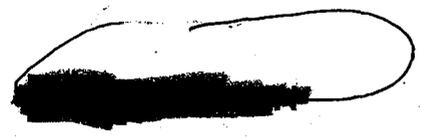


2009-4437b1-06

Amendment 1 to DuraSeal Xact Sealant System



June 26, 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 P080013 DuraSeal Xact™ Sealant System

Dear Mr. Ngatha:

The purpose of this Amendment is to communicate Confluent Surgical's panel meeting preference as requested in the FDA Notice of Filing Letter dated June 2nd, 2008.

We believe that an FDA Panel meeting will **not** be required to evaluate the safety and efficacy of the DuraSeal Xact Sealant System. In accordance with FDA's guidance document "Panel Review of Premarket Approval Applications (May 3, 1996)" (hereinafter referred to as the "Panel Review Guidance"), in order to make the determination to take a PMA before an advisory committee, the following questions must be addressed:

1. FDA does not have the knowledge or experience to properly evaluate the types of safety and effectiveness questions posed by the new device without panel input;
2. The PMA raises a new issue that is best addressed by employing the breadth of knowledge and experience afforded by convening an advisory panel meeting; or
3. The data establishing the clinical performance of the device reveals unanticipated safety and effectiveness questions that would best be addressed through panel deliberations.

Our position on each of these questions noted in the Panel Review Guidance is as follows:

Firstly, FDAs knowledge and experience to evaluate the safety and effectiveness of a dural sealant product such as the DuraSeal Xact Sealant System is well established. The Proposed DuraSeal Xact Sealant has the identical formulation to the FDA approved DuraSeal Dural Sealant approved under PMA P040034. The clinical trial results of the pivotal study DRS-05-001 demonstrate safety and effectiveness of the device for use in the Spine. In addition, the information provided in PMA P080013 shows a history of safe use outside the United States which further emphasizes the safety of the dural sealant use in the spine. The DuraSeal Dural Sealant marketed outside the United States and the DuraSeal Xact Sealant System, 2 ml configuration, marketed outside the United States has the identical formulation as the FDA approved DuraSeal Dural Sealant approved under PMA P040034 and proposed DuraSeal Xact Sealant, PMA P080013.

The DuraSeal Dural Sealant, PMA P040034, and the proposed DuraSeal Xact Sealant are both intended as an adjunct in sutured dural repair to provide watertight closure. Results of the ongoing post-approval study for the DuraSeal Dural Sealant System, currently being conducted in the United States, further characterize the use of the DuraSeal Sealant formulation in a post-PMA approval setting as compared to "standard of care", have not shown any safety concerns to date. Subjects participating in this post-approval study are evaluated similarly to those in the DRS-05-001 pivotal Spine study, including incidence of major neurological complications (e.g., post-operative CSF leak, surgical site infection), wound healing, and neurological exam. As presented in the 36 month report, of the 192 subjects enrolled, the neurological complications were anticipated and are consistent with the type and complexity of the procedures performed. No complications were reported to be device related.

Secondly, The DuraSeal Xact Sealant System PMA Does Not Raise Any New Issues That Are Best Addressed by the Panel. There are no unexpected findings relative to the safety assessment of the Spinal Sealant. The information provided in PMA P080013 shows a history of safe use outside the United States which further emphasizes the safety of the dural sealant use in the spine. In particular, the DuraSeal Dural Sealant has been marketed outside the United States since 2003 and is intended as an adjunct to standard methods of dural repair to provide watertight closure in cranial *and spine* procedures. The DuraSeal Xact Sealant System, 2 mL configuration, has been marketed outside of the United States since 2005 and is intended as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure during *spine* procedures

Commercial Sales outside the United States for the DuraSeal Xact Sealant and DuraSeal Dural Sealant from 2005 to 2008 are 3195 units and 24,987 respectively. The number of complaints over the same time period is 6 complaints for the DuraSeal Xact Sealant and 37 for the DuraSeal Dural Sealant. Sales figures and complaints for the DuraSeal Xact and DuraSeal Dural Sealants marketed outside the United States from 2005 to February 2008 are presented in Table 1 and Table 2.

Table 1: Current Commercial Sales

DuraSeal Xact Sealant System (2ml configuration, Spine Indication Only)	
	2005 - 2008
Total # of Units	3,195 units
DuraSeal Dural Sealant System (5ml kit configuration)	
	2005 - 2008
Total # of Units	24,987 units

** The DuraSeal Dural Sealant System sales figures represent use of the dural sealant for cranial and spine procedures.

Table 2: Complaint History

DuraSeal Xact Sealant System (2ml configuration, Spine Indication only)	
	2005 - 2008
Total # of Complaints	6 complaints
DuraSeal Dural Sealant System (5ml kit configuration)	
	2005 - 2008
Total # of Complaints	37 complaints

Neither the DuraSeal Xact Sealant System nor the DuraSeal Dural Sealant System has been withdrawn in any country due to reasons related to safety and effectiveness of the device. Based upon the complaint history to date and results of the ongoing post-approval study, it is concluded that there are no significant malfunctions/failures or difficulties associated with the currently marketed formulation of the DuraSeal Xact Sealant System or the DuraSeal Dural Sealant System.

Thirdly, data establishing the clinical performance of the DuraSeal Xact Sealant System does not reveal any unanticipated safety or effectiveness questions. The results of the pivotal study DRS-05-001, "A Prospective, Multi-Center, Randomized Controlled Study to Compare the Spinal Sealant System as an Adjunct to Sutured Dural Repair with Standard of Care Methods during Spinal Surgery" illustrates that the DuraSeal Xact Sealant System is both safe and effective when used as intended.

The primary efficacy endpoint in the clinical trial was the percent success in obtaining a watertight closure following assigned treatment (Spinal Sealant or Control) where success is defined as:

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

Of the 158 subjects randomized, all 102 subjects (100.0%) treated with the Spinal Sealant and 36 of the 56 subjects (64.3%) treated with Standard of Care displayed a watertight closure after assigned treatment. See Figure 1 for these results:

Figure 1: Primary Efficacy Endpoint Analysis

Intent to Treat Population				
Treatment Groups	Total Number of Patients	Number of Primary Endpoint Successes	Percent of Successes	95% Confidence Interval
Spinal Sealant	102	102	100.0	96.4, 100.0
Control	56	36	64.3	50.4, 76.6
p-value ⁽¹⁾	<0.001			
p-value ⁽²⁾	1.000			

Per Protocol Population				
Treatment Groups	Total Number of Patients	Number of Primary Endpoint Successes	Percent of Successes	95% Confidence Interval
Spinal Sealant	102	102	100.0	96.4, 100.0
Control	53	36	67.9	53.7, 80.1
p-value ⁽¹⁾	<0.001			
p-value ⁽²⁾	1.000			

⁽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.

Based on these results, we believe that the efficacy of the DuraSeal Xact™ Sealant System is well established and has been adequately demonstrated.

The safety in the clinical trial was evaluated as the:

- Presence or absence of CSF leaks within 90 days post-procedure as determined by clinical diagnosis using one of the following methods:
 1. CSF leak or pseudomeningocele related surgical intervention (i.e., breaking skin) within 90 days post-procedure; or
 2. CSF leak confirmation by diagnostic testing within 90 days post-procedure; or
 3. CSF leak confirmation by clinical evaluation within 90 days post-procedure

- Presence or absence of surgical site infection within 90 days post-procedure as determined from clinical diagnosis based on the CDC definitions of surgical site infection.
- Adverse Events
- Laboratory Testing
- Neurological Assessment, including cranial nerve, neurological, motor, sensory, reflex, gait, and symptoms of nerve root compression
- Wound Healing Assessment

The incidence of protocol defined post-operative CSF leaks was not statistically significant between the two treatment groups of Sealant versus Control (Spinal Sealant 7.8% vs. Control 5.4% (p= .0748)). See Figure 2 below for the time to CSF leak onset (p=0.578, log rank test):

Figure 2: Incidence of Protocol Defined Post-Operative CSF Leaks

Category	Statistic	Spinal Sealant (N=102)	Control (N=56)	Difference (%)	p-value (1)
Presence of endpoint CSF leak within 90 days post-procedure	n (%)	8 (7.8)	3 (5.4)	2.5	0.748
CSF Fistula	n	3	0		
Pseudomeningocele	n	5	3		

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

The rate of post-operative CSF Leak was similar between the DuraSeal Xact Sealant and Control groups, despite the fact that the number of adjunctive therapies used in the Control subjects for obtaining an intraoperative watertight closure was greater. Per the study protocol, if an intraoperative watertight closure (primary efficacy endpoint) was not obtained after assigned treatment; further adjunctive therapy was permitted to achieve the dural closure. Due to the fact that all Spinal Sealant subjects (100%) met the primary endpoint for intraoperative watertight closure, no subjects received additional adjunctive therapies to achieve dural closure. Within the Control group, the primary efficacy endpoint success rate was 64.3% (36/56 subjects). Therefore, nearly a third of the subjects within this group received additional adjunctive closure methods including the use of synthetic duraplasty materials, collagen surgical sealants and adhesives to achieve dural closure.

It is significant that there were no clinically relevant differences in safety outcomes between the two treatment groups with respect to laboratory evaluations, neurological exams, vital signs, physical examination and wound healing. In evaluation of the neurological assessment data and neurological complications, there is no indication of symptom complexes consistent with nerve root compression for subjects treated with the Spinal Sealant, a potential concern when using hydrogel-based devices along the nerve roots. There were no unexpected worsening of neurological symptoms and the type of neurological symptoms that were reported was consistent with the complexity of the surgical procedures performed and the medical conditions of the studied subject population.

There was also no statistical difference in the incidence of serious adverse events (SAEs) between the two groups; Spinal Sealant 29.4% vs. Control 17.9% ($p=0.11$). A review of the clinical data demonstrates that the overall incidence of adverse events, including serious adverse events, was comparable between Spinal Sealant and Control subjects. Overall, the adverse event profile for subjects treated with the Spinal Sealant was similar to that of the Control group within the majority of System Organ Classes (SOCs). Where differences were noted, reports within the Spinal Sealant group were consistent in nature and severity for this study population, a population undergoing complex neurosurgical procedures. There were no unexpected findings relative to the safety assessment of the Spinal Sealant.

Confluent Surgical believes the use of the FDA approved DuraSeal Dural Sealant as a spinal sealant does not raise any new issues requiring panel evaluation. Similar safety questions were previously raised during review of the DuraSeal Dural Sealant, PMA P040034. The clinical trial results of the pivotal study DRS-05-001 demonstrate safety and effectiveness of the device for use in the Spine. All 102 subjects (100.0%) treated with the Spinal Sealant displayed a watertight closure after assigned treatment and there were no unexpected findings relative to the safety assessment of the Spinal Sealant. Additionally, the known history of use of the product marketed outside the United States as a cranial and spinal sealant provides an understanding of the behavior of this product in the hands of the Surgeon and strengthens the safety profile of the device. Furthermore, it is also important to note that no audit observations were identified during the DuraSeal Xact PMA directed audit of the Confluent Surgical manufacturing site conducted recently during June 2-5th, 2008 in Waltham, MA.

In summary, Confluent Surgical believes that data included in the DuraSeal Xact Sealant System PMA is information already reviewed by the panel and that FDA has the expertise and knowledge in-house to review the data. Additionally, the data supporting the DuraSeal Xact Sealant System PMA do not raise any new issues or reveal any unanticipated safety or effectiveness issues that would best be addressed by a Panel. Therefore, Confluent Surgical does not believe a Panel meeting is necessary in the review of the DuraSeal Xact Sealant System PMA P080013.

We thank you in advance for your review of this amendment and look forward to FDA's review and decision regarding the requirement of a FDA advisory panel committee meeting for this technology.

Sincerely,

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

James McMahon
Manager, Regulatory Affairs

cc: P Steinborn, Vice President, Clinical / Regulatory Affairs

Attach: FDA Guidance, Panel Review of Premarket Approval Applications, May 3, 1996

Encl: (3 copies)