

2009-4437q1

FDA Questions

FDA DRAFT PANEL QUESTIONSPrimary endpoint

1. The FDA-approved study protocol used a surrogate endpoint of an intra-operative CSF leak prevention as tested by an induced Valsalva maneuver. At the end of 3 months, there was an equivalent incidence of CSF leakage between patients treated with the device and the control patients. Please comment and discuss on the following issues:
 - a. Use of the intra-operative surrogate CSF leak assessment as an adequate indicator of clinical effectiveness for the device. If you do not believe this assessment is sufficiently predictive, or reflective of clinical effectiveness, please discuss other means of determining clinical benefit for dural sealants.
 - b. In overall consideration of the potential benefits of the sealant, e.g., immediate CSF leak prevention, possible reduction in surgical closure time/OR time, possible pain/morbidity reduction, etc..., do you believe these apparent (CSF leak) and potential benefits outweigh risks associated with device use? Please discuss the appropriate role the sealant may play in spinal surgical procedures involving incision and suturing of the dura mater.

Labeling concern

2. The potential amount of swelling, i.e., $\leq 200\%$ was considered compatible for cranial-based surgical procedures. Due to the restricted anatomical space limitations in spine-based surgical procedures, 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 and warnings should be identified to sufficiently address concerns, or other risks, regarding adverse events that may be caused by the potential degree the gel could swell.

Labeling concern

3. A practical concern that arises is based on how DuraSeal will be used 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. FDA believes that the best way to alleviate this problem is to clearly and emphatically state the equivalency in 90 day CSF leak rate between DuraSeal and SOC 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.

Labeling/training

4. Medical Device Reports as well as published literature has been identified that indicate adverse events occur, in part, with use of the device for the approved indication, i.e., cranial dura adjunctive sealant use, which could be avoided if users adequately reviewed the product instructions for use. Or, 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 for both the cranial and spinal DuraSeal products.
5. The PMA clinical trial data indicate that the proportion of patients who experienced post-operative CSF leaks within 90 days post-procedure was slightly higher in the DuraSeal Sealant group than in the Control group: 7.8% (8/102) vs. 5.4% (3/56), $p=0.748$, respectively. In

addition, 29.4 % (30/102) of patients in the DuraSeal Sealant group experienced at least one serious adverse event, while in the Control group this percentage was only 17.9% (10/56), $p=0.11$. Furthermore, of the 7 surgical site infections (SSIs) in the DuraSeal Sealant group, 5 cases were deep surgical site infection and 2 were superficial, while in the control group there was only 1 deep surgical site infection and 3 superficial surgical site infections. Therefore, the percentage of patients who experienced Deep SSIs in the DuraSeal Sealant and the Control group were 4.9% (5/102) vs. 1.8% (1/56), respectively (Fisher Exact $p=0.40$). The reason none of the results comparing the two groups on the three measurements were statistically significant may be related to the small sample size of the Control group ($n=56$). If the PMA for this device is recommended for approval, we would like to ask the panel to comment on:

- a. Should a recommendation of approvable or approvable with conditions be made, please comment on the need for a Post-Approval Study (PAS). Please identify the questions to be addressed by a PAS such as the risk of post-operative CSF leaks, Serious Adverse Events and deep surgical site infections.
- b. If you believe a PAS is advisable, we would like the panel to comment on suggestions for the primary outcome, and parameters for assessment that should be included in the PAS.

Effectiveness

6. 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.

Safety

7. 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.