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**Before the Plastic and Reconstructive Surgeries Devices Panel
of the Medical Devices Advisory Committee
Center for Devices and Radiological Health
Food and Drug Administration
Meeting on Premarket Approval Application
for Confluent's DuraSeal Xact Sealant System for Spinal Use**

**Gaithersburg, Maryland
May 14, 2009**

Today the committee will consider the premarket approval (PMA) application for DuraSeal Xact Sealant System (an absorbable polyethylene glycol sealant) as an adjunct to sutured repair of the dura mater during spinal surgery. In our view, the clinical evidence assembled by the company is insufficient to meet the statutory requirement for approval of a medical device: that the company provide a "reasonable assurance of ... safety and effectiveness."¹

The sponsor conducted a patient-blinded, randomized trial comparing DuraSeal to standard of care (SOC) treatments in spinal surgery patients who intra-operatively demonstrated CSF leaks following closure of the dura mater, the sheath that surrounds the spinal cord and brain. One hundred and fifty-eight patients with leaks were enrolled and randomized in an approximately 2:1 ratio favoring DuraSeal. SOC treatments were other methods for closing the dura, including additional sutures, adhesive/glue, soft tissue/vascular patch, hemostatic agent, and others.* For those randomized to DuraSeal, a syringe delivery system applied the synthetic, absorbable sealant to dural tears. Immediately after the randomly assigned treatment was performed, patients were evaluated intra-operatively for continued CSF leakage visually and with a Valsalva maneuver (increasing intra-abdominal pressure to test for a leak). If leaking continued, the surgeon could reapply the same therapy (DuraSeal or SOC) and reevaluate. The prespecified primary endpoint was lack of intra-operative leaking, confirmed by a Valsalva maneuver.

Interpretation of the prespecified primary endpoint is relatively straightforward. There was a highly statistically significant difference in the leak rate between DuraSeal and the SOC treatments (100% vs. 64.3%, respectively; $p < 0.001$, Fisher's Exact test).²

* Because no products are FDA-approved for dural closure in spinal surgery, use of any FDA-approved product in this setting is off-label.

Despite this apparently strong finding, there was no difference between the DuraSeal and SOC groups in CSF leaking in the 90 days following the procedure (8.4% vs. 5.6%, respectively; $p=0.578$, Kaplan-Meier). This finding has been presented as a safety outcome,³ but is, in fact, an efficacy outcome (and one that tends to favor the SOC treatments) in that it represents the failure of the assigned treatment to prevent long-term leakage. In our view, post-operative leak should have served as the primary endpoint. From that perspective, the findings are unimpressive. As the FDA reviewers point out, "the study does not demonstrate a relationship [between] prevention of an intra-operative dural leak [and] prevention of post-operative (*clinically meaningful*) CSF leak"⁴ (emphasis added)

Indeed, supporting the sponsor's application requires acceptance of intra-operative leaking as an appropriate surrogate marker for true clinical benefit. The sponsor asserts that intra-operative leak is an acceptable endpoint because intra-operative leakers were more likely to leak post-operatively than those who did not leak intra-operatively (15% vs. 5.8%, respectively). While this finding might establish that intra-operative leak is a risk factor for subsequent leaking, this is not sufficient to justify its use as a surrogate. As Fleming and DeMets explain:

A correlate does not a surrogate make. It is a common misconception that if an outcome is a correlate ... it can be used as a valid surrogate end point (that is, a replacement for the true clinical outcome) ... [Prentice's criteria] essentially require that the surrogate must be a correlate of the true clinical outcome and fully capture the net effect of the treatment on the clinical outcome. Although the first criterion is usually easy to verify, the second is not.⁵

That is precisely the case here. In fact, the statistics presented by the sponsor fail even to establish correlation because they fail to reach statistical significance (RR=2.59; 95% CI= 0.75-8.95; $p=0.15$, Fisher's Exact test). Thus, the FDA was correct when it asserted in its questions to the sponsor that the intra-operative leak rate "did not correlate" with the post-operative leak rate.⁶

Even if intra- and post-operative leaking were correlated, the sponsor's analysis cannot assess the surrogate's ability to evaluate the efficacy of DuraSeal (the second element in Fleming and DeMets' formulation) because the sponsor combined the treated and control groups in its analysis.

Finally, if intra-operative leaking were a good surrogate marker, one would at least expect intra- and post-operative leaks to trend together. As we have noted, if anything, the opposite is true.[†]

One reason that the study failed to reach statistical significance on the 90-day endpoint may have been that it was underpowered. By the FDA's calculation, with the total population of 158 patients and assuming the observed SOC leak rate of 5.6%, the DuraSeal leakage rate would have had to have been 15% in order to reach statistical significance (power=0.80).⁷ In other words, DuraSeal-treated patients would have had to have leaked post-operatively at almost three times the control rate for the study to have reached statistical difference. Thus, because the trial was underpowered, it remains unknown whether DuraSeal produces a clinically meaningful benefit, and the committee cannot have the legally required "reasonable assurance" that DuraSeal is effective.

In addition to these efficacy concerns, there were signs of possible dangers associated with the device. Serious adverse events occurred more frequently in the DuraSeal group than the SOC group (29.4% v. 17.9%, respectively) and, despite the sample size limitations, this outcome nearly reached statistical significance (p=0.11, Pearson's chi-square test).⁸ In the DuraSeal-treated patients, there was a trend toward higher rates of deep surgical site infections (even though the overall rates of surgical site infections were comparable) and serious neurological deficits (4.9% vs. 1.8% in both instances, respectively).⁹ Furthermore, post-operative leaks in the DuraSeal group also appeared to result in more severe sequelae, including more frequent fistula formation (37.5% vs. 0% of those with leaks, respectively) and more re-operations (62.5% vs. 33% of those with leaks, respectively).¹⁰ Even though none of these results is statistically significant, the study was underpowered, as we have noted. The consistent direction of the adverse effects observed, even if non-significant, is concerning and is hardly a "reasonable assurance of ... safety."

Two other elements undermine the study's findings. First, surgeons were not blinded to treatment allocation, introducing a source of potential bias presumably favoring DuraSeal. Second, while all patients who leaked following the first DuraSeal application underwent another attempt to seal the leak (which was successful in all instances), only 19% of SOC patients who had such leaks after the first treatment received a second treatment, likely because the surgeons were restricted to reapplying the same SOC treatment used in the first, unsuccessful attempt. Together, these two factors suggest that the efficacy of DuraSeal on the primary endpoint may have been overestimated.

[†] In addition, post-operative leaks occurred earlier in the DuraSeal group (mean 27.2 days vs. 42.0 days), a finding that seems inconsistent with the product's intra-operative sealing benefit.[†]

We are left with a study that demonstrates the effectiveness of the device on an inappropriate surrogate outcome, but that was underpowered to provide insight into the outcome the FDA itself has characterized as "a more clinically meaningful endpoint than intra-operative watertight closure."¹¹ Along with several worrisome safety signals, these data can hardly be considered sufficient to justify approval of this device.

¹ 21 USC § 360c(a)(1)(C).

² Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 35-6. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.

³ Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 37-40. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.

⁴ Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 43. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.

⁵ Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med.* 1996;125:605-13.

⁶ Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 42. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.

⁷ Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 45. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.

⁸ Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 41-2. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.

⁹ Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 40-1. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.

¹⁰ Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 43-4. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.

¹¹ Food and Drug Administration. FDA summary for DuraSeal Xact Sealant System. May 14, 2009. p. 46. Accessed May 13, 2009, at: <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4437b1-01%20FDA%20Executive%20Summary.pdf>.