

ETHICON, INC.

a *Johnson & Johnson* company

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Mr. Mark Melkerson
Acting Director, DGRND
Office of Device Evaluation
Food and Drug Administration
HFZ-410; Rm 350C
9200 Corporate Blvd.
Rockville, MD 20850

Re: Proposed reclassification of absorbable hemostats

Dear Mr. Melkerson:

As you know, the General and Plastic Surgery Devices Panel met in July 2002, and again in July 2003, to discuss the Food and Drug Administration's (FDA's) proposed reclassification of absorbable hemostats, 21 C.F.R. § 878.4490, from Class III to Class II. ETHICON, a manufacturer and distributor of absorbable hemostats, attended and presented at both meetings. At the 2003 meeting, FDA proposed a regulatory identification of absorbable hemostats, and discussed various special controls the agency stated would be adequate to address the risks posed by these products.

Since these discussions, ETHICON has obtained new information, which is relevant to the reclassification process. We reviewed published market research and other information to identify high volume users of absorbable hemostats. We then initiated a study of the use by surgical specialty. We surveyed over 400 surgeons in seven surgical specialties and found there were high volume uses of these products in cardiovascular, vascular, neurosurgery, orthopedic (spine) and ENT surgery. This finding is important because these specialties were not consulted during the FDA

advisory panel process in 2002 and 2003, and these uses present different kinds of risks than general, plastic and reconstructive surgery, which were the focus of the panel meetings. In addition, under our sponsorship, a group of experts in different surgical fields (trauma, vascular, transplant, cardiac, urology, neurosurgery and pathology) met and reviewed a number of topics relating to reclassification. They raised a number of concerns, discussed below, that did not arise during the FDA advisory panel discussions. In accord with 21 C.F.R § 14.80(b)(i), we strongly encourage FDA to consult with representative and diverse users of these products before proceeding with a proposed reclassification and special controls guidance. By focusing on general, plastic and reconstructive surgical applications, the proposed special controls guidance will fail to reasonably ensure the safety and effectiveness of absorbable hemostats in a significant proportion of the procedures in which they are used.

We would also like to comment on FDA's proposed definition for absorbable hemostats, and highlight additional considerations, which ETHICON believes must be addressed in a special controls guidance document for absorbable hemostats, should these products be reclassified, to ensure the requisite "reasonable assurance of safety and effectiveness."

For the reasons stated at both panel meetings, ETHICON continues to believe that reclassification should not occur. The safety record that the agency cited and the 2003 panel relied upon exists precisely because of the regulatory requirements imposed due to the Class III status of these products. No set of special controls will be sufficient to ensure that this level of safety and effectiveness will be maintained. However, if the agency nevertheless decides to pursue reclassification, we believe these additional elements need to be added to the special controls to ensure that safety risks are minimized.

I. Scope of Proposed Reclassification Category

As presented to the 2003 panel, FDA's proposed classification regulation for absorbable hemostats read:

§ 878.4490 – Absorbable hemostatic agent, surgical

(a) Identification. An absorbable hemostatic agent, surgical is an absorbable device intended to produce hemostasis by accelerating the clotting process of blood during surgical procedures.

(b) Classification. Class II (special controls). The special control for the class II device is FDA's "Class II Special Controls Guidance Document: Absorbable Hemostatic Agent, Surgical Device; Draft Guidance for Industry and FDA."

ETHICON believes this definition is too inclusive, and needs to be revised to clarify that hemostatic agents composed of novel materials, and/or produced by novel processes, remain in Class III, subject to premarket review and approval through the premarket approval (PMA) process.

In the briefing materials provided to the 2003 Panel, FDA indicated that the absorbable hemostats for which it has extensive safety and efficacy data are those consisting of gelatin, oxidized cellulose, regenerated oxidized cellulose, and microfibrillar collagen, Memorandum Regarding the Reclassification of Absorbable Hemostatic Agent and Dressing Devices from Regulatory Class III to Class II (hereinafter, “2003 Panel Memo”) p.8,^{1[1]}. FDA noted that these products have different mechanisms of action, 2003 Panel Memo p. 8, and acknowledged, “...the manufacture of these devices can be complex.” 2003 Panel Memo, p. 9. Further, in its outline of proposed special controls addressing “Material and Performance Characterization,” the agency observed that “any modifications from standard techniques could [a]ffect time to hemostasis, absorption properties or other important characteristic[s] of the device.” 2003 Panel Memo, p.12. Yet FDA proposed in its special controls outline that the manufacturing process for a hemostatic agent needed only to be “briefly described and compared to standard methods.” 2003 Panel Memo, p.12. The products that fell within this classification could obtain marketing clearance based on limited clinical data.

As drafted, the proposed regulatory identification will allow hemostatic agents formulated from new materials, and by different processes, to be marketed without the critical FDA review and evaluation that is afforded only through the PMA process. New types of materials, processes, and conditions could affect safety and efficacy in ways that may only be evident in clinical use. Requiring only a “brief description” of the manufacturing process in the 510(k), and minimal or no clinical data, is inadequate to provide reasonable assurance of safety and effectiveness for a product composed of novel materials and/or manufactured by novel processes. In the 510(k) process, FDA does not conduct a pre-approval inspection of the manufacturing facilities and processes, any of which could significantly impact the product’s performance. Indeed, FDA is barred from considering good manufacturing practice compliance in a 510(k) notice. 21 U.S.C. § 360e(f)(5). Thus, products with novel manufacturing methods – for example, an oxidized regenerated cellulose product manufactured with a different oxidizing agent or reaction condition - would undergo minimal scrutiny unless these products are in Class III. Therefore, such products should remain in Class III.

FDA should revise the proposed regulatory identification of a Class II hemostatic agent to encompass only those types of products and materials with which the agency currently has significant experience. For example, the identification might clarify that the

^{1[1]} FDA also listed combination products containing collagen and thrombin.

device is composed of materials that have been demonstrated to be safe and effective in controlled clinical trials, and list these materials. FDA should also require a more detailed description of the manufacturing process in any 510(k) notification, including a listing and description of all materials, specifications, and test methods.

II. Animal Studies

FDA proposed that the animal studies conducted to support a general use indication for a hemostatic agent evaluate the time to hemostasis, time to resorption of the hemostatic agent, and any complications, including infection, hematoma, coagulopathy, and increased wound healing. 2003 Panel Memo, p. 14. ETHICON agrees that these are important endpoints to be assessed. However, there are additional endpoints we believe are critical, and need to be evaluated in animal studies. FDA should also incorporate each of these endpoints in its special controls guidance:

- **Rate of re-bleeding:** Variability in clot strength or durability may result in re-bleeding. Re-bleeding is a significant concern, particularly in enclosed spaces, such as cranium, spine or sinus, because of the increased pressure that may result.
- **Immunologic response:** Potential immunologic response is important, and can vary based on materials or processing/manufacturing conditions. Clinically relevant considerations should include the potential for development of antibodies to the product, as well as agents which may be co-administered with the product (e.g., thrombin), and related coagulation factors (e.g., Factor Va). Animal tests for immune sensitization should be conducted with the proposed product alone and in conjunction with any co-administered coagulants (e.g., thrombin).
- The special controls document should clearly state that the animal studies must comply with the Good Laboratory Practice (GLP) regulations, 21 C.F.R. Part 58, and that applicants must certify to GLP compliance.

We also agree with the agency that “animal testing [should] include arteriolar, venous and capillary bleeding from various tissues and organs.” 2003 Panel Memo, p.13. Among the tissues and organs relevant to a general use indication, and which should be specifically referenced in the special controls guidance, are the spleen, liver, and vascular retroperitoneal tissues.

III. Clinical Studies

FDA’s proposed special controls outline suggests that clinical studies “will not be needed for most absorbable hemostatic agent devices” for general use. 2003 Panel

Memo, p.14. ETHICON disagrees. FDA should not issue 510(k) clearances for hemostatic agents without requiring at least some clinical data, and, depending on the proposed indication, a larger-scale study may be needed.

ETHICON concurs that appropriate animal models can provide substantial information on some product characteristics, such as time to hemostasis, time to resorption, and many potential complications. Animal models, however, simply cannot adequately reflect the relevant human patient population in which absorbable hemostatic agents are used. Numerous, frequently encountered patient disease states, co-morbidities, and compromised conditions such as aging and poor nutrition can all affect hemostasis. These disease states and conditions are not represented in animal studies. Animal models cannot predict, for example, how a hemostatic agent will work for a cancer patient in a catabolic state, or in a patient taking multiple drugs that may affect blood pressure, platelet function, etc. During the expert discussion sponsored by ETHICON, a prominent vascular surgeon expressed concern about the growing number of patients taking anti-thrombotic drugs such as Plavix, aspirin, and coumadin, often in combination. This surgeon wanted to know how new absorbable hemostatic products would perform in such patients. Other surgeons echoed the need for data on drug interactions, preferably from clinical studies.

Given the pharmacologic, surgical and medical complexities associated with the use of these products, ETHICON believes it is essential for FDA to require at least some clinical data in relevant, expected patient populations and disease states. Such studies should be of adequate size and sensitivity to ensure clinical comparability by valid statistical methods. The studies should evaluate time to hemostasis, re-bleeding rates, hematoma formation, reoperation rates, immunological response to the product and any concurrently administered coagulants (e.g., thrombin), foreign body reaction, infection, and systemic effects on coagulation, as well as monitor for other types of adverse events. Animal data from one – or even two – well-characterized species of healthy animal will not be sufficient to provide adequate assurances of safety and effectiveness in a heterogeneous human surgical population.

IV. Specific Indications for Use

At the 2003 panel meeting, there was discussion suggesting that specific intended uses for hemostatic agents, e.g., neurologic, urologic, and ophthalmic, should be explicitly excluded from the labeled indications, unless adequate data are submitted establishing equivalent safety and efficacy for such uses compared to a predicate that is also labeled for such uses. In addition, FDA's proposed special controls outline stated in the "Clinical Testing," section: "Safety and effectiveness should be demonstrated for each surgical specialty for which the device is to be indicated beyond the general surgery indication."

ETHICON concurs that particular uses of hemostatic agents require specially-tailored supporting data. For such uses – neural, urinary tract, and ophthalmic – there are unique concerns for which different types of biocompatibility and animal and clinical performance data are essential. Below are specific recommendations for the types of animal and clinical data FDA should require supporting clearance for these indications.

A. Neural Use

Neural tissues are especially sensitive, and damage to such tissues is often irreversible. Thus, a hemostatic agent labeled for neural use should be subject to higher standards of pyrogenicity and biocompatibility. Additionally, the CNS anatomy and serious consequences of post-operative hemorrhage require specialized studies of initial hemostasis and rebleeding. FDA should identify the specific test method and minimum standard for pyrogenicity in its special controls guidance. In addition, animal studies should be done to assess neurotoxicology and neural tissue response.

With regard to biocompatibility, we would note that the FDA Bluebook Memorandum concerning the application of ISO-10993 to medical devices states:

Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity may be necessary for some devices. For example, a neurological device with direct contact with brain parenchyma and cerebrospinal fluid (CSR) may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb CSF. The specific clinical application and the materials used in the manufacture of the new device determine which tests are appropriate.

In our view, any hemostatic agent labeled for neural use needs to be supported by clinical data. FDA has issued a Public Health Notification for hemostatic agents warning about swelling of materials when used in confined spaces or near bony foramina through which nerves or blood vessels flow. (<http://www.fda.gov/cdrh/safety/040204-hemostatics.pdf>.) Swelling can result in compression of nerves and vessels, resulting in paralysis or loss of function. Oozing and re-bleeding can cause similar problems. Neurosurgeons have special concern for oozing and re-bleeding in the closed cranial space. FDA's special controls guidance should contain requirements for clinical evaluation of re-bleeding rates, and the effects of product swelling. Required clinical studies evaluating neural use should also include monitoring for febrile reactions and other effects on neurological function.

B. Urologic Use

Absorbable hemostats to be used in urologic settings also need to be supported by clinical data. These products should be evaluated for obstructive or calculogenic (stone forming) potential when used in kidney or bladder surgery. The potential effects of contact with urine should also be evaluated – in particular, tissue reaction potential and rate of absorption of the hemostatic agent.

C. Ophthalmic Use

Concerns about ophthalmic use are similar to the concerns noted above for neural use – in particular, the increased sensitivity of ophthalmic tissue, and the use of hemostatic agents in confined spaces where increased pressure may cause damage. FDA should require appropriate animal studies and an adequate number of clinical evaluations.

D. Concerns About Off-Label Use

In an ideal world, physicians would not use a product for an indication that has been explicitly excluded from the product's labeling based on the absence of safety and effectiveness information supporting such use. As the agency well knows, however, that is not what happens in practice. Nevertheless, to the extent possible, physicians need to be made aware of the distinctions between various brands of high volume products like hemostatic agents. Decisions on which brand of a high volume product to use, especially in the surgical suite, are often made by the hospital staff, and not the surgeon. Cost plays a significant role in such decisions and if reclassification occurs, some hospitals are likely to purchase bulk quantities of one or two brands with only general indications, rather than different products indicated for specific uses. All of these factors make it likely that a general use hemostatic agent, with labeled exclusions for neural, urinary tract, or ophthalmic use, will be used for those indications even though not proven for such uses, putting patients at risk.

Thus, it is essential that the labeling for hemostatic products clearly, prominently, and explicitly state the uses for which the product is indicated, and the uses for which it is not cleared. In addition, FDA should utilize its authority under 21 U.S.C. § 330c(i)(E) and find that there is a reasonable likelihood that the device will be used for an unlabeled intended use, which could cause harm.

In addition to labeling, we believe that distributors of hemostats whose labeled indications are not as broad as other marketed hemostats be required to notify directors of surgery and OR officials in some additional way, e.g., on invoices and/or other direct communication, that the product labeling excludes certain identified indications, e.g., neurology.

V. Conclusion

Absorbable hemostatic products play a critical role in surgical procedures. The risks associated with these products include vascular and nerve compression, prolonged bleeding, rebleeding, hematoma formation, re-operation immunological response, foreign body reaction, infection and possible interactions with drugs and biologics on coagulation and immunogenicity. A hemostatic product that is not effective can result in irreversible, serious injury or death. As noted above, ETHICON continues to believe that special controls will not adequately ensure that absorbable hemostatic products are safe and effective. However, if FDA does decide to down-classify these products, it is imperative that the special controls be substantially tightened beyond what FDA has proposed. We therefore urge FDA to incorporate the special controls as set forth in this letter.

Sincerely,

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