P080013
DuraSeal Xact™ Sealant System
Neurological Devices Panel
May 14, 2009

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FDA Review Team

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- Clinical Review: Ryan M. Kretzer, M.D.
- Statistical Review: Phyllis Silverman, M.S.
- Bioresearch Monitoring: Lynette Salisbury
- Manufacturing/QC/GMP: LTJG George K. Ngatha & Laura Adams
- Post-Approval Study: Cunlin Wang, M.D., Ph.D

Device History

- Applicant previously submitted and received agency approval for the DuraSeal™ Dural Sealant System (PMA P040034, approved on April 7, 2005)
- Dural Sealant System is indicated and approved for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.
- Applicant is now seeking premarket approval for use of the same Polyethylene Glycol (PEG)-based device in patients undergoing procedures in the spine.

Proposed Indication for Use

- The DuraSeal Xact™ Sealant System is intended for use as an adjunct to sutured dural repair during spinal surgery to obtain watertight closure.

- The chemical composition of the DuraSeal Xact™ Sealant precursors and, therefore, of the resulting hydrogel are identical to that of the DuraSeal Dural Sealant.

Rationale for Panel

- FDA believes that the clinical information obtained for the previously approved indication (i.e., adjunctive use in cranial dural watertight closure) does not provide safety and effectiveness data that reflects the physiological concerns for use of the sealant in the spine.

- Therefore, FDA believes use of the device in the spine represents a new indication for use.

- The primary endpoint of the investigation (i.e., intra-operative assessment of sealing) is a surrogate evaluation for device clinical performance. The Panel will be asked to comment on the adequacy of this endpoint.

Preclinical Evaluations

- Device Description
- Toxicology/Biocompatibility
- Preclinical animal evaluations

Device Description

- The DuraSeal Dural Sealant System consists of:
  - components for preparation of an absorbable polyethylene glycol (PEG) hydrogel sealant
  - 2 delivery systems packaged in a single use kit

- The sealant is also composed of two solutions, which when mixed together, provide rapid *in situ* polymerization via a nucleophilic substitution reaction to form a biocompatible absorbable hydrogel:
  - a PEG ester solution, and
  - a trilysine amine solution

- The polymerization requires no external sources of energy and results in a conformal coating that adheres to the tissue surfaces.

Key Product Parameters

- The cross linked solid hydrogel is more than 90% water at application. Due to this high water content, the hydrogel has physical properties similar to tissue.
- **Gel time** - upon mixing precursors, a gel is formed in $\leq$ 3.5 seconds.
- **Pot Life** - can be used for up to one hour following reconstitution
- **Swelling** - In vitro swelling is < 200%. For a 2 mm thick hydrogel that isotropically swells 200%, the maximum linear dimensional change in any direction is <1 mm.
- **Degradation rate** -The hydrogel implant is absorbed in approximately 4 to 8 weeks with excretion from the body primarily through the kidneys.
- The device is synthetic and contains no human or animal derived products and all components are provided sterile.

Preclinical Evaluations Toxicology/Biocompatibility

- Cytotoxicity
- Sensitization
- Intracutaneous Reactivity
- Acute Systemic Toxicity
- Subchronic Toxicity
- Implantation (2 weeks)
- Implantation – subcutaneous (10 days)
- In vitro hemolysis
- Pyrogenicity
- Mutagenicity (Ames, Chromosomal Aberration, Mouse Micronucleus, Mouse Lymphoma)

Preclinical Evaluations Biocompatibility/Applicator Function

- MicroMyst Applicator-2 mL volume, an air assisted applicator
- Dual Liquid Applicator – 5 mL volume
  - Biocompatibility
  - Functional assessments
    - Solution mixing
    - Applicator integrity, e.g., air pressure, clogging
    - Delivery reliability
- Applicators shall disperse gel in a pattern < 10 mm diameter when Spray Tip is 2-4 cm from target tissue

Prior Preclinical Evaluations/ Animal Studies

- Canine Cranial Sealing Study
- Rat Brain Parenchymal Implant Study
- Neurotoxicity study in the rat following injection into the brain
- Evaluation of DuraSeal persistence following subcutaneous implantation in the rat
- Reproductive Toxicity/Teratology

Additional Preclinical Evaluations/Animal Studies Performed to Support Spinal Indication

- Canine Lumbar Laminectomy Study
- Canine Cauda Equina Study

Preclinical Findings

- Device chemical components do not raise toxicological concerns.
- Device demonstrated to be biocompatible.
- Animal evaluations in models approximating device use in humans indicated the device worked as intended and did not cause tissue toxicity.
- The device was not mutagenic or genotoxic. It did not cause reproductive or teratologic toxicities.

P080013
DuraSeal Xact™ Sealant System

FDA - Clinical Discussion

Ryan M. Kretzer, M.D.
Medical Officer
May 14, 2009

Indication for Use

- "The DuraSeal Xact™ Sealant System is intended for use as an adjunct to sutured dural repair to provide watertight closure during spinal surgery. "

Background

- Cranial indication previously approved via PMA in 2005 (P040034)
- Chemical composition identical
- Two Delivery Systems:
  - MicroMyst Applicator - 2 mL (K050998)
  - Dual Liquid Applicator - 5 mL (K061183)

Pivotal Clinical Trial

- Design: Prospective, multi-center, randomized, two-arm, single blind clinical trial

- Objective: To evaluate the safety and effectiveness of the DuraSeal Xact™ Spinal Sealant as an adjunct to sutured dural repair compared with standard of care methods (control) to obtain watertight dural closure in patients undergoing spinal surgery.

Treatment Arms

- DuraSeal Spinal Sealant
- Standard of Care (Control)

- Randomization
  - 2:1 (DuraSeal : SOC)
  - Randomized intra-operatively

Standard of Care

- "Devices designed to provide an intra-operative watertight closure":
  - Suture
  - Autologous duraplasty materials
    - Fascia
    - Fat
    - Pericranium
    - Muscle
  - Adhesive glue (e.g., Fibrin glue)

Note: Both attempts to obtain a watertight closure had to employ the same SOC method.

Surgical Indications

- Chiari malformation
- Intradural tumor resection
- Intradural AVM resection
- Spinal cord untethering
- Syringomyelia
- Other (e.g., planned elective spinal procedure requiring a dural incision)

Intra-Operative Inclusion/Exclusion Criteria

Inclusion:

1. Non-watertight closure, spontaneously or upon Valsalva maneuver at 20-25 cm H_2O for 5-10 s.

Exclusion (2 most relevant):

1. Patient requires synthetic or non-autologous duraplasty material
2. Gap > 2 mm remaining after primary dural closure

Treatment Paradigm

1. Dural closure
2. Confirmation of intra-operative eligibility
3. Randomization
4. Treatment with up to 2 applications of either sealant or control
5. Post-treatment Valsalva (to evaluate primary endpoint)
6. If failure of the primary effectiveness endpoint in either arm, investigators could add additional devices that were *not* designed to provide a watertight closure (e.g., Gelfoam)

Blinding

- Patients: blinded until completion of study
- Physicians: blinded until intra-operative randomization, but not blinded in post-operative follow-up

Clinical Assessments

- Discharge
- 30 days post-procedure
- 90 days post-procedure

Primary Effectiveness Endpoint

- The percent success in obtaining an intra-operative watertight closure following up to 2 treatments with either DuraSeal or control
  - Confirmed by Valsalva maneuver at 20-25 cm H_2O for 5-10 s.
  - Non-watertight closure was defined as "any overt flow, seepage, weeping, or sweating of CSF through the dura, regardless of volume."

Safety Evaluations

1. Rate of CSF leak within 90 days post-procedure, defined as:

   - CSF leak or pseudomeningocele related surgical intervention
   - CSF leak confirmation by diagnostic testing
   - CSF leak confirmation by clinical evaluation

Safety Evaluations cont.

2. Surgical site infection (superficial vs. deep) within 90 days post-procedure
3. Adverse events
4. Wound healing assessment
5. Neurological status
6. Laboratory testing

Additional Information

- ASA Score
- Duration of surgery
- Indication for surgery
- Location and surgical approach
- Length of dural incision
- Autologous duraplasty materials used
- Valsalva maneuver pressures
- Size and nature of non-watertight closure
- Use of shunts/drains
- Sealant application information: applicator type, volume, number of applications, time of application(s), ease of use
- Standard of care ("control") information: tissue/suture used, number of attempts, ease of use
- Any further adjunctive therapy used
- Prophylactic antibiotic and anti-inflammatory regimens
- Estimated blood loss

Patients Treated

- 158 patients treated:
  - DuraSeal: 102 patients
  - SOC: 56 patients
- Centers: 24

Patient Demographics

Characteristics	Spinal Sealant (N=102)	Control (N=56)
Age (years)		
Mean (SD)	47.7 (13.68)	42.3 (14.57)
Range (min, max)	(18.7 ,74.5)	(19.5 ,74.2)
Gender, n(%)		
Female	54 (52.9)	30 (53.6)
Male	48(47.1)	26 (46.4)
Height (cm)		
Mean (SD)	169.9 (11.74)	169.8 (12.52)
Range (min, max)	(132.1 ,188.0)	(132.1 ,193.0)
Weight (Kg)		
Mean (SD)	80.8 (20.62)	83.9 (24.31)
Range (min, max)	(45.7 ,147.4)	(36.0 ,180.0)
BMI (Kg/m2)		
Mean (SD)	27.8 (6.09)	29.0 (7.74)
Range (min, max)	(17.9 ,46.2)	(16.0 ,64.0)
Smoking Status, n(%)		
Never	62 (60.8)	27 (48.2)
History	21 (20.6)	20 (35.7)
Current	19 (18.6)	9 (16.1)
ASA Score, n(%)		
I	13 (12.7)	4 (7.1)
II	66 (64.7)	40 (71.4)
III	22 (21.6)	12 (21.4)
IV	1 (1.0)	0 (0)

There were no significant differences between treatment groups.

Surgical Indications

Type of Procedure	Spinal Sealant (N=102) n(%)	Control (N=56) n(%)
A-V malformation	0 (0.0)	1 (1.8)
Chiari	22 (21.6)	18 (32.1)
Cyst	8 (7.8)	0 (0.0)
Syringomyelia	4 (3.9)	1 (1.8)
Syringomyelia with arachnoid cyst	1 (1.0)	0 (0.0)
Tethered cord	3 (2.9)	1 (1.8)
Tumor removal	64 (62.7)	35 (62.5)

The majority of patients treated in both groups underwent intradural tumor resection.

Procedural Demographics

Procedure Characteristics	Spinal Sealant (N=102) n(%)	Control (N=56) n(%)
Location[1], n (%)		
Cervical	47 (46.1)	32 (57.1)
Thoracic	39 (38.2)	15 (26.8)
Lumbar	25 (24.5)	15 (26.8)
Sacral	9 (8.8)	1 (1.8)
Approach, n (%)		
Anterior	0 (0.0)	1 (1.8)
Posterior	102 (100.0)	55 (98.2)
Duration of Surgery (hrs)		
Mean (SD)	3.9 (1.80)	3.8 (1.31)
Median	3.4	3.6
Range (Min, Max)	(1.3,9.2)	(1.6,6.3)
Length of Durotomy (cm)		
Mean (SD)	5.1 (2.72)	5.3 (2.79)
Median	4.7	5.0
Range (Min, Max)	(1.0,18.0)	(1.6,16.0)
Autologous Duraplasty Materials Used[1], n (%)	31 (30.4)	23 (41.1)
Fascia	11 (10.8)	12 (21.4)
Fat	4 (3.9)	2 (3.6)
Pericranium	13 (12.7)	11 (19.6)
Muscle	5 (4.9)	1 (1.8)
Other	1 (1.0)	0 (0.0)
Further Adjunctive Therapy[1], n (%)	0 (0.0)	19 (33.9)
Adhesive/Glue	0 (0.0)	7 (12.5)
Absorbable Gelatin Sponge	0 (0.0)	5 (8.9)
Dural Substitute	0 (0.0)	1 (1.8)
Dural Graft Matrix	0 (0.0)	7 (12.5)
Hemostatic Agent	0 (0.0)	5 (8.9)
Other	0 (0.0)	3 (5.4)
Wound Closure Materials Used[1], n (%)	39 (38.2)	26 (46.4)
Absorbable Gelatin Sponge	21 (20.6)	12 (21.4)
Hemostatic Agent	25 (24.5)	16 (28.6)
Other	16 (15.7)	10 (17.9)

Results – *Primary Effectiveness Endpoint*

Intent to Treat Population				
Treatment Groups	Number of patients	Number of Successes	Percentage 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			
As Treated Population(2)				
Treatment Groups	Number of patients	Number of Successes	Percentage 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			

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

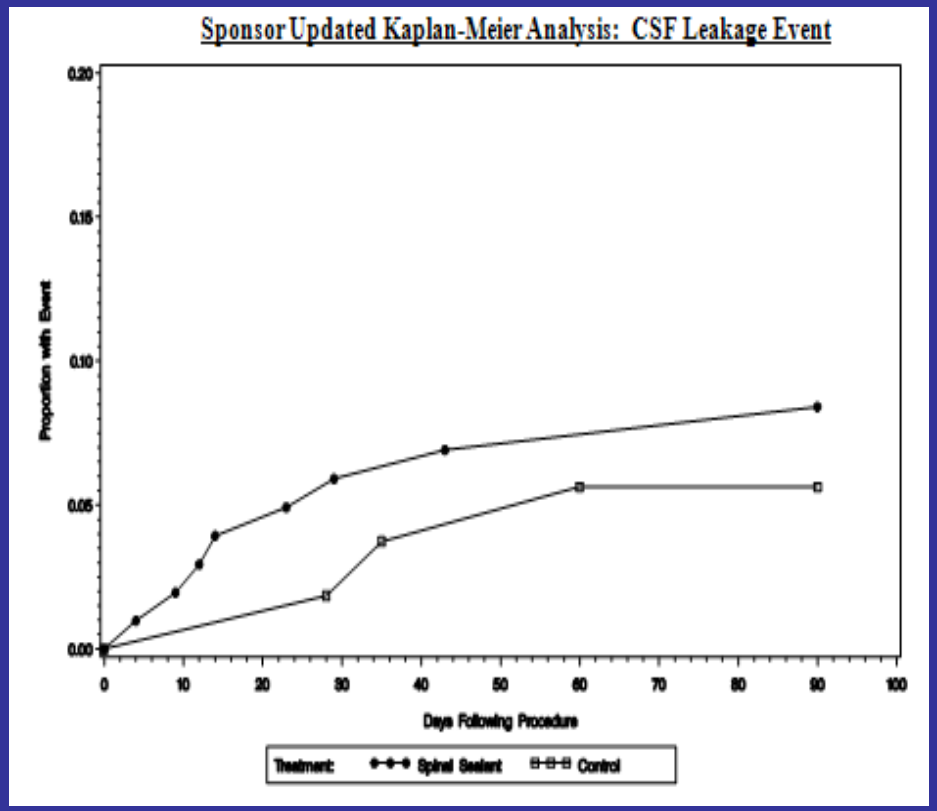
(2) 3 controls received no standard of care attempts.

Results - *Safety*

- CSF leak rate at 90 days
- Surgical site infection at 90 days
- Wound healing assessment
- Adverse events

Post-Operative CSF Leaks at 90 Days

- Binomial Proportion:
  - DuraSeal: 7.8%
  - Control: 5.4%
    - P = 0.75
- Kaplan-Meier Estimate:
  - DuraSeal: 8.4%
  - Control: 5.6%
    - P = 0.58



Subgroup Analysis of Post-Operative CSF Leaks at 90 Days

2:1 Randomization (DuraSeal : SOC)

- Type of procedure:
  - DuraSeal: **3 Chiari malformation** (3/22 = 14%), 3 tumor removal (3/64 = 5%), 1 tethered cord (1/3 = 33%), 1 syringomyelia (1/5 = 20%)
  - SOC: 2 tumor removal (2/35 = 6%), 1 tethered cord (1/1 = 100%)
- Location of surgery:
  - DuraSeal: **6 posterior cervical (4 craniocervical junction)**, 2 lumbosacral
  - SOC: **2 posterior cervical (2 craniocervical junction)**, 1 lumbosacral
- Timing of treatment failure:
  - DuraSeal: **3-42 days (mean 22 days)**
  - SOC: **27-59 days (mean 42 days)**

Subgroup Analysis of Post-Operative CSF Leaks at 90 Days

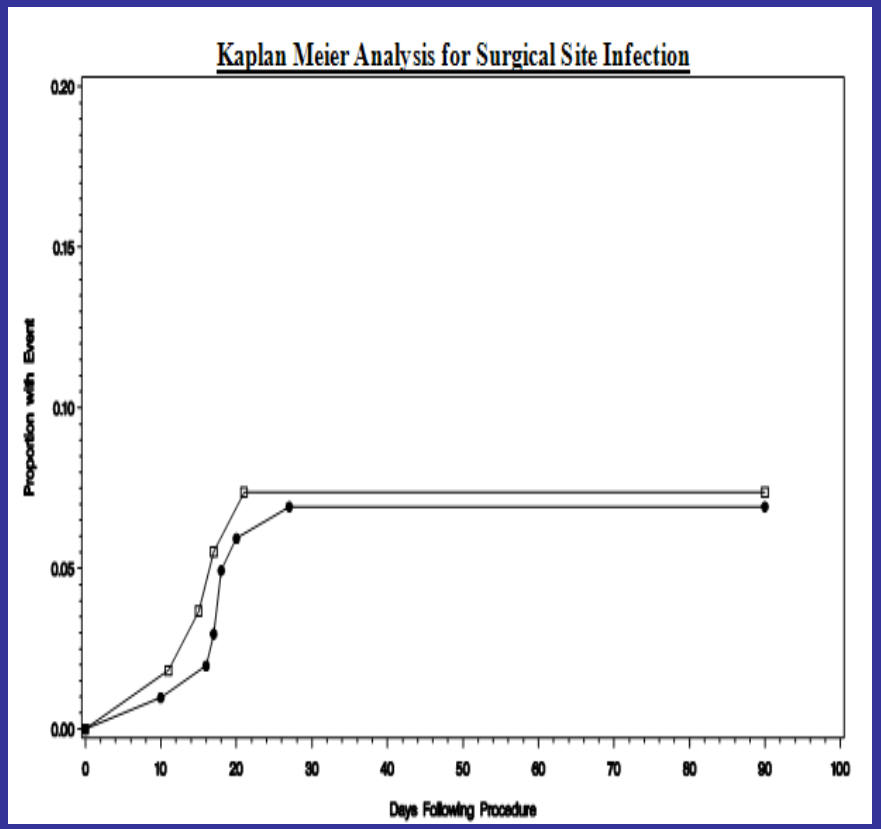
- CSF leak through the skin vs. pseudomeningocele:
  - DuraSeal: **3 through the skin**, 5 pseudomeningocele
  - SOC: **0 through the skin**, 3 pseudomeningocele

- Need for re-operation:
  - DuraSeal: **5 re-operations**, 1 aspiration of pseudomeningocele, 1 lumbar drain, 1 unknown
  - SOC: **1 re-operation**, 1 aspiration of pseudomeningocele, 1 lumbar drain

- No significant differences in: length of dural opening, skin closure techniques, time to first activity post-operatively, or co-morbidities that might limit wound healing/dural closure

Surgical Site Infections (SSI)

- SSI at 90 days:
  - DuraSeal: 6.9%
  - Control: 7.1%
    - P = 1.00
- Well healed wound at 30 days:
  - DuraSeal: 96%
  - Control: 94.5%



AEs and SAEs

Table 15: Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs)

Category	Spinal Sealant (N=102) n (%)	Control (N=56) n (%)	p-value (1)
Number of Subjects (%) With At Least One AE	95 (93.1)	51 (91.1)	0.639
Number of Subjects (%) With At Least One SAE	30 (29.4)	10 (17.9)	0.110
Number of Subjects (%) With At Least One Device-Related AE	1 (1.0)	0 (0.0)	0.646

(1) p-value from Pearson's chi-square test or Fisher's exact test for a difference between treatment groups in the percer of patients experiencing at least one AE in that given category as appropriate.

- All events adjudicated by an independent CEC
- After FDA review of all AEs and SAEs, these events were felt to be consistent with the subject population undergoing serious and invasive neurosurgical procedures.

Issues

- The primary effectiveness endpoint of intra-operative watertight dural closure did not correlate with the CSF leak rate at 90 days.
  - The study was not powered to statistically assess non-inferiority in post-operative CSF leak rates.
  - There is concern that the achievement of intra-operative watertight dural closure with DuraSeal may lead to less diligence during layered wound closure, predisposing to higher post-operative CSF leak rates.
  - Can this be adequately addressed through labeling and physician training?

Summary

- DuraSeal was superior to SOC in intra-operative watertight dural closure.
- FDA has questions regarding the clinical relevance of an intra-operative endpoint given the equivalency of post-operative CSF leak rates between DuraSeal and SOC.
- FDA will ask the Panel to comment on this concern in the afternoon session.

Post-Approval Study Considerations for DuraSeal Xact Sealant

Cunlin Wang, MD, PhD
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Office of Surveillance and Biometrics / CDRH

Neurological Devices Panel
May 14, 2009

Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.

- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.

- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

General Principles for PAS

- Objective is to evaluate device performance and potential device-related issues in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.

- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

PAS – Established Need

- Gather essential postmarket information
  - Longer-term performance including effects of re-treatments & product changes
  - Real-world device performance (patients and clinicians)
  - Effectiveness of training programs
  - Sub-group performance
  - Outcomes of concern (safety and effectiveness)
- Balance premarket burdens
- Panel recommendations

Issues for PAS Consideration

- In the PMA data:

Safety Outcomes	DuraSeal Xact Sealant	Control	p-value
Post-operative CSF leaks (K-M)	8.4%	5.6%	0.58
At least one SAE	29.4%	17.9%	0.11
Deep SSIs	4.9%	1.8%	0.40

PAS Outline (05/04/2009)

- Prospective, multi-center, single-arm
- Consecutive enrollment, n=300 to 500 patients
- Follow-Up : 30 days post-operatively
- Endpoints: CSF leak, pseudomeningocele, SSIs

Assessment of Sponsor's PAS Study Control Group

- No control group
- Absence of control group significantly:
  - diminishes scientific rigor
  - limits the meaningful interpretation and utility of study results
- Potential safety issues for DuraSeal, in comparison to control.

Assessment of Sponsor's PAS (cont.) Length of Follow-up

- The follow-up is 30 days post-procedure
- In the PMA trial, post-operative CSF leakage occurred:
  - DuraSeal: 3-42 days
    - 2/8 occurred >30 days
  - Control: 27-59 days
    - 2/3 occurred >30 days

Issues for Panel Discussion

If the device is recommended for approval, we would like you to comment on:

- The need for a post-approval study (PAS).
- If a PAS is recommended, please discuss:
  - the objectives
  - primary and secondary endpoints
  - appropriate control
  - duration of follow-up of study subjects
  - other specific issues that you would like to be addressed in the PAS

Thank You!

Issues for PAS Consideration

Safety Outcomes	DuraSeal Sealant	Control	P	Power
Post-operative CSF leaks (K-M)	8.4%	5.6%	0.58	9.4%
≥ One SAE	29.4%	17.9%	0.11	35%
Deep SSIs	4.9%	1.8%	0.40	13%

Sample Size Consideration

Without CSF Leakage (Control)	Non-inferiority margin	N1	N2
94%	5%	420	210
94%	6%	292	146
94%	7%	214	107
94%	8%	164	82

* with power = 0.8, α= 0.05, 2:1 randomization

MDRs for DuraSeal Dura Sealant

- 05/2005-04/2007: 7 MDRs (NBE):
  - 6 off-label (2 pediatric, 2 spinal, 1 with procedure penetrating air sinus and 1 IM compromised)
  - 1 CSF leak/infection
- 05/2007-05/2008:
  - Product Code (NQR: Sealant, DuraSeal): 11 MDRs
    - 8 injuries: 1 wound dehiscence, 5 infections, 1 quadriplegia, 1 CSF leakage
    - 3 malfunctions: non-specific infections
  - Product Code (NBE: Sealant, Polymerizing): 41 MDRs
    - 24 injuries: 11 infections, 12 CSF leakages, 1 pseudomeningocele
    - 17 malfunctions: 8 CSF leakages, 8 infections and 1 pseudomeningocele

FDA Questions

FDA PANEL QUESTIONS

Safety

1. Under CFR 860.7(d)(1), safety is defined as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of the intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks. Considering the adverse events for the device, please discuss whether the clinical data in the PMA/Supplement provide reasonable assurance that the device is safe.

FDA PANEL QUESTIONS cont.

Effectiveness

2. Under CFR 860.7(e)(1), effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. Considering the study design and endpoints discussed today, please discuss whether the clinical data in the PMA/Supplement provide reasonable assurance that the device is effective.

FDA PANEL QUESTIONS cont.

Primary Endpoint

3. The FDA-approved study protocol used a surrogate endpoint of **intra-operative** watertight closure as tested by an induced Valsalva maneuver. At the end of 3 months, there was an equivalent incidence of CSF leak between patients treated with the device and standard of care. Please comment on the following issues:

   a. The use of the **intra-operative** surrogate as an adequate indicator of clinical effectiveness for the device. If you do not believe this assessment is sufficiently predictive of clinical effectiveness, please discuss other means of determining clinical benefit for dural sealants.

   b. In consideration of the potential benefits of the sealant, including intra-operative watertight dural closure, ease of use, reduction in operative time, and possible decreased risk of disease transmission compared to biological materials, do you believe these potential benefits outweigh the risks associated with device use?

FDA PANEL QUESTIONS cont.

If you believe that the information supports product safety and effectiveness, please consider the following:

Labeling

4. A practical concern that arises is based on DuraSeal's potential use in daily clinical practice. For instance, surgeons might be less diligent during wound closure when using DuraSeal because they have achieved a watertight intra-operative result. This may then predispose to higher CSF leak rates in the post-operative setting. One way to alleviate this potential problem is to clearly state the equivalency in 90 day CSF leak rates between DuraSeal and standard of care in the product labeling. Please comment on this recommendation and discuss any additional labeling information you believe should be added to the product's package insert.

FDA PANEL QUESTIONS cont.

Labeling

5. The potential amount of swelling (e.g., ≤ 200%) was considered compatible for cranial-based surgical procedures. Due to the anatomical space limitations in the spine, the product label contraindicates the following:

   – *The DuraSeal Spine Sealant System is contraindicated for use as a void filler in enclosed spaces in the spine (such as the lateral gutters and neural foramen), as post-operative hydrogel swelling may impinge on surrounding tissues.*

   Please discuss whether this contraindication, or other contraindications, precautions, or warnings, should be included in the product labeling to address the risk of device swelling following use.

FDA PANEL QUESTIONS cont.

Labeling/Training

6. In addition to off-label use, Medical Device Reports (MDRs) and published literature indicate that adverse events also occur with use of the device for the approved indication, e.g., adjunctive dural sealing following cranial surgery. Many of these adverse events could be avoided if users adequately reviewed the product "Instructions for Use." Alternatively, potential adverse events could be avoided with adequate pre-use product training. Please comment on whether you believe the sponsor should employ a physician/user training program prior to DuraSeal use in the spine.

FDA DRAFT PANEL QUESTIONS Contd.

7. In the PMA clinical trial, when compared to standard of care, the DuraSeal cohort had a slightly higher incidence of post-operative CSF leak within 90 days post-procedure, a higher proportion of patients with at least one serious adverse event, and a higher proportion of patients with deep surgical site infections. The small sample size of the IDE cohort may explain why these results were not statistically significant.

FDA DRAFT PANEL QUESTIONS (Contd.)

Given the currently available safety and effectiveness data, if the device is recommended for approval, we would like you to comment on:

a. The need for a Post-Approval Study (PAS).

b. If a PAS is recommended, please discuss:

- the objectives
- primary and secondary endpoints
- appropriate control
- duration of follow-up of study subjects
- other specific issues that you would like to be addressed in the PAS