to secure a watertight closure. Therefore the subject was considered a primary endpoint failure." Elsewhere in your PMA you describe an investigator who was unclear of the SOC methods. Furthermore, of the 21 patients that were leaking CSF intraoperatively only 4 patients underwent a second treatment. The others were considered failures.

Sponsor Response:

Watertight dural closure with sutures is not possible in many cases. Standard of care practices differ, but in general, neurosurgeons commonly use some type of adjunctive therapy to achieve an intraoperative watertight seal. Standard of care methods to achieve intraoperative watertight dural closure vary between surgeons based on the clinical circumstances of the case and the technique by which the surgeon trained. Various devices are used, including but not limited to, fibrin glue, hemostatic agents and synthetic duraplasty materials.

As a result, the Standard of Care (control) group in this study included devices designed to provide a watertight closure. Specifically, application of additional sutures, adhesive glues such as human fibrin or bovine, and/or soft tissue patch/graft.

As a result of the IDE conditional approval letter and discussions with FDA, the final protocol included a Control group in which the investigator's "Standard of Care" would be applied. Since neurosurgeons use several different types of products that are not designed to provide a watertight dural closure (and thus would constitute off-label use e.g., duraplasty, hemostatic agents), an additional parameter was placed around the "Standard of Care". The study protocol dictated that while "Standard of Care" methods were to be employed for Control subjects, the devices chosen must be those that were designed to provide a watertight closure, "Patients that are randomized to the control group may be treated with up to two treatments with the chosen standard of care method (i.e., devices that are designed to provide an intraoperative watertight closure)." This additional parameter also ensured that the investigator would use "Standard of Care" devices that allowed him/her to adequately visualize and confirm the primary endpoint outcome with a Valsalva maneuver. With this additional parameter around the "Standard of Care" in place, the Control treatment chosen by a majority of study investigators was either the application of additional sutures or adhesive glue (Fibrin Glue). Fibrin Glue is

FDA-approved for use as a hemostatic agent in cardiopulmonary bypass and splenic injury procedures, but is commonly used off-label by neurosurgeons for purposes of spinal dural sealing. While the safety and efficacy of Fibrin Glue for this indication has not been proven in a randomized controlled clinical study, the device is designed to seal by means of providing a mechanical barrier over the leaking area. Dural replacement/grafts, such as commercially available DuraGen® Dural Graft Matrix, were not permitted as a Standard of Care method, as the device is designed as a duraplasty material, not as a sealant. Hemostatic agents, such as commercially available Gelfoam®, were not permitted as a Standard of Care method, as this device is designed to pack the wound and not as a sealant.

The additional parameter set around the “Standard of Care” methods permitted by the study protocol was identified by FDA in the IDE conditional approval letter. FDA indicated, “Surgeons may opt to add additional devices that are not designed to provide an intraoperative watertight closure (such a Gel-foam or Duragen) after the Valsalva maneuver is completed”.

Intraoperative Procedure (Per Study Protocol):

Application of the “Standard of Care” Method (Control)

After primary dural closure, if a study subject was randomized to the Control arm, the Investigator would choose their standard of care method (i.e., devices designed to provide an intraoperative watertight closure). In most cases, this included either adding additional sutures or applying adhesive glue. In one case, this included the use of graft. The investigator could make up to two attempts to achieve a watertight closure evidenced by a Valsalva maneuver. The choice whether a second attempt was necessary was at the discretion of the investigator and was not mandatory per the study protocol. If the investigator chose to make a second attempt, they were required by the study protocol to be consistent in using the same Control technique they chose for their first attempt.

Further Adjunctive Add-On Therapy

If the investigator was not able to obtain a watertight dural closure with the chosen Standard of Care (Control) method after two attempts then the subject was deemed to be a primary endpoint failure. The Investigator was then permitted to use any further add-on materials/methods of their choosing to achieve a watertight closure of the dura in order to ensure adequate patient care. These materials were captured as “Adjunctive Therapy” (Refer to Attachment 3). Once the subject was deemed a primary endpoint failure, the protocol permitted the investigator to use additional materials, including DuraGen®, Tisseel®, and Gel-foam. Note that these devices are commonly used by surgeons to provide a watertight dural closure but they are not approved by the FDA for this use. Also, note that the use of DuraSeal (Spine or Cranial) was not permitted in the Control group at any time. The adjunctive add-on therapy was completed per the investigators

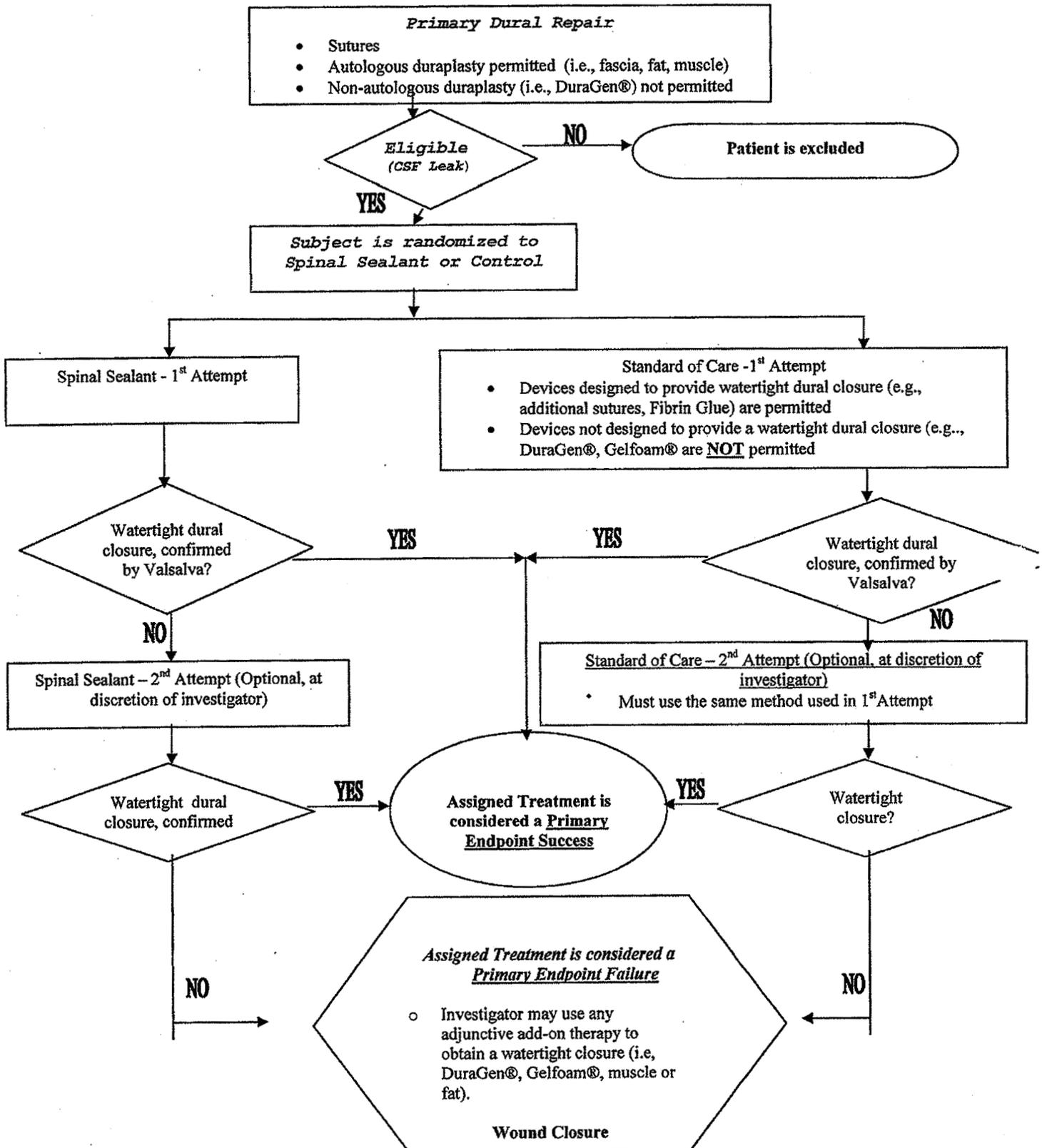
standard procedure and an additional Valsalva maneuver was not required by the protocol since the subject was already considered a primary endpoint failure.

Wound Closure

Per the study protocol, after the dural closure was completed, including application of the assigned treatment (either Standard of Care or DuraSeal), the primary endpoint evaluation, and application of further adjunctive add-on therapies (as required), the Investigator completed the surgery according to his/her standard practice, closing the subsequent layers, including the muscle and soft tissue. The use of any material used to assist in the wound closure (e.g., Gelfoam®) was documented on the procedure CRF as "Wound Closure Materials".

Figure 1, below, outlines the flow of the intraoperative procedure for this protocol, including detail on which materials were permitted for dural and wound closure.

Figure 1 – Procedural Flowchart



FDA Question:

2a. Please explain why 16 patients were considered failures without a second SOC treatment such as Duragen or fibrin glue.

Sponsor Response:

Thirteen (13/16) subjects were randomized to the Control group and received a first SOC attempt; after the first attempt was declared a failure by the investigator, a second attempt was not chosen. The additional three (3/16) subjects were cases that the investigator chose no standard of care method per the protocol due to reasons of patient safety. Specifically 10/13 received additional suturing, 2/13 received an application of Fibrin Glue, and 1/13 was treated with soft tissue/vascular graft. These 13 subjects continued to have a non-watertight closure after the first SOC attempt. At this time, the investigator opted not to make a second SOC attempt. The specific reason why a second attempt was not made was not collected on the CRF. Despite this, discussions with study investigators frequently revealed concern that in cases where primary sutures failed to control the leak, the use of additional sutures would only worsen the leak by creating more tears in the tissue. Similarly, in those cases where Fibrin Glue was chosen as the SOC treatment (2/13), discussions with study investigators confirmed that often, if one is not successful with the use of Fibrin Glue in an attempt to close the dura, the time to prepare an additional volume of Fibrin Glue is not desirable and surgeons move on to another adjunctive add-on method.

As stated above, per the study protocol "Standard of Care" methods (Control) included devices designed to provide a watertight dural closure. Therefore, the use of DuraGen® as an SOC treatment was not permitted, as it is not designed to provide a watertight dural closure. To ensure parity, the study protocol stipulated that the investigator must be consistent between SOC attempts. For example, the investigator was not permitted to make a first SOC attempt with sutures, deem it unsuccessful and then make a second attempt with Fibrin Glue.

FDA Question:

2b. Please consider the 16 patients who did not undergo a second SOC treatment as successes of your primary endpoint and provide the sensitivity analysis thereof.

Sponsor Response:

Refer to **Table 2b** for this analysis. The success rate for the Control group is 92.9% (52/56) vs. 100% (102/102) for the Spinal Sealant, $p = 0.015$.

Table 2b – Success Rate in Obtaining a Watertight Closure with 16 Control Patients Who Only Received One SOC Application Imputed as Success

	Statistic	Spinal Sealant (N=102)	Control (N=56)	Difference (%)
Success Rate	n/N (%)	102/102(100.0)	52/56(92.9)	7.1
	95% CI for %	(96.4,100.0)	(82.7, 98.0)	(0.4, 13.9)
	p-value (1)	0.015		

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(1) p-value from two-sided Fisher's Exact Test testing for a difference in success rates between treatments.

FDA Question:

2c. In table 6-12 you list autologous duraplasty materials and further adjuvant therapy. Please further develop this tabular reporting to include the number of duplicate or more applications to a single patient. Further please provide a line item listing of all materials used for dural closure in the control patients (e.g. suture, fibrin glue, Duragen etc).

Sponsor Response:

Please refer to **Attachment 3** for full details on all materials for all Control subjects.

FDA Question:

2d. In table 6-15 you list the use of suture and fibrin glue among others for the closure within the control group. It is unclear which patients had both suture and fibrin glue and which had only one in addition to the other materials used. Please further elaborate this table so that FDA may understand better the control group closure.

Sponsor Response:

Refer to **Table 2d** for details on which materials were used for each SOC attempt. In summary, for the first SOC attempt, 44.6 % of Control subjects received an application of adhesive glue (Fibrin Glue) and 37.5% received additional sutures, while 7.1% received both additional sutures and adhesive glue. Per the protocol, if a second SOC attempt was employed due to persistent CSF leak after the 1st attempt, the surgeon was instructed to use the identical therapeutic approach.

Table 2d – Standard of Care Details, ITT Population

Parameter	Statistic	Control (N=56)
Material Used in First Attempt		
Suture, No Adhesive/Glue	n (%)	21(37.5)
Adhesive/Glue, No Suture	n (%)	25(44.6)
Suture and Adhesive/Glue	n (%)	4(7.1)
Material Used in Second Attempt		
Suture, No Adhesive/Glue	n (%)	3(5.4)
Adhesive/Glue, No Suture	n (%)	1(1.8)
Suture and Adhesive/Glue	n (%)	0(0.0)
Material Used Overall		
Suture, No Adhesive/Glue	n (%)	21(37.5)
Adhesive/Glue, No Suture	n (%)	25(44.6)
Suture and Adhesive/Glue	n (%)	4(7.1)

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FDA Question:

2e. The use of hemostatic agents for dural closure is not supported by the literature but you have listed 12% of the patients being “closed” with a hemostatic agent in table 6-12. Please clarify if this was the only closure method as requested above in 2c. Further please explain why you believe this is a valid comparison to your investigational device.

Sponsor Response:

Upon a re-review of the medical records for those subjects, including the operative reports, it was determined that in a majority of subjects (5/7) where the CRF stated a hemostatic agent was used as a SOC material for dural closure, it was truly used to close the wound (muscle, soft tissue) after the dural closure was already complete. The study protocol allowed the investigator to close the wound per standard practice, therefore allowing the use of hemostatic agents for wound closure was permitted. In two subjects ██████████ hemostatic agents were used as a SOC treatment for dural closure, in deviation to the protocol. Refer to Table 2e for a summary of previously reported and revised SOC materials.

In summary, in a vast majority of Control subjects (51/53, 96.2%), a device designed to provide a watertight closure (additional sutures, Fibrin Glue) was used, per the study protocol, as the investigator’s chosen SOC method. The use of a hemostatic agent as a SOC method in two subjects (2/51, 3.9%) represents a small part of the population and does not impact the overall efficacy/safety conclusions of the study.

Note: the Clinical Study Report will be amended to accurately reflect the use of hemostatic agents in the listed subjects.

Table 2e – Clarification of SOC Materials Used in Subjects Previously Reported with Use of Hemostatic Agents Used for Dural Closure

Subject	Previous Reported Standard of Care material	Revised Standard of Care material	Revised Use of autologous duraplasty	Wound Closure
██████████	Adhesive glue Soft tissue graft Hemostatic agent	Adhesive glue	Yes	Hemostatic agent
██████████	Sutures Adhesive glue Soft tissue graft Hemostatic agent	Sutures Adhesive glue	Yes	Hemostatic agent
██████████	Adhesive glue Hemostatic agent	Adhesive glue	NA	Hemostatic agent

[REDACTED]	Hemostatic agent Other- Topical 4x8			
[REDACTED]	Adhesive glue Hemostatic agent	Adhesive glue	NA	Hemostatic agent
[REDACTED]	Adhesive glue Hemostatic agent			
[REDACTED]	Sutures Hemostatic agent	Sutures	NA	Hemostatic agent

FDA Question:

3. **In your IDE study you allowed the application of your device with either the MicroMyst applicator or the Dual Liquid applicator. Please provide an analysis stratified for each of these distinct application techniques. Please report all the outcomes that were included in your most recent submission dated June 27, 2008 (e.g. tables 6-12, 13, 14, 18, 19, 27, and 28 etc).**

Sponsor Response:

Use of either the MicroMyst Applicator (2ml kit with Reusable Air Pump) or the Dual Liquid applicator (5ml kit) for application of the Spinal Sealant was at the surgeon's discretion. Of the 102 subjects assigned to the Spinal Sealant group, 55 were treated with the MicroMyst Applicator, 42 were treated with the Dual Liquid Applicator and 5 subjects had application of the Spinal Sealant with both the 2 and 5 mL kit. The following provides an analysis stratified for each of these distinct application techniques. The 5 subjects for whom both applicator types were used have not been included, as inclusion of these subjects would not be meaningful to the by applicator comparative analysis [REDACTED]

Refer to Tables 3a- 3i below for the requested details by kit configuration.

Table 3a presents procedural characteristics stratified by applicator type. The distribution of procedure location varies by applicator type. The Dual Liquid Applicator was used in a higher proportion of Cervical procedures (59.5%) versus the MicroMyst Applicator (32.7%), while the MicroMyst Applicator was used more often in Thoracic procedures (56.4%) versus the Dual Liquid Applicator (16.7%); these differences are likely due to surgeon preference for one applicator type for specific anatomical locations. Although, not shown in Table 3a below, significantly more subjects who underwent a Chiari malformation procedure treated using the Dual Liquid Applicator compared with those treated with the MicroMyst applicator (47.6% vs. 3.5%, $p < 0.001$ Fishers exact test).

Duraplasty was used in a larger proportion of subjects treated with the Dual Liquid Applicator. This observation is consistent with the larger number of Chiari Malformation dural closures treated with the Dual Liquid Applicator, as in this study all Chiari subjects required autologous duraplasty.

Table 3a: Neurosurgical Procedural Characteristics Stratified by Applicator Type

Procedure Characteristics	Spinal Sealant Applicator	
	MicroMyst (N=55) n(%)	Dual Liquid (N=42) n(%)
Location, n (%)		
Cervical	18 (32.7)	25 (59.5)
Thoracic	31 (56.4)	7 (16.7)
Lumbar	15 (27.3)	9 (21.4)
Sacral	4 (7.3)	5 (11.9)
Approach, n (%)		
Posterior	55 (100.0)	42 (100.0)
Duration of Surgery		
Mean (SD)	3.9 (1.83)	3.6 (1.45)
Median	3.4	3.3
Range (Min, Max)	(1.8,9.2)	(1.3,8.5)
Length of Durotomy, cm		
Mean (SD)	4.8 (2.91)	5.4 (2.53)
Median	4.0	5.0
Range (Min, Max)	(1.5,18.0)	(1.0,13.5)
Autologous Duraplasty Materials Used, n (%)	4 (7.3)	26 (61.9)
Fascia	2 (3.6)	8 (19.0)
Fat	0 (0.0)	4 (9.5)
Pericranium	1 (1.8)	12 (28.6)
Muscle	1 (1.8)	3 (7.1)
Other	0 (0.0)	1 (2.4)
Wound Closure Materials Used, n (%)	27 (49.1)	11 (26.2)
Absorbable Gelatin Sponge	16 (29.1)	4 (9.5)
Hemostatic Agent	15 (27.3)	9 (21.4)
Other	14 (25.5)	2 (4.8)

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As summarized in Tables 3b, 3c and 3d, there were no differences in the post treatment Valsalva maneuver results or Spinal Sealant Application characteristics. As would be expected, the volume of Spinal Sealant applied per application was greater with the 5mL Kit Configuration with Dual Liquid Applicator (Table 3c).

Table 3b: Post-Treatment Evaluation of Watertight Closure

	Spinal Sealant Applicator	
	MicroMyst (N=55)	Dual Liquid (N=42)
Post Treatment Valsalva Maneuver (CSF Leak) - First Application		
No Leak Upon Valsalva	51 (92.7)	39 (92.9)
Spontaneous Leak (No Need for Valsalva)	1 (1.8)	0 (0.0)
Overt Leak	0 (0.0)	0 (0.0)
Seepage at suture points	1 (1.8)	0 (0.0)
Leak Upon Valsalva	3 (5.5)	3 (7.1)
Overt Leak	1 (1.8)	0 (0.0)
Seepage at suture points	2 (3.6)	3 (7.1)
Post Treatment Valsalva Maneuver (CSF Leak) - Second Application		
No Leak Upon Valsalva	4 (7.3)	3 (7.1)
Spontaneous Leak (No Need for Valsalva)	0 (0.0)	0 (0.0)
Overt Leak	0 (0.0)	0 (0.0)
Seepage at suture points	0 (0.0)	0 (0.0)
Leak Upon Valsalva	0 (0.0)	0 (0.0)
Overt Leak	0 (0.0)	0 (0.0)
Seepage at suture points	0 (0.0)	0 (0.0)

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Table 3c- Spinal Sealant Application Characteristics Stratified by Applicator Type

	Parameter	Spinal Sealant Applicator	
		MicroMyst (N=55)	Dual Liquid (N=42)
Number of Spinal Sealant Applications per Patient			
1	n (%)	51(92.7)	39(92.9)
2	n (%)	4(7.3)	3(7.1)
Total Volume of Spinal Sealant Used - First Application (mL)			
	n	55	42
	Mean	1.6	4.5
	Median	1.6	5.0

	Parameter	Spinal Sealant Applicator	
		MicroMyst (N=55)	Dual Liquid (N=42)
	SD	0.61	1.11
	SE	0.08	0.17
	Minimum - Maximum	0.5-3.6	1.0-8.0
Total Volume of Spinal Sealant Used - Second Application (mL)			
	n	4	3
	Mean	1.4	4.3
	Median	1.5	5.0
	SD	0.71	1.15
	SE	0.36	0.67
	Minimum - Maximum	0.6-2.0	3.0-5.0

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Table 3d - Spinal Sealant Kit Usage Stratified by Applicator Type

	Parameter	Spinal Sealant Applicator	
		MicroMyst (N=55)	Dual Liquid (N=42)
Number of Kits Used per Patient	n	55	42
	Mean	1.3	1.5
	Median	1.0	1.0
	SD	0.64	0.63
	SE	0.09	0.10
	Minimum - Maximum	1.0-4.0	1.0-3.0

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As summarized in Table 3e, both applicator types were ranked as “Very Easy” or “Easy” in >95% of subjects (MicroMyst – 98.2, Dual Liquid – 95.2). The number of device malfunctions was similar between the two groups.

Table 3e - Spinal Sealant Ease of Use and Malfunctions Stratified by Applicator Type

	Parameter	Spinal Sealant Applicator	
		MicroMyst (N=55)	Dual Liquid (N=42)
Ease of Use			
Very Easy	n (%)	26 (47.3)	30 (71.4)
Easy	n (%)	28 (50.9)	10 (23.8)
Difficult	n (%)	1 (1.8)	2 (4.8)
Device Malfunction*			
Yes	n (%)	1 (1.8)	2 (4.8)
No	n (%)	54 (98.2)	40 (95.2)

*Note: Among subjects receiving both types of applicator types there were an additional 3 malfunctions; 2 of the MicroMyst Applicator and one for the Dual Liquid Applicator.

Primary Efficacy Endpoint

As noted in the original clinical report, the primary endpoint of the clinical study is the percent success in obtaining a watertight closure following treatment (Spinal Sealant or Control) where success is defined as:

A watertight closure of the dural repair intraoperatively after treatment, confirmed by Valsalva maneuver at 20-25 cm H₂O for 5-10 seconds.

As stated in the original PMA clinical report (reference Section 11.3.2) and as summarized in Table 3f below, there is no difference in primary endpoint outcome with data stratified by applicator type.

Table 3f: Intraoperative CSF Leakage Following Spinal Sealant Application Stratified by Applicator Type

Intent to Treat Population				
Treatment Groups	Total Number of Patients	Number of Primary Endpoint Successes	Percent of Successes	95% Confidence Interval
MicroMyst	55	55	100.0	93.5, 100.0
Dual Liquid	42	42	100.0	91.6, 100.0
p-value (1)	---			
p-value (2)	---			

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(1) p-value from two-sided Fisher's Exact Test testing for a difference in success rates between treatments.

(2) p-value for interaction from logistic regression model with terms for treatment group, investigative site, and the treatment by site interaction.

Safety

As summarized in Table 3g, there was no statistically significant difference in the incidence of postoperative CSF leaks when stratified by applicator type; however, the observed rate of postoperative CSF leak in the Dual Liquid applicator group is two times greater than the MicroMyst Applicator group. As previously indicated, there was a higher proportion of subjects undergoing surgical treatment for Chiari Malformation within this group. All subjects experiencing postoperative CSF leaks within the Dual Liquid Applicator Group underwent surgery for either Chiari Malformation (CM) or Syringomyelia. In a recent meta-analysis, the rate of postoperative CSF complications for patients undergoing surgical treatment for CM using an intradural approach was calculated to be 18.5%.²⁴ Therefore, the rate of postoperative leak within the Dual Liquid Applicator group (11.9%) is lower than that reported in the literature for this procedure.

Table 3g: Incidence of Postoperative CSF Leaks Stratified by Applicator Type

Category	Statistic	Spinal Sealant Applicator		p-value (1)
		MicroMyst (N=55)	Dual Liquid (N=42)	
Presence of endpoint CSF leak within 90 days post-procedure	n (%)	3 (5.5)	5 (11.9)	0.287
CSF Fistula	n	1	2	
Pseudomeningocele	n	2	3	

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(1) p-value is based on two-sided Fisher's exact test testing for a difference between treatments.

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Table 3h and Table 3i present data for adverse events and serious adverse events stratified by applicator type. There is a difference in the Adverse Event rate between the two applicators however with the exception of two System Order Classification categories "General Disorders and Administration Site Conditions and "Vascular Conditions" there were no statistical differences in the rate. The overall proportion of subjects experiencing any adverse event or serious adverse event is similar between the two applicator groups.

With the exception of two System Order Classification categories "General Disorders and Administration Site Conditions and "Vascular Conditions" there were no statistical differences in the rate of the adverse events. Within these noted two categories, there was a higher rate of events for subjects in whom the Spinal Sealant was applied using the MicroMyst Applicator. As noted in Table 3h, the General Disorders and Administration Site Conditions" category covers a diverse range of procedural-events that are expected medical complications following surgery/neurosurgery. The event that appears to be affecting the higher overall event rate for subjects treated with the MicroMyst Applicator within this category are reports of pyrexia (with a total of 15 subjects noted to have this event). The majority of pyrexia events were isolated transient events that occurred during the early postoperative period and resolved prior to discharge. These are likely associated with the inflammatory stimulus of surgery as they resolved spontaneously or with minimal medical therapy (i.e., administration of Tylenol or other anti-pyretics). For 6 patients, the event was associated with either a concomitant diagnosis of infection or signs and symptoms of infection (i.e., cough/nasal congestion, atelectasis, urinary tract or wound infection) and likely due to differences in concomitant diagnosis and/or the surgical procedures performed with the two different applicators and are not related to the DuraSeal Spinal Sealant or to the particular delivery device used.

As noted in Table 3h, the incidence of vascular related complications was also statistically greater for subjects treated with the MicroMyst Applicator. For the subjects who experienced hypotension, these occurred as isolated transient events which responded to fluid therapy. For one of the three subjects the event was deemed to be related to concomitant medications, one was deemed procedure related, the third the relatedness was designated as "unable to determine". Of the 5 subjects with events of hypertension/rebound hypertension, 2 occurred in subjects with a prior history for this condition [REDACTED] it was noted that the subject had no prior cardiac history; however, the subject's hypertensive episodes were diagnosed concomitant with a left bundle branch block. Subsequent to surgery the subject was treated with and prescribed anti-hypertensive medication. In review of these events, there does not appear to be any possible causative association between the occurrence of these vascular disorders and the type of Spinal Sealant applicator employed during the neurosurgical procedure.

Table 3h: Adverse Events by System Organ Class (Safety Population) Stratified by Applicator Type

System Organ Class/ Preferred Term	Spinal Sealant Applicator		p-value (1)
	MicroMyst (N=55)	Dual Liquid (N=42)	
Any Adverse Event	51 (92.7)	40 (95.2)	0.695
Blood And Lymphatic System Disorders	6 (10.9)	4 (9.5)	1.000
Cardiac Disorders	5 (9.1)	3 (7.1)	1.000
Eye Disorders	3 (5.5)	3 (7.1)	1.000
Gastrointestinal Disorders	11 (20.0)	6 (14.3)	0.593
General Disorders And Administration Site Conditions	24 (43.6)	7 (16.7)	0.008
Adverse Drug Reaction	1 (1.8)	3 (7.1)	
Chest Pain	3 (5.5)	0 (0.0)	
Feeling Cold	1 (1.8)	0 (0.0)	
Gait Disturbance	3 (5.5)	0 (0.0)	
Oedema	1 (1.8)	0 (0.0)	
Oedema Peripheral	0 (0.0)	1 (2.4)	
Pain	4 (7.3)	0 (0.0)	
Pyrexia	15 (27.3)	4 (9.5)	
Immune System Disorders	1 (1.8)	0 (0.0)	1.000
Infections And Infestations	11 (20.0)	7 (16.7)	0.794
Injury, Poisoning And Procedural Complications	24 (43.6)	17 (40.5)	0.837
Investigations	25 (45.5)	23 (54.8)	0.416
Metabolism And Nutrition Disorders	4 (7.3)	5 (11.9)	0.495
Musculoskeletal And Connective Tissue Disorders	16 (29.1)	8 (19.0)	0.343
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (1.8)	2 (4.8)	0.577
Nervous System Disorders	22 (40.0)	22 (52.4)	0.304
Psychiatric Disorders	1 (1.8)	2 (4.8)	0.577
Renal And Urinary Disorders	12 (21.8)	6 (14.3)	0.433
Reproductive System And Breast Disorders	1 (1.8)	0 (0.0)	1.000
Respiratory, Thoracic And Mediastinal Disorders	11 (20.0)	3 (7.1)	0.088
Skin And Subcutaneous Tissue Disorders	5 (9.1)	2 (4.8)	0.695
Vascular Disorders	8 (14.5)	0 (0.0)	0.009
Hypertension	4 (7.3)	0 (0.0)	
Hypotension	3 (5.5)	0 (0.0)	
Rebound Hypertension	1 (1.8)	0 (0.0)	

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(1) p-value from Fisher's exact test for a difference between treatment groups in the percentages of patients experiencing at least one AE in that given system organ class.

Table 3i: Serious Adverse Events by System Organ Class and Preferred Term (Safety Population) Stratified by Applicator Type

System Organ Class/ Preferred Term	Spinal Sealant Applicator		p-value (1)
	MicroMyst (N=55)	Dual Liquid (N=42)	
Any Serious Adverse Event	13(23.6)	15(35.7)	0.259
Gastrointestinal Disorders	2(3.6)	1(2.4)	1.000
Diverticular Perforation	1(1.8)	0(0.0)	
Pancreatitis	1(1.8)	0(0.0)	
Vomiting	0(0.0)	1(2.4)	
General Disorders And Administration Site Conditions	0(0.0)	1(2.4)	0.433
Pyrexia	0(0.0)	1(2.4)	
Infections And Infestations	1(1.8)	0(0.0)	1.000
Diverticulitis	1(1.8)	0(0.0)	
Injury, Poisoning And Procedural Complications	5(9.1)	10(23.8)	0.087
Graft Complication	0(0.0)	1(2.4)	
Incision Site Complication	1(1.8)	3(7.1)	
Nerve Injury	1(1.8)	0(0.0)	
Post Lumbar Puncture Syndrome	0(0.0)	2(4.8)	
Pseudomeningocele	1(1.8)	4(9.5)	
Subdural Hematoma	1(1.8)	0(0.0)	
Wound Dehiscence	1(1.8)	0(0.0)	
Musculoskeletal And Connective Tissue Disorders	1(1.8)	0(0.0)	1.000
Mobility Decreased	1(1.8)	0(0.0)	
Nervous System Disorders	3(5.5)	4(9.5)	0.462
Cerebrospinal Fistula	0(0.0)	2(4.8)	
Headache	0(0.0)	1(2.4)	
Loss Of Proprioception	1(1.8)	0(0.0)	
Paralysis	1(1.8)	0(0.0)	
Sensory Loss	0(0.0)	1(2.4)	
Syncope Vasovagal	1(1.8)	0(0.0)	
Renal And Urinary Disorders	1(1.8)	1(2.4)	1.000
Urinary Retention	1(1.8)	1(2.4)	
Respiratory, Thoracic And Mediastinal Disorders	2(3.6)	1(2.4)	1.000
Pulmonary Embolism	0(0.0)	1(2.4)	
Respiratory Failure	2(3.6)	0(0.0)	

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(1) p-value from Fisher's exact test for a difference between treatment groups in the percentages of patients experiencing at least one serious AE in that given system organ class.

Based on the stratified analysis presented, the DuraSeal Spine Sealant used in conjunction with either the MicroMyst Applicator or Dual Liquid Applicator has been established to be safe and effective for providing a watertight closure when used as an adjunct to suture dural repair during spinal surgery. The differences in adverse event rates observed for the MicroMyst and Dual Liquid applicators are most likely due to differences in the surgical procedures performed with the two different applicators and are not related to the DuraSeal Spine Sealant or to the particular delivery device used.

FDA Question:

4. You state in your proposed labeling that “in many control subjects the primary dural repair was reinforced.” FDA does not judge 19 cases, some of which are duplicates, to be many.

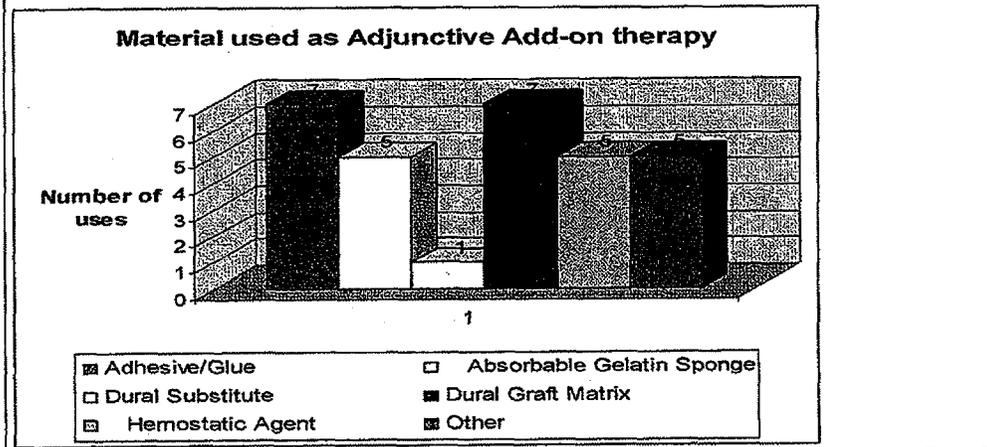
4a. Please revise this labeling to state the exact number that was reinforced and create a table to delineate the number and types of products used in the control group. In this table please include the number of patients with additional material used, the number of additional materials used per patient, and the range of materials used.

Sponsor Response:

As shown in Table 4a below, the exact number of subjects that was reinforced is nineteen. The Instructions for Use is updated to include this information, provided as Attachment 4.

Table 4a - Further Adjunctive Therapy (ITT Population)

Parameter	Statistic	Control (N=56)
Number of Patients with Further Adjunctive Therapy		
Yes	n (%)	19(33.9)
No	n (%)	32(57.1)
NA	n (%)	5(8.9)
Material Used in Further Adjunctive Therapy		
Adhesive/Glue	n (%)	7(12.5)
Absorbable Gelatin Sponge	n (%)	5(8.9)
Dural Substitute	n (%)	1(1.8)
Dural Graft Matrix	n (%)	7(12.5)
Hemostatic Agent	n (%)	5(8.9)*
Other	n (%)	5(8.9)



Parameter	Statistic	Control (N=50)
Number of Materials Used in Further Adjunctive Therapy		19
	Mean	1.6
	Median	1.0
	SD	1.02
	Minimum Maximum	1.0-4.0

*As described in Covidien's response to question 2e, two subjects (2/51, 3.9%) received the hemostatic agent as a SOC method and the Clinical Study Report will be amended to accurately reflect the use of hemostatic agents in the listed subjects.

FDA Question:

4b. In the first paragraph in the right column on page 3 of your labeling you state that there are no statistically significant differences in the two groups with regard to the safety outcomes. Please highlight that there was no difference between the two groups specifically with regard to CSF leak at 90 days.

Sponsor Response:

The Instructions for Use have been modified and include the statement; there was no difference between the two groups specifically with regard to CSF leak at 90 days.

FDA Question:

4c. In the second table of your proposed labeling you have listed the clinically meaningful endpoints of pseudomeningocele, CSF fistula, and surgical site infection (deep and superficial). For each of these listings please provide the percentage total patients affected.

Sponsor Response:

The second table in the Instructions For Use has been modified to include a column that identifies the percentage of total patients affected.

FDA Question:

5. You state in Vol. 1, p. 136 that the control (SOC) would “involve methods other than sutured dural repair”. However, Table 6-15 (p.170) lists 25 control patients (44.6%) as receiving sutures, and it can not be determined if they received other materials as well. Please provide a table that clearly enumerates what SOC each control received, (e.g., sutures alone, sutures + glue, etc.). Please clarify if SOC failed after 2 tries, could they be given DuraSeal? This information will assist us in clearly understanding the standard of care received by each patient.

Sponsor Response:

Refer to Attachment 3 for a by-subject listing that details which materials were received by each Control subject. To clarify, if after up to 2 attempts with the investigator's chosen SOC method (i.e., devices designed to provide a watertight dural closure), a non-watertight closure remained and the subject was considered a primary endpoint failure, the investigator was permitted to use further adjunctive add-on therapy to close the dura. As stipulated in the protocol, DuraSeal was not be used in a Control subject at any time during the procedure.

FDA Question:

6. Because the primary endpoint was assessed intraoperatively, there were no lost-to-follow-ups at this assessment or at hospital discharge. However, there were 5 subjects who did not complete the 90-day study: 2 sealant and 3 controls. Please explain how these subjects were counted in the ITT analysis of postoperative leaks where your calculations are based on sample sizes of 102 sealant and 56 controls. It appears you have counted them as if they were leak-free. If so, please perform a sensitivity analysis of postoperative leaks where all missing are leaking, and a worst case where the 2 missing sealant are leaking and the 3 missing controls are leak-free.

Sponsor Response:

The five Lost-to-Follow-Up subjects were counted as "leak free" in the ITT analysis. Refer to Section 10.1 of the Clinical Study Report for details on the postoperative course of these subjects. Of the two Spinal Sealant subjects that were considered Lost-to-Follow-Up, [REDACTED] returned for the 30-day visit, with a well healed incision and no signs of a CSF leak. The second [REDACTED] refused to return after discharge. At hospital discharge, the subject's incision was partially healed, with localized swelling along the suture line and no signs of a CSF leak. Refer to Table 6 for the requested analyses. The sensitivity analysis provided shows no statistically significant differences between groups related to the postoperative leak rate.

Table 6 - Sensitivity Analysis Post Operative Leak (ITT Population)

Parameter	Statistics	Spinal Sealant (N=102)	Control (N=56)	p-value (1)
90-Day Leak Rate without Imputation	n/N (%)	8/100 (8.0)	3/53 (5.7)	0.749
	95% CI for %	(3.5, 15.2)	(1.2, 15.7)	
90-Day Leak Rate with All Patients Lost to Follow-up Imputed as Leaking	n/N (%)	10/102 (9.8)	6/56 (10.7)	1.000
	95% CI for %	(4.8, 17.3)	(4.0, 21.9)	
90-Day Leak Rate with Patients Lost to Follow-up Imputed as Leaking in Spinal Sealant Group and as Leak Free in Control Group	n/N (%)	10/102(9.8)	3/56(5.4)	0.384
	95% CI for %	(4.8, 17.3)	(1.1, 14.9)	

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(1) p-value based on Fisher's Exact Test.

FDA Question:

7. You have stated that for [REDACTED] “a commercially available DuraSeal Dural Sealant System (PMA P040034) was used off-label after multiple attempts with the 5 mL study kit configuration were unsuccessful”. By unsuccessful, do you mean unsuccessful in the “application” or unsuccessful in the water tight closure? Either way, it appears this subject should be counted as an effectiveness failure. Please provide a complete description of this patient’s clinical course.

Sponsor Response:

In [REDACTED], the DuraSeal Dural Sealant System was used after three unsuccessful attempts of the 5 mL study kit based on unsuccessful application attempts to deliver the liquid precursor. Specifically, there were four devices opened for this case, summarized as follows (Table 7):

Table 7: Device Failures

Device Use #	Kit Type	Success/Failure
1	Clinical Device	Assembly Error (not considered a device malfunction)
2	Clinical Device	Device malfunction (clogged tip)
3	Clinical Device	Device malfunction (clear syringe turned blue)
4	Commercial Kit	Kit used successfully to achieve a watertight closure.

During uses #2 and #3 listed above, the sealant was never applied on the patient because of incorrect assembly of the kit that created a pressure difference between the blue precursor and the clear precursor. This led to the blue precursor pushing back into the clear syringe. It is likely that the two precursors contacted each other within the Y-connector, therefore forming a blockage and thereby making it impossible to apply the polymer on the patient.

The [REDACTED] continued in the study as an effectiveness success since watertight closure was achieved in the final device that was utilized, and the patient continued to have a clinical success during the course of this study. The commercial kit that was utilized contained exactly the same product formulation and application configuration as that which has been provided to clinical sites in the clinical devices.