UNITED STATES FOOD AND DRUG ADMINISTRATION

CITIZEN PETITION REGARDING THE CONDITIONS OF THE PRE-MARKETING APPROVAL OF THE DURASEAL® SPINAL SEALANT	))))	DOCKET NO. 2013P-___

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CITIZEN PETITION

The undersigned submits this petition under Section 515(g) of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to order the sponsor of Duraseal® Spinal Sealant to complete enrollment in its post-approval study of infection rates associated with use of the Spinal Sealant ("product"), to investigate risks disclosed in serious adverse effects that were not discussed in the PMA, to investigate the sponsor's compliance with its duties to report serious adverse effects to the United States Food and Drug Administration *("agency")*, to order such revisions in the Spinal Sealant's labeling and/or package inserts as are appropriate to the findings of the agency and to disclose reporter's identities and contact information.

A. ACTIONS REQUESTED

This petition is submitted by a tort plaintiff, Ms. Marteen Moore of Las Vegas, Nevada, who was paralyzed after surgery during clinical trials of the product. She contends that the Spinal Sealant caused an infection that caused the failure of her surgery to fuse surgical hardware to the spine, and also that the Spinal Sealant probably expanded or swelled in the confined bony spaces and gutters surrounding her spine, and caused injury to her peripheral spinal nerves and nerve roots. Ms. Moore brings this Petition, pursuant to *21 C.F.R. §10.30*, for U.S.F.D.A. *("agency")* enforcement of post-approval conditions of the PMA and investigation of false advertising, improper labeling and

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possible adulteration of the product. She recommends temporary suspension of the PMA to punish the violation(s) of the Federal Food Drug & Cosmetic Act ("Act").

Ms. Moore had a verbrectomy at levels T8 through T10 of the spine in 2001, and a fusion of the spinal hardware with her spine at levels T8 through T10. In 2006, the fusion *"failed,"* causing the hardware to migrate and threaten to compress her spine. In her revision surgery on September 6, 2006, the surgeon enrolled her in the clinical trials. He used the product to repair the durotomy. She experienced a deep and large infection in her surgical wound, and the surgeon re-operated to treat the infection nine days after surgery.

Ms. Moore was confined thirty-three days in the hospital. Almost immediately after her discharge from the hospital, the symptoms of the hardware compressing her spine began to return. Surgeons confirmed the re-compromise of her spinal function. Another surgeon advised her to have a *"rescue"* operation in April of 2007 because her symptoms were rapidly progressing to total paralysis. She became totally paralyzed in this *"rescue"* surgery.

Ms. Moore's enrollment in the clinical study contradicted a pre-exclusion condition of the study of revision surgeries. Ms. Moore's surgeon did not obtain a waiver of this exclusionary condition from the Institutional Review Board, nor did he explain to Ms. Moore in requesting her informed consent that her enrollment violated this pre-exclusion criteria.

Ms. Moore sued for damages. The trial court dismissed her case because she did not retain a medical expert opinion witness who could testify that the product caused her injuries. She lost her suit in court because she was unable to find a surgeon who neither felt threatened by retaliation by Tyco Healthcare/Covidien, nor did not feel ethically restrained by peer group norms or medical society rules to not testify against a medical device that he or she had not used in clinical practice. The appeals courts affirmed the trial court.

During her lawsuit, Ms. Moore made several discovery requests of the product sponsor to disclose complaint files and serious adverse effect reports by the sponsor or by health care providers to the agency, and she repeated these requests periodically. The sponsor Tyco Healthcare/Covidien refused her requests. She also made repetitive Freedom of Information Act requests to the agency for these reports and/or complaint files and following standard agency policy regarding products under a pending PMA, was refused these requests.

These denials from the sponsor and the agency proved to be the *coup de grace* to her efforts to engage the medical expert opinion witness on causation that the court ruled that she needed to prove that the product caused her injuries. The court would not accept substitute evidence of causation for the missing medical expert's opinion the evidence that the sponsor cited her case in one proposed package insert as a revision surgery for which the product is always contraindicated. The agency needs to investigate to determine whether this package insert was used for the product as

compared to the other "draft" package insert which does not refer to her case as a contraindication. Ms. Moore seeks disclosure of the reporter's identities and contact information in *Exhibits D and E*, and any reporters' identities and contact information for any Freedom of Information Act information provided to her.

Ms. Moore seeks enforcement of the Neurological Devices Panel's recommendation for the completion of a post-marketing approval study of the infection rates involved with use of the product, under *21 C.F.R. §814.82(a)(3)*. She seeks enforcement of the Panel's recommendation for inclusion in the labeling of a warning to the surgeon to be as diligent as possible to close the durotomy using traditional methods. She requests clarification of the precaution in the labeling against use of the product with another non-autologous sealant or assistive agent. She seeks a stronger *("black box")* warning against the use of the product with another non-autologous agent such as Duragen® or Gelfoam® in the labeling and the warning against application of the product in the gutters of the spine and/or confined bony spaces enclosing nerves adjacent to the spine, under *21 C.F.R. §814.82(a)(3)*. She seeks a *"black box"* warning against use of the product in revision surgeries. She recommends temporary suspension of the PMA as a sanction. *21 C.F.R. §814.47.*

The agency should investigate false advertising that misrepresents an important safety feature of the product, concerning the blue dye that causes the product to have a blue color. In the PMA, the sponsor touted the blue color of the product as a diagnostic tool for re-operations after a surgery in which the product was used. *See text at fn. 2, infra.* The authority for her request is *21 C.F.R. §814.82(a)(3)*.

She seeks a public hearing under *Section 515(g)(1)* of the Act, which the agency is compelled to hold because of the continuing violation of her rights to procedural due process and substantive due process because she was denied disclosure of the sponsor's complaint files and serious adverse effects reports for the product by both the sponsor and the agency. She still cannot be sure that she has all of the relevant available reports, unless and until the agency works with her to verify that she does possess them, and the reporter's identities.

B. STATEMENT OF GROUNDS

1. MS. MOORE'S STANDING TO BRING THIS PETITION UNDER THE FFDCA AND THE FOURTEENTH AMENDMENT TO THE U.S. CONSTITUTION

Ms. Moore is an *"interested person"* who is seeking the Commissioner's action *"to issue, amend or require a regulation or order"* under the Act. *21 C.F.R. §10.25(a)*. This regulation expressly authorizes the interested person to bring a citizen petition under *21 C.F.R. §10.30* for this purpose as Ms. Moore is doing in this petition.

Ms. Moore also has Article III *"case or controversy"* standing to assert her right to a public hearing under the due process of the laws clause of the Fourteenth Amendment. She alleges injury in fact from the invasion of a legally protected interest – her right to information contained in serious adverse effect reports and complaint files of the

sponsor required to be maintained at the sponsor s offices by the agency under *21 C.F.R. 820.198* – which is *"property"* under the Fourteenth Amendment because these reports were (and may yet be) indispensable to the success of her tort lawsuit and this petition.

The agency has now provided some of these reports to Ms. Moore and stated to her counselor at law that the reports are available to her on its website. But the injury to her is continuing because the agency has not confirmed compliance to its duty under the Freedom of Information Act to provide these reports to Ms. Moore in writing. Nor has the agency investigated the compliance of the sponsor with its duties to make these reports to the agency under *21 C.F.R. §814.80* and the sponsor' duty to maintain complaint files under *21 C.F.R. §820.198*. This injury is concrete and particularized, and the harm is actual or imminent, not conjectural or hypothetical. *Lujan v. Defenders of Wildlife (1992) 504 U.S. 555, 560-61.*

As explained in A, *supra*, Ms. Moore could not obtain either the serious adverse effect reports or the complaint files of the sponsor because the sponsor would not release them to her and neither would the agency, until very much time had passed after the court dismissed her case. This happened to her, although multiple formal written requests were made by her counselor at law and served according to the law on both while her law suit was pending.

The evidence in her case of the cause of her injuries by the product was circumstantial but it was highly relevant and material nonetheless. If provided to her, the serious adverse effect reports probably would have enabled Ms. Moore to make contact with a medical expert opinion witness to testify that the product caused her injuries. The serious adverse effect reports were not merely cumulative of the evidence of a product malfunction from other sources; they were (and are) the *sine qua non* to her case.

The evidence that the sponsor provided directly or indirectly to her (albeit in a form that violated the Federal Rules of Civil Procedure and the oath of office of the attorneys at law for the sponsor) strongly suggested a product malfunction. The surgeon testified that he didn't witness a leak of Ms. Moore's cerebrospinal fluid (CSF) during her re-operation on September 15, 2006. But the surgeon's testimony did not disprove that the CSF didn't leak before the re-operation and spontaneously heal before the re-operation. She notes that the surgeon originally reported to the sponsor that he didn't know whether her infection was related to the use of the product or not.

Ms. Moore learned after the court dismissed her case that one of the patients enrolled in the study at the same investigation site as her was originally reported to the sponsor in error as not experiencing a leak of CSF after surgery had actually suffered from a leak of CSF fluid after use of the product and was re-operated. She knew that another patient enrolled in the study had suffered a leak of CSF fluid after use of the product. There were only five patients enrolled in the study at the same location, and only five kits of the product were used there. Ms. Moore knew that one kit was opened during her surgery and rejected and not used on her. There was no testimony as to the ultimate disposition of the unused kit or the reason why it was not used, and there were no records of its disposition, which violates *21 C.F.R. §812.140(a)(2)* and *21 C.F.R.*

§812.140(b)(2), and *21 C.F.R. §820.90(b)(1)* (record of disposition of nonconforming product). Since it seems very likely without the required record of its fate that the unused kit opened during Ms. Moore's surgery malfunctioned, three out of five kits in the *"lot"* of five kits at the same study location were associated with a leak of CSF or a malfunctioned product.

21 C.F.R. §812.38(d) states that *"except as provided otherwise in this section"* the availability for public disclosure of data and information in an IDE shall be handled in accordance with *21 C.F.R. §814.9*. *21 C.F.R. §814.9(a)* states that *"data or information contained in the [PMA] file are not available for public disclosure before the order issues."* *21 C.F.R. §814.9(f)* states that data and information contained in serious adverse effect reports are available for public disclosure once the order issues. The agency has never made an exception to the nondisclosure rule in Part 814 to permit disclosure of serious adverse effect reports relating to a product under consideration in a pending PMA, to the knowledge of Ms. Moore's counselor at law. Certainly it did not make an exception in her case to the nondisclosure rule in Part 814.

Ms. Moore's case was mentioned in one proposed package insert (*see Exhibit A*, which was apparently the package insert reviewed by the Panel for its meeting, yet another proposed package insert does appear as a *"draft"* with other materials made available to the public for the meeting which does not discuss her surgery as a contraindication, *see Exhibit B*) as a revision surgery that should never be considered appropriate for the use of the product. Yet the sponsor did not highlight this *"never use"* warning in the sort of *"black box"* that the agency reserves for these kinds of hazards with respect to pharmaceutical preparations; and it should do so.

The serious adverse effect reports in the possession of the agency at the time that Ms. Moore requested them were, and are, *"property"* under the Fourteenth Amendment to Ms. Moore because of their use as evidence in her lawsuit. These reports were, or are, *"adjudicative"* in nature, because these reports or the complaint files of the sponsor were the only existing records of the identities of health care providers and surgeons who had complaints of the performance of the product. They were the only sources of information that Ms. Moore could have used in the circumstances to convince a surgeon or other medical doctor to testify against the use of the product in her case.

And when the agency first opened its records and disclosed serious adverse effect reports to her approximately one year and two months after the court dismissed her case on summary judgment, in November of 2010, Ms. Moore analyzed them for the first time. She that several of these reports prove that some known risks of use of the product in her case were not discussed in the PMA or addressed in the sponsor's proposed labeling and/or package insert, most notably the harmful interaction between the product and non-autologous agents such as Gelfoam® (a hemostatic agent) and/or Duragen® (a dural substitute). Her information based on these reports and other reports obtained later suggests that the sponsor inadequately warned patients of the harmful interactions between the product and these other agents, and that the sponsor inadequately warned of the harmful effects of the expansion or swelling of the product in spinal gutters or confined bony spaces surrounding the spine for damages to nerves

and nerve roots therein. These reports establish a harmful interaction between the product and these pre-existing agents, which the sponsor never discussed in the PMA. These adverse effect reports from the period of experimental use of the product are probably the only source of the actual risk information for the experimental version of the product used in clinical trials, ie. the version of the product used on Ms. Moore.

Ms. Moore was denied due process of the laws because the agency refused to disclose these reports to her, even after she informed the agency that she could not obtain them through civil discovery techniques from the sponsor. These reports were *"adjudicative"* in nature, and Ms. Moore was, and is, entitled to an adjudicative *"trial-type"* hearing prior to the agency's final refusal to disclose them. *Goldberg v. Kelly (1970) 397 U.S. 254.* Ms. Moore seeks disclosure of the reporter's identities and contact information in *Exhibits D and E,* and any reporters' identities and contact information for any Freedom of Information Act information provided to her.

Because the agency has refused to assist her in confirming the source of these reports and that she has all of these reports, the denial of due process of the laws continues. She is entitled to an adjudicative *"trial-type"* hearing to review the status of the agency's subsequent disclosure of these records to her, for compliance with the Freedom of Information Act and for the sponsor's compliance with the reporting and disclosure requirements of the Act.

2. THE THREE CONDITIONS PLACED ON THE APPROVAL OF THE PMA FOR SPINAL SEALANT BY THE NEUROLOGICAL DEVICES PANEL THAT VOTED TO APPROVE THE PMA

As a condition of the pre-marketing approval of the Duraseal® Spinal Sealant, on May 14, 2009, the Neurological Panel to the Medical Devices Advisory Committee, voted for the approval of the Pre-Marketing Application with three conditions (hereafter the Transcript of that meeting is denoted as *"Transcript"*):

<<<Transcript 206:8 – 206:24>>>

> *"DR. BATJER: With no further motions, it has been moved and seconded that the PMA P080013 for the DuraSeal Xact Sealant System be found approvable with three conditions the Panel has just approved. Those conditions relate to labeling -- the first one concerns labeling, the second concerns the possibility of swelling related to narrow locations in the neuraxis, and the third, recommending a PAS.*
>
> *We will now vote on the main motion and that is to -- that is approvable with conditions. With a show of hands, please indicate if you concur with the recommendation that the above-named PMA be found approvable with conditions. Dr. Yaszemski?*
>
> *DR. YASZEMSKI: Yes.*

DR. BATJER: All four panelists have voted in favor. That is Drs. Hanley, Yaszemski, Haines, and Evans. There are no abstentions....

Ms. Moore challenges the sponsor's failure to comply unconditionally with these three conditions on the approval of the PMA. The sponsor, Covidien – Tyco Healthcare, failed to enroll sufficient numbers of patients in the post approval study of the infection rates among users of the product, and the study seems not to have collected any data for analysis yet. Data which is recorded in the serious adverse effect reports which were made available to her by the agency long after the court dismissed her lawsuit (which the agency has not confirmed to her that it has made all of the reports available, or explained to her how the reports can be identified by so-called unique identifiers as a discrete event which is not the subject of another *"duplicate"* or similar report) proves that there may be a very harmful interaction between the swelling of the product and the swelling of substances such as Gelfoam® which are sometimes used in the same surgery which was never discussed in the PMA.[1] Therefore this interaction is not addressed in the product labeling and/or package insert. If the agency will investigate this heretofore undisclosed risk, it may cause the agency to strengthen or revise the labeling and/or package insert.

Finally, Ms. Moore also challenges recent false advertising by the sponsor which misrepresents the function of the blue dye in the product which is supposed to retain its blue color for fourteen days after the surgery as a tool for diagnosis after re-operation. Contrary to the representation made in the PMA, the sponsor now advertises that the product loses its blue color and becomes clear instantly after application in the body.

3. THE PANEL'S REASONS FOR REVISING THE LABELING OR PACKAGE INSERT AS CONTAINED IN THE SPONSOR'S PMA APPLICATION

The Neurological Panel to the Medical Devices Advisory Committee recommended a change or revision to the label or package insert approved in the PMA package submitted by the sponsor. It was one of three conditions of the approval of the PMA for the product, as summarized briefly in these few pages from the Transcript of the May 14, 2009 meeting of the Panel in Gaithersburg, Maryland:

<<<Transcript 185:1 – 187:6>>>

DR. HAINES: I would propose that the labeling should include a statement that no difference in the long-term prevention of CSF leakage has been demonstrated, and that usual standard diligence in wound closure should be carried out when the device is used.

DR. BATJER: Thank you.

DR. HANLEY: Second.

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[1] FDA, Public Health Notification, April 2, 2004, *"Paralysis from Absorbable Hemostatic Agent." Exhibit C.*

DR. BATJER: Is there discussion on that condition? Or, sorry, is there a second?

DR. HANLEY: Second.

DR. BATJER: Dr. Hanley, thank you. Is there discussion? No response.)

DR. BATJER: Mr. Melkerson, could you read that again? Or do you have it or -- I'm sorry. Yes, please.

DR. HUDSON: So you propose that the labeling should include a statement to the effect that there was no difference identified in the prevention of CSF leak, long-term -- prevention of long-term CSF leak; that that has not been demonstrated and that standard diligence in wound closure techniques should be carried out when the device is used.

DR. BATJER: Dr. Spindell, we'll make a brief discussion if anybody has points.

DR. SPINDELL: I don't know. Are we allowed to be in this discussion, since it's the Panel vote?

DR. BATJER: They're non-voting, but can they discuss?

MR. MELKERSON: You wait until after. As far as the discussion of the motion discussion, you can invite them.

DR. SPINDELL: He can invite them. I agree with those recommendations.

MS. DALRYMPLE: Yeah, I agree also.

DR. HAINES: Agree.

DR. BATJER: Dr. Hanley.

DR. HANLEY: Agree.

DR. BATJER: Dr. Yaszemski.

DR. YASZEMSKI: Agree.

DR. BATJER: Dr. Evans is in support, as am I. We will now vote on that first condition. That basically states that the practitioners will be informed that there's no clear difference in long-term outcome and that

we are recommending diligence in routine wound management. All in favor.

MR. MELKERSON: By a show of hands.

DR. YASZEMSKI: Dr. Yaszemski, is your hand up?

DR. YASZEMSKI: Yes, it is.

DR. BATJER: Thank you. The names of those voting in affirmative are Drs. Hanley, Yaszemski, Haines and Evans. That is unanimous."

On the agency's website, Supplement S007 to the PMA submitted to the agency on July 20, 2011 and approved by the agency on August 18, 2011 is described as a revision to the label as *"[a]pproval for a modification to the instructions for use to instruct the surgeon in the best practices in applying the sealant."* It may have been the intent of the sponsor to submit this revision to the label to comply with the Panel's Recommendation.

But even if the agency approves this revision to the labeling as complying with the Panel's recommendation, the agency must still determine in the light of Ms. Moore's first-time disclosures of previously omitted risks in the PMA, as discussed *infra*, whether or not the Panel or Advisory Committee would now find that this additional information about the risks of using the product requires additional revisions to the label and/or package insert needed to protect the public health.

Especially, Ms. Moore's case was mentioned in the package insert as a revision surgery that should never be considered appropriate for the use of the product. Yet the sponsor did not highlight this *"never use"* warning in the sort of *"black box"* that the agency reserves for these kinds of hazards with respect to pharmaceutical preparations. The agency must now consider whether it should require its first ever *"black box"* warning for a medical device for this hazard.

4. THE RISK PROFILE OF THE SPINAL SEALANT THAT THE SPONSOR DID NOT INCORPORATE IN THE LABELING AND/OR PACKAGE INSERT AND THAT IT DID NOT ADDRESS IN THE INVESTIGATOR'S BROCHURE OR THE PROTOCOL FOR THE CLINICAL STUDY

The administrator makes the Product as he mixes two solutions of trilysine amine (blue colored) and polyethyelene glycol (clear) together. The Product is a cross-linked hydrogel polymer, which begins to swell in volume the instant that it is applied therapeutically. This behavior is by design. The polymer swells by as much as fifty percent (50%) of the original volume after mixed together and cross-linked.

The PMA disclosed the swelling behavior. The investigator's brochure, and the final label and package insert approved in the PMA warned against application of an excessive amount of the device in or near confined bony spaces surrounding the spinal

column where the swelling of the product could damage nerve roots and peripheral nerves by compressing of the nerve roots and nerves against bones. The Panel of the Medical Devices Advisory Committee approved this sponsor-submitted warning against use of, or runoff of excess applied product to; confined bony spaces surrounding the *dura mater* and spinal *"gutters."*

<<<Transcript pp. 164- 65 of the May 14, 2009 meeting of the Neurological Devices Panel>>>

> *"LT. NGATHA: Question 5. Labeling.*
>
> *The potential amount of swelling (e.g., less than 200 percent) 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 postoperative 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."*

This swelling after use in the body was also a concern in the approval of the PMA for the Duraseal® Cranial Sealant (PMA #40034). But it assumed to be a more important concern in the labeling and instructions for use of the product than it was for the Cranial Sealant. The surgeon's view of the nerve roots and nerves in the confined bony spaces and spinal gutters is occluded by the narrow configuration of the small confined bony spaces.

Some hemostatic agents which are used in conjunction with repairs of durotomies, most notably Gelfoam® (in either of their alternate formulations - powder or gel), also are designed to swell as much as fifty percent (50%) by volume and weight after application in the body. This must be the reason that the product's sponsor included a precaution to avoid use of the product concurrently with other non-autologous agents in the same surgery. The reason for this precaution is not clearly stated in the PMA. Presumably the sponsor considered that the swelling of Gelfoam® when used together with the product could exponentially increase the risk of compression of peripheral nerves and/or nerve roots from swelling agents and sealants, and therefore, greatly increase the potential damage to these nerves and nerve roots. Therefore, Ms. Moore respectfully requests that the agency ask the sponsor to clarify the purpose of this precaution in the labeling and/or package insert, and to include it in a *"black box"* warning.

The surgeon who operated on Ms. Moore also used Gelfoam® as a hemostatic agent in her surgery, although the labeling and the investigator's brochure for the product

contradicted the concurrent use of this agent. The surgeon testified in his deposition under oath that when he re-operated on Ms. Moore on September 15, 2006, nine days after her surgery in which the product was applied in the clinical trial, that the product appeared to be *"clear"* and lack blue color. Since the sponsor represented in materials presented with the PMA that the product retains its blue dye and therefore its blue color for fourteen days after surgery as a safety feature, the surgeon's observation of *"clear"* product means either that the product malfunctioned, or that the surgeon was looking at the clear Gelfoam® on the *dura mater* and not the product.[2]

If the surgeon was looking at the Gelfoam® instead of the product, the Gelfoam® *as it expanded after the surgery in situ* must have *"pushed"* or forced the product off of, and away from, the *dura mater* into the gutters of the spine and in confined bony spaces. Did the expanding Gelfoam® *"kick"* the expanding product off of the *dura mater* into the spinal gutters and confined bony spaces surrounding the spine where it compressed and injured her spinal nerve roots and peripheral spinal nerves? The answer to this question could have been (and may yet still be) provided by a medical expert opinion witness working with, among other data, the record of experience with the product contained in the serious adverse effect reports and complaint files of the sponsor and health care providers.[3]

Ms. Moore requested all serious adverse effect reports and complaints made by health care providers and patients to the agency or to the sponsor which the sponsor provided to the agency, in a Freedom of Information Act *("FOIA")* request to the agency (and Ms. Moore made this same request to the agency twice before the federal district court dismissed her case on summary judgment). And of course the agency has a firm rule of not disclosing these serious adverse effect reports and patient and health care provider complaints during clinical trials of pharmaceuticals and medical devices, as discussed *supra*. But if there were many such reports of harmful interaction, the agency should expect that these reports would be disclosed and discussed in the PMA. Despite that there were several such reports of harmful interaction between these other non-autologous agents and the product, the sponsor never discussed this risk in the PMA. Consequently the agency, the medical profession and the panelists on May 14, 2009 seem not to have considered this possible interaction when they approved the PMA because it is not discussed in the transcript of that meeting.

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[2] In re-examining the exact claim made for safety of the blue dye's persistence, Petitioner did not retrieve the exact claim made for the petition, but she presents an exhibit proving that the *"bluish color"* was present in a few patients four weeks after implantation of the product. *Exhibit D.*

[3] Petitioner notes that a patient in MFR 3003157248-2010-001 experienced paralysis due to hematoma where the Duraseal® appeared to be a clear gelatin-like substance upon reoperation. This sounds very much like the Petitioner's injury and her re-operation. *Exhibit E, infra at fn. 4.*

Petitioner discovered at least fifteen of these case reports in number in the reports provided to her by the agency, and there may be more reports.[4] This is because the agency may have permanently exempted some of these reports from the database due to its consideration that either exemption 4 or exemption 6 of the FOIA requires the reports to be confidential always. Certainly if the Petitioner were permitted access to the sponsor's complaint files, there would be more such reports in those files that were not fully investigated or that were determined to be not "serious" because of inadequate information. Several reports in these adverse effect reports which the agency began to make available to Petitioner beginning in November of 2010, describe a harmful interaction upon re-operation such that the surgeon reported a visible transformation of either the Duragen® or the Gelfoam® and/or the product.

As Petitioner investigated, she learned that the MAUDE database of the agency contained some reports of injuries associated with use of the product that were not provided to her by the FOIA office of the Center for Devices and Radiological Health of the agency in its response to her request delivered to her counselor at law by mail in November of 2010.[5] In the reports in the MAUDE database were several reports of severe damages to neurological function to patients upon whom the product was used in their surgeries (as opposed to reports of the chemical transformation and malfunction of the product). Notably, in several of these reports of the latter type, the product was used concurrently with the hemostatic agents Duragen® or Gelfoam®.

In two cases discussed by the neurosurgeon Dr. Nancy Epstein, of New Hyde Park, New York, in her peer-reviewed entitled *"Dural Repair with Four Spinal Sealants: Focused Review of the Manufacturer's Inserts and the Current Literature," The Spine Journal 10 (2010) 1065 – 68*, paralysis resulted to the two patients on whom the product was used, immediately after surgery or a few weeks after surgery. The Petitioner has reviewed the available MDR reports on the agency website and has found two reports corresponding to the timing of the reports discussed by Dr. Epstein and the magnitude

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4 The identifiers for some of these reports are as follows: MFR 3003157248-2006-00002, MFR 3003157248-2007-00034, MFR 3003157248-2007-00038, MFR 3003157248-2007-00055, MFR 3003157248-2008-00004, MFR 3003157248-2008-00005, MFR 3003157248-2008-00006, MFR 3003157248-2008-00019, MFR 3003157248-2008-00023, MFR 3003157248-2009-00001, MFR 3003157248-2009-00002, MFR 3003157248-2010-00002, MFR 3003157248-2010-00004. *Exhibit E.* Some of the reports omitted the 'MFR no.', eg., a report received on September 10, 2008, for an event described by user on October 31, 2008, the first sentence of the description is: *"Using Duraseal (ready made dural sealant) with Duraseal (dural graft matrix) has created problems with a couple of our patients. . . ."* Another such report was received on March 26, 2010, for an event described by user on March 30, 2010, the first sentence is: *"Patient underwent right side discectomy." Ibid.* Some of these reports appear to have been submitted to the agency for the Cranial Sealant.

5 MAUDE ## 787641, 743549, 762830, 740375, 706420, 879811, 886227, 886228, 886229, 886231, 900144, 903844, 953592, 974356, 997493, 1001938, 1100821, 1216083, 1225134, 1359416, 1407939, 1413549, and 1593599.

of the symptoms that she reports.[6] Petitioner notes that in one of these two reports the product was applied concurrently with Gelfoam®, and Petitioner has found similar reports in the MDR reports provided to her.[7]

Furthermore, with the assistance of the information in the recently serious adverse effect and MDR reports, there is an obvious enhanced risk of damage to neurological function of the spine because of product pushed off or run off to the gutters or confined bony spaces surrounding the spine, when combined with simultaneous administration of Gelfoam® or other non-autologous agents also intended to swell after application in the body by design. The Petitioner recommends that the agency investigate the risk of this kind of injury from the simultaneous use of these non-autologous sealants or agents to confirm the increase in the risk factor. This is the kind of risk unknown to the medical profession when the PMA was approved, that the agency may find it necessary to disclose in the labeling and/or package insert, in the sort of strong precaution made very conspicuous in a *"black box"* type of warning.

5. THE FALSE ADVERTISING OF THE "RETENTION OF THE BLUE DYE" SAFETY FEATURE OF THE PRODUCT

As discussed supra at B.4., the retention of the blue color of the dye to the product for fourteen days after surgery is an important safety feature of the Product. It is a diagnostic tool which assists the surgeon who must reoperate on the patient to determine whether the Product was effective to seal the *dura mater*, and to prevent a leak of CSF. It also assists the surgeon to determine whether the Product malfunctioned because it was applied to the wrong body part, or whether another agent or sealant used after surgery interacted with it in a harmful manner.

The surgeon who operated on Ms. Moore on September 6, 2006 and reoperated on her on September 15, 2006 to perform the irrigation and drainage, commented strangely enough in his deposition in the course of Ms. Moore's lawsuit that the Product appeared to be colorless and clear to him on September 15, although this occurred only nine days after surgery and the sponsor wrote in the PMA application that the product was designed to lose all of its blue dye and become colorless and clear only after fourteen days after surgery. As mentioned in the context of the earlier discussion, if the Product did not malfunction and the blue color had not turned to clear, then it seems that the surgeon might have been looking at the Gelfoam® as the *"clear"*substance which he saw over the *dura mater*.

Ms. Moore has discovered promotional literature intended for comprehension by health care providers, published by the sponsor which states that the blue dye of the product fades instantly upon application and the blue color is not retained after application. *Exhibit G.* If this is true of the product today, then the sponsor has eliminated an important safety feature of the product which was prominently disclosed and discussed

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[6] Maude ## 974356, 1593599. *Exhibit F.*

[7] Maude #974356; fn. 2, *supra, passim.*

in the PMA. *See fn.2, supra.* And certainly, there is no supplement to the PMA since its approval concerning the persistence of the blue dye to the knowledge of Petitioner. This brochure published by the sponsor appears to be false advertising which minimizes or conceals an important safety feature of the product that surgeons and others who are involved with administration of the product should know and understand.

6. THE IMPORTANCE OF COMPLETING THE CONDITION OF POST MARKETING APPROVAL STUDIES BY CAUSING THE SPONSOR TO FILL THE ENROLLMENT IN THE STUDY AND CLOSE ENROLLMENT

The clinical study was a single-armed study which designed to test a measure of short-term effectiveness of the product, namely, the effectiveness of the device to stop leakage of the cerebrospinal fluid from the *dura mater* because of either an intentional or incidental durotomy during the operation. A patient was admitted to the study, if upon performance of a Valsalva maneuver by the anesthesiologist after the surgeon had used standard of care methods to sew up or to repair the durotomy caused by the surgery. Admittedly this event did not test the null hypothesis of the effectiveness of the Product to stop a long term or more serious leak of cerebrospinal fluid because of an unrepaired durotomy after surgery. The leaking of fluid after a Valsalva maneuver was simply a proxy for the measurement of the long term leak of cerebrospinal fluid because of an unrepaired durotomy after surgery.

The Panel's issue with the data from the clinical study was that incidence of deep wound infection in the treatment arm of the clinical study was greater than it was in the nontreatment arm of the study. The Panel noted this at page 82 of the Transcript of the May 14, 2009 meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee: *"[a]nd also the percentage of patients with deep surgical site infection is also higher in DuraSeal group."*

The sponsor's presenters at the May 14, 2009 meeting admitted that the size of the clinical study's sample was too small to evaluate the rate of deep wound infections in the use of Duraseal® Product. *Testimony of Xavier Lefebvre, Ph.D., Vice-President of Clinical Affairs, Covidien, Transcript 122:10 -19.* For these reasons, the Advisory Committee decided to require that a follow up study of the infection rates be performed after approval.

Since the null hypothesis of a leakage of cerebrospinal fluid was not tested in the clinical study and the size of the sample in the clinical study was small, the Panel judged that the data from the clinical study was insufficiently reliable to prove the infection rates involved in the use of the product. The Panel deemed the data too unreliable to permit it to be published on the label or package insert for the device, and found that the sponsor would be required to complete a post-approval study of infection rates in the

long term to have infection rates sufficiently reliable to publish in the label or package insert for product.

The Panel debated whether or the post approval study should be a true prospective cohort study, that is, a true controlled study. Three of the voting members abstained from voting on, or rejected an absolute requirement of a controlled study. The fourth voting member of the Panel voted for controls. The Panel finally adopted a resolution recommending a post approval study of infection rates with the design of the study subject to the *"flexible"* judgment of the agency.

The following excerpt from the transcript of the May 14, 2009 meeting summarizes the criteria discussed and considered by the Panel at the Gaithersburg meeting for the post approval study of infection rates:

<<<Transcript 203 – 06>>>:

> *"DR. BATJER: Thank you. Any further discussion in support of that recommendation to include a control?*
>
> *DR. EVANS: I think if we leave that open so that wise people can decide what kind of control group to construct, that's fine.*
>
> *DR. BATJER: Dr. Hanley.*
>
> *DR. HANLEY: Well, I prefer the proposal as it was initially stated by Dr. Haines, which leaves all of that up to the FDA. So the statement -- he can restate his proposal. I'm not against the control group, but I'm certainly not for one. I'm for the appropriate accumulation of valid information that leads us to understand better long-term infection rates and spinal fluid leakage rates.*
>
> *DR. BATJER: We have a motion seconded now, and we were in the process of a vote. One possibility would be to -- could I ask for a revote or a motion to overturn the motion?*
>
> *MR. MELKERSON: You should finish the vote as it was proposed. And then, if you need to modify it, you can modify it.*
>
> *DR. BATJER: Then we have -- essentially we have a vote of three to one in favor of the motion.*
>
> *DR. EVANS: I'm assuming I'm the one you're referring to.*
>
> *UNIDENTIFIED SPEAKER 1: We didn't vote, we didn't vote.*
>
> *UNIDENTIFIED SPEAKER 2: We did.*

UNIDENTIFIED SPEAKER 1: We did? I did?

DR. BATJER: We did.

UNIDENTIFIED SPEAKER 2: You raised your hand.

DR. BATJER: We did.

DR. EVANS: Let me just clarify the motion. The motion is for a post-approval study.

DR. BATJER: Correct.

DR. EVANS: And what further clarification beyond that?

DR. BATJER: That the key issues to be looked at would be CSF leak and infection. It would be a 90-day study. And, Steve, your original language did not include a control group.

DR. HAINES: It said nothing –

DR. BATJER: It did not.

DR. HAINES: -- pro or con.

DR. EVANS: It didn't address it. It didn't address it.

(Simultaneous comments.)

DR. EVANS: I'm in favor that motion. I think we should go stronger, but I'm in favor of that motion.

DR. BATJER: But leaving flexibility –

DR. EVANS: Yes.

DR. BATJER: -- to the FDA. That said, the motion has been seconded and now voted with all four panelists in support of that third condition. Do you have a reasonable sense of that motion?

MR. MELKERSON: I think we'll mull it over, but thank you.

DR. BATJER: We do recommend a PAS. It would have those three elements with flexibility for the FDA....."

It is more than four years after the Panel voted to require a post-approval study of infection rates. It is almost three years after the agency approved supplement S001 on June 29, 2010 to the PMA application approving a design and a method for the post-approval study of infection rates. But as of the date of this Petition, the sponsor of the Product – Tyco Healthcare/Covidien – has not yet enrolled sufficient numbers of subjects in the study to begin to collect data from the subjects and to analyze the results.

And if the sponsor doesn't close enrollment in the study or the agency does not compel the sponsor to close the enrollment in the study and to begin to analyze the data from the subjects, Ms. Moore submits that the agency should suspend use of the product until the enrollment in the post-approval study of infection rates is completed and the study is on track to be completed within one year. Alternatively, the agency could require the sponsor of Product to publish the results of the pre-PMA approval clinical study on the product label or in the package insert confirming that the was a higher rate of deep wound infection in the treatment group than in the control group of the clinical study.

7. THE AGENCY MUST INVESTIGATE THE ISSUES RAISED IN THIS PETITION NOW

The agency must accept this petition and investigate the carefulness of application of, and the labeling and package inserts for this product. Ms. Moore was unfairly denied an opportunity in the courts to argue that she did not receive proper informed consent for enrollment in the study, and that the surgeon was not properly instructed in the use of the Product because of the deliberate suppression of the information concerning the risk of use of the product by the sponsor. She seeks the reporter's identities and contact information in *Exhibits D and E*, and any reporters' identities and contact information for any Freedom of Information Act information provided to her

Because Ms. Moore knows that the sponsor of the experimental product suppressed information under the Freedom of Information Act as to the risks involved in use of an experimental medical device in clinical trials, the agency must investigate and examine the claim that the administration of the product with the Gelfoam® causes a two to three times the increase in the already increased risk of using the product in and around the gutters of the spine and the confined bony spaces adjacent to the spine where the compressive forces of the product and the Gelfoam® may cause harm. The agency must investigate and examine the facts to know whether or not this neglected side-effect of the use of the product with other non-autologous sealing and hemostatic agents should be warned against in a kind of *"black box"* conspicuous warning statement on the label or package insert. The agency should investigate and examine whether or not the precaution against use of the product with other non-autologous agents should be discussed on the package insert and/or labeling in connection with the warning against improperly applying excess product which *"runs off"* into the confined bony spaces and gutters of the spine. And of course, the agency should also investigate the nature of the toxic or harmful interaction between the product and Gelfoam® and Duragen®.

Especially, Ms. Moore's case was mentioned in the package insert as a revision surgery that should never be considered appropriate for the use of the product. Yet the sponsor did not highlight this *"never use"* warning in the sort of *"black box"* that the agency reserves for these kinds of hazards with respect to pharmaceutical preparations. The agency must now consider whether it should require its first ever *"black box"* warning for a medical device for this unique hazard.

Ms. Moore has already been injured by the product. If the agency acts on her petition, it cannot return her health to the *status quo ante* or undo her paralysis. But if the agency grants her petition, and re-examines the data and considers her claim for stronger warnings and precautions in the product label and the package insert, and votes to require stronger warnings, the population as a whole may benefit from her experience and become informed in the true risks of use of product.

C. ENVIRONMENTAL IMPACT

This petition is categorically exempt from environmental review under the National Environmental Policy Act, *42 U.S.C. §4321 et seq.* and *21 C.F.R. §§25.30(h), 25.30(k)* and *25.34(a)*.

D. ECONOMIC IMPACT

(The following information is to be submitted only when requested by the Commissioner following review of the petition: A statement of the effect of requested action on: (1) Cost (and price) increases to industry, government, and consumers; (2) productivity of wage earners, businesses, or government; (3) competition; (4) supplies of important materials, products, or services; (5) employment; and (6) energy supply or demand.)

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the petition.

(Signature) Jeffrey G Thomas

(Name of petitioner) for Marteen Moore

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