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January 29, 2007

**BY HAND DELIVERY**

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane  
Room 1062 (HFA-305)  
Rockville, MD 20852

Re: Comments on the Reclassification Proposal and Draft Special Controls  
Guidance Document for Absorbable Hemostats (Dockets 2006N-0362 and  
2006D-0363)

On behalf of Ethicon, Inc. ("Ethicon"), the manufacturer or distributor of three FDA-approved absorbable hemostatic devices,<sup>1</sup> we appreciate this opportunity to comment on the agency's proposed reclassification of absorbable hemostats and the associated "Draft Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Absorbable Hemostatic Device" (hereinafter, "Draft Guidance"). Ethicon is well aware of FDA's mandate to apply the "least burdensome" approach in its regulation of medical devices. The Company is opposed, however, to the reclassification of absorbable hemostats as currently proposed. In particular, Ethicon is extremely concerned that the proposed regulatory definition and special controls are inadequate to ensure the safety and efficacy of such critical and widely used devices.<sup>2</sup> Ethicon further questions the legal

<sup>1</sup> Ethicon is the manufacturer of Surgicel (N12159) and Instat (P830079). Ethicon is the U.S. distributor for Surgifoam (P990004) (manufactured by Ferrosan A/S).

<sup>2</sup> As FDA acknowledges in the Draft Guidance at page 11, absorbable hemostats are "significant risk" devices subject to the full IDE requirements including prior agency approval of any proposed clinical studies.

**2006N-0362**

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sufficiency of the notice contained in the agency's proposed rulemaking document and of the associated public docket.<sup>3</sup>

Given the significant defects in and the magnitude of the issues raised by FDA's proposal, Ethicon believes that publication of a final rule and final guidance document that merely contain changes and corrections will be inadequate to meet Administrative Procedure Act ("APA") rulemaking requirements. Therefore, if FDA decides to proceed with reclassification, it should issue a corrected proposed rule and revised draft guidance for further comment. The agency should also consult publicly with an appropriate range of experts, industry, and other stakeholders on its revised special controls before implementing regulatory changes.

**I. There are Significant Deficiencies in the Notice of Proposed Rulemaking and Docket**

In the proposed reclassification notice,<sup>4</sup> FDA cited only two references: the now 4- and 3-year-old 2002 and 2003 transcripts of the General and Plastic Surgery Devices Panel meetings.<sup>5</sup> FDA did not identify, discuss, or place in the docket any of the materials provided to the panel members in preparation for these meetings, or prepared by FDA in connection with the meetings. Nor did FDA identify, discuss, or place in the docket any evaluation of new information that has emerged since these Panel meetings were held. Such omissions are significant because they impede the ability of interested parties to be fully aware of the relevant background information and to evaluate the data on which FDA is relying.

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<sup>3</sup> On December 21, based on deficiencies in the rulemaking notice and docket, Ethicon, through counsel, requested a 90-day extension of the comment period to allow interested parties a fair and adequate opportunity to identify and address information critical to the preparation of fully informed comments. As of the date of this comment, Ethicon has received no response.

<sup>4</sup> 71 Fed. Reg. 63,728, 63,732 (Oct. 31 2006).

<sup>5</sup> All citations to the 2002 and 2003 Panel Transcripts appearing within in these comments are to the electronic versions posted on FDA's website *available at* <http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3876t2.rtf> and <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3973t1.htm>.

For example, the briefing materials that FDA provided to the 2003 Panel (hereinafter “2003 Panel Memo” or “Panel Memo”) contained an outline and summary description of proposed special controls on which the Panel relied to recommend reclassification. The special controls that FDA described to the 2003 Panel differ in notable ways from the special controls FDA is now proposing. The agency has neither mentioned nor justified these differences in the proposed reclassification rule or the notice announcing the Draft Guidance. The differences are important, however, because the 2003 Panel based its recommendations on what FDA presented at the meeting – not on the currently proposed special controls. The 2003 Panel Memo makes clear that the 2002 Panel voted to defer any recommendation on reclassification “until the panel had the opportunity to review the proposed special controls guidance document.”<sup>6</sup> Moreover, the proposed reclassification notice confirms that the 2003 Panel’s recommendations were based in large part “on the information provided by FDA, the presentations to the panel by . . . FDA, [and] the “Panel’s deliberations” on such information. 71 Fed. Reg. at 63,730. Yet this key briefing document is not in the docket, and not readily available to the public. An interested party who wished to analyze and comment on this key document and how the current proposal departs from it would have a difficult time doing so.

In addition, the proposed reclassification notice states that FDA determined the risks to health presented by absorbable hemostatic devices “[a]fter considering the information in the panel’s recommendation, as well as the published literature and Medical Device Reports.” *Id.* The agency has not, however, identified the published literature or Medical Device Reports on which it relied. Assuming the agency prepared a report evaluating this information, that report is not in the docket. Nor are we aware of it having been made public. Interested parties cannot comment on an analysis that has not been released.

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<sup>6</sup> 2003 Panel Memo at 3, *available at* <http://www.fda.gov/ohrms/dockets/ac/03/briefing/3973b1.htm>.

Moreover, it is unclear from the Federal Register notice whether the agency reviewed or considered any of the more recent published literature or the MDRs that have been submitted for absorbable hemostats since the 2003 Panel meeting over three years ago.<sup>7</sup> Ethicon's recent search of the FDA on-line MAUDE database retrieved 41 additional MDR reports for absorbable hemostats dating from August 2003, after the 2003 Panel meeting, through September 2006, prior to FDA's publication of the proposed reclassification notice. For example, one of these reports, a Baxter Floseal MDR dated August 24, 2004 (MAUDE #4095894), describes life-threatening bleeding. In response, the company proposes to educate customers that the product cannot prevent post-operative bleeding. FDA has not placed in the docket or referenced a Public Health Notice it issued in April of 2004 concerning risk of paralysis from use of absorbable hemostatic agents in or near bony and neural spaces.<sup>8</sup>

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<sup>7</sup> This is in contrast to the 2003 Panel Meeting where FDA made a point of noting that it had reviewed the most current MDR data in preparation for the discussion:

I think what I'm pointing out to you here is what's been reported to the FDA, and when you consider that there probably have been millions of uses of these devices during this time, there is an amazingly small amount of what we call medical device reports which report problems with the device as perceived by those using them . . . . This list is complete up until June 13<sup>th</sup>, 2003, which is when I accessed the system to get the data.

2003 Panel Tr. at 42.

<sup>8</sup> FDA Public Health Notification: Paralysis From Absorbable Hemostatic Agent (Apr. 2, 2004), available at <http://www.fda.gov/cdrh/safety/040204-hemostatics.html>.

Similarly, the most recent literature reference cited by FDA in the 2003 Panel briefing materials (not referenced or placed in the docket) is a 1999 publication. Many additional articles pertaining to absorbable hemostats have been published since 2003.<sup>9</sup> These publications demonstrate changes in surgical technique and innovative uses of these products. They illustrate that past results may not predict future performance in new surgical situations or in combination with other technologies. It is impossible to tell from the rulemaking notice or docket whether FDA considered this new information in proceeding with the proposal to down-classify, or in developing the special controls.

Another key piece of information missing from FDA's notice and docket is that there have been two additional PMA approvals for absorbable hemostatic devices issued since the 2003 Panel meeting. One of these products is composed of an entirely different

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<sup>9</sup> See, e.g., Tomizawa Y., Clinical benefits and risk analysis of topical hemostats: a review. *J. Artif. Organs.* 2005; 8(3): 137-42.; Doita M, Nishida K, Kurosaka M, Radiculopathy due to microfibrillar collagen hemostat mimicking recurrence of disk herniation. *Skeletal Radiol.* 2006 Dec; 35(12): 953-5. (Epub 2006 Mar 16); Jameson M, Gross CW, Kountakis SE, FloSeal use in endoscopic sinus surgery: effect on postoperative bleeding and synechiae formation. *Am. J. Otolaryngol.* 2006 Mar-Apr; 27(2): 86-90; Gill JS, Ramani AP, Spaliviero M, Xu M, Finelli A, Kaouk JH, Desai MM, Improved hemostasis during laparoscopic partial nephrectomy using gelatin mix thrombin sealant. *Urology.* 2005 Mar; 65(3): 463-6; Sandrasegaran K, Lall C, Rajesh A, Maglinte DT, Distinguishing gelatin bioabsorbable sponge and postoperative abdominal abscess on CT. *AJR Am. J. Roentgenol.* 2005 Feb; 184(2): 475-80; Sabel M, Stummer W, The use of local agents: Surgicel and Surgifoam. *Eur. Spine J.* 2004 Oct;13 Suppl 1: S97-101. (Epub 2004 May 15); Ribalta T, McCutcheon IE, Neto AG, Gupta D, Kumar AJ, Biddle DA, Langford LA, Bruner JM, Leeds NE, Fuller GN, Textiloma (gossypiboma) mimicking recurrent intracranial tumor. *Arch. Pathol. Lab. Med.* 2004 Jul; 128(7): 749-58; Abs R, Cutaneous necrosis in a clinical case of one face lift after the use of Surgicel, *Ann. Chir. Plast. Esthet.* 2004 Feb; 49(1): 43-6; Oz MC, Rondinone JF, Shargill NS, FloSeal Matrix: new generation topical hemostatic sealant. *J. Card. Surg.* 2003 Nov-Dec; 18(6): 486-93; Chandra RK, Kern RC, Advantages and disadvantages of topical packing in endoscopic sinus surgery. *Curr. Opin. Otolaryngol. Head Neck Surg.* 2004 Feb; 12(1): 21-6.

material than the products considered in 2003.<sup>10</sup> The material composition of absorbable hemostats was a significant topic of discussion during the 2003 Panel meeting. Several Panel members expressed the view that reclassification be limited to materials that were already well-known. These recently approved PMAs do not have the long history of use. Yet it was the long history of use that influenced the 2003 Panel to recommend down-classification. The proposals do not address the rationale for allowing down-classification for absorbable hemostats comprised of this or other new materials, and there is no publicly available information in which FDA considers the impact of these approvals.

Finally, on November 23, 2005, Ethicon submitted a letter to FDA providing new information about the types of risks that concern surgeon-users of absorbable hemostat devices.<sup>11</sup> These risks include unique surgical specialty considerations, interactions with concurrently administered medications, and performance of novel products in critical applications. Many of these risks were not raised or only briefly considered during the 2002 and 2003 Panel meetings. There is no evidence in the proposed rule or the docket that FDA reviewed or considered this information in issuing the proposed reclassification; FDA did not directly comment on any of the issues raised.

In notice-and-comment rulemaking under the APA, “[a]gency notice . . . must be sufficient to fairly apprise interested parties of the issues involved, so that they may present responsive data or argument relating thereto.” S. Doc. No. 248, 79<sup>th</sup> Cong. 2d Sess., 200 (1946). “It is not consonant with the purpose of a rule-making proceeding to promulgate rules on the basis of inadequate data, or on data that [in] critical degree, is known only to the agency.” Portland Cement Ass’n v. Ruckelhaus, 486 F.2d 375, 393 (D.C. Cir. 1973). Moreover, “where an agency relies upon data to come to a rulemaking decision, it generally has an obligation under the APA to provide such data for public inspection.” Endangered

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<sup>10</sup> Arista AH Absorbable Hemostat (P050038) (water-insoluble, hydrophilic, microporous polysaccharide particles prepared from purified plant starch); Vitagel Absorbable Hemostat (P050044) (collagen-based).

<sup>11</sup> A copy of this letter was submitted to this docket as an attachment to Ethicon’s December 21, 2006 request for an extension of the comment period.

Species Comm. V. Babbitt, 852 F. Supp. 32, 36 (D.D.C. 1994).<sup>12</sup> For the reasons noted above, Ethicon believes that FDA has failed to meet the APA “adequate notice” requirement with respect to its proposed reclassification of absorbable hemostats. The agency should correct these deficiencies before proceeding further with the reclassification effort.

## **II. The Composition of the 2002 and 2003 Advisory Panels Was Inappropriately Narrow**

In proposing this reclassification, FDA relies on the recommendation of the 2003 Panel that absorbable hemostats be reclassified to Class II. The agency notes in the proposal that the Panel’s recommendation was based on “the information provided by FDA, the presentations to the panel by manufacturers and FDA, the Panel’s deliberations at the meeting, and their personal experience with the device.” 71 Fed. Reg. at 63,730 (emphasis added).

A review of the membership of the 2002 and 2003 Panels, however, shows that the range of both Panels’ experience with absorbable hemostats was quite limited compared to the broad scope of surgical applications in which absorbable hemostats are routinely used. The voting members of the 2002 Panel, for example, included a biostatistician, an orthopedic and microsurgeon, a dermatologist, a surgical oncologist, an attorney and bioethics expert, and a handful of plastic surgeons. The voting members of the 2003 Panel

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<sup>12</sup> See also, Chemical Mfrs. Ass’n v. EPA, 870 F.2d 177, 200 (5<sup>th</sup> Cir. 1989) (“fairness requires that the agency afford interested parties an opportunity to challenge the underlying factual data relied on by the agency”); United States v. Nova Scotia Food Prods. Corp., 568 F.2d 240, 252 (2d Cir. 1977) (“[t]o suppress meaningful comment by failure to disclose the basic data relied upon is akin to rejecting comment altogether”); Endangered Species Comm., 852 F. Supp at 37:

Where, as in this case, the underlying data . . . is readily available to the Secretary, even though he chose not to review the data, it was error for the Secretary not to make the data available to those interested parties from whom the Secretary sought comment. These parties, by not having the data underlying the report, were deprived of important and material information from which they could make meaningful analysis in order to provide their views to the Secretary.

(only two of whom had also been on the 2002 Panel) included a biostatistician, two surgical oncologists, two general surgeons, a thoracic surgeon, and a plastic surgeon. Neither of the Panels consulted by FDA included any experts in the medical specialties in which absorbable hemostats pose different and unique risks, e.g., cardiovascular, vascular, neurological, ENT, trauma, transplant, or urological surgery. Indeed, it appears that the 2003 Panel was hand-picked to deal with the other matter FDA asked it to consider – clinical trial issues for devices designed for percutaneous removal of breast tumors.

As described in its November 23, 2005 letter to FDA, Ethicon conducted a study of absorbable hemostat use by surgical specialty. The company surveyed over 400 surgeons in seven surgical specialties and found that there was high volume use of absorbable hemostats in cardiovascular, vascular, neurosurgery, orthopedic (spine), and ENT surgery. These areas represent a large majority of all uses of absorbable hemostats. Yet none of the 2002 or 2003 Panel members appeared to practice in these disciplines, where absorbable hemostats may present higher – and different – risks than general, thoracic, or plastic surgery. Ethicon notes that most of the recent MDR reports submitted for absorbable hemostatic devices have involved use during neurological surgery.

FDA's regulation concerning "technical advisory committee[s]" states that voting members "[s]hall have expertise in the subject matter with which the committee is concerned and have diverse professional education, training, and experience so that the committee will reflect a balanced composition of sufficient scientific expertise to handle the problems that come before it." 21 C.F.R. §14.80(b)(1)(i). Given the wide range of surgical specialties in which absorbable hemostats are commonly used, Ethicon does not believe that the voting members of the 2002 or 2003 Panels encompassed diverse training and experience, or reflected the required "balanced composition of sufficient scientific expertise." *Id.* On the contrary, the relatively narrow expertise of the Panels calls into question the value of their recommendations on this issue. FDA should consult with a more representative and diverse range of experts before proceeding any further with this reclassification proposal.

### **III. The Proposed Definition/Identification of the Category is Excessively Broad**

FDA proposes to identify the reclassified category of absorbable hemostats by the following language: "An absorbable hemostatic device is an absorbable device that is placed in the body during surgery to produce hemostasis by accelerating the clotting

process of blood.” 71 Fed. Reg. at 63,732 (proposed 21 C.F.R. § 878.4490(a)). In presenting nearly the same proposed definition to the 2003 Panel,<sup>13</sup> FDA acknowledged that it was “a pretty nebulous and very general description” but that it was “intentionally so, so that products that fit that general description can be looked at for the use as a hemostatic agent.” 2003 Panel Tr. at 34-35. At least one 2003 Panel member, who was also a member of the 2002 Panel, expressed concern that this language was too broad:

I’m still concerned that this idea of absorbable hemostatic agent intended to produce hemostasis is, as we move into the future with new products and perhaps polymers, over the years it has been fairly consistent, subtle variations perhaps in these products, but recently now with the addition of thrombin and autologous platelets, there will be new devices, perhaps polymers or that are completely distinct.

Similarly, the vibrant [sic] sealants which have a different role, the Tisseal and HemoCure products and so forth may have a different role and don’t fit into this category, but they are absorbable. They do provide hemostasis, and are there opportunities to get other devices or other products to fit into this classification based on this definition?

Id. at 52.

Ethicon strongly disagrees with the agency’s sweeping approach and submits that the proposed regulatory definition is much too inclusive – especially in light of FDA’s recognition that the performance and function of absorbable hemostats reviewed through the PMA process are highly dependent upon the products’ material composition, manufacturing processes, and mechanisms of action.

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See 2003 Panel Memo at 9: “Absorbable hemostatic agent, surgical . . . . An absorbable hemostatic agent, surgical is an absorbable device intended to produce hemostasis by accelerating the clotting process of blood during surgical procedures.”

**A. The Reclassified Category Should Be Restricted to Previously-Approved, Well-Known Materials**

In the briefing materials presented to the 2003 Panel, FDA explained 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. 2003 Panel Memo at 8. FDA also observed that these products have different mechanisms of action and acknowledged that “the manufacture of these devices can be complex.” *Id.* at 8-9. As drafted, however, the proposed regulatory identification would allow hemostatic agents formulated from new materials, and by different processes, to be marketed without the thorough FDA review and evaluation provided by the PMA process. New types of materials, processes, and conditions could all affect safety and efficacy in ways that might not be discovered until after widespread clinical use, unless applicants are required to generate and submit the kinds of data required for PMA approval.

For example, as noted above, FDA recently approved a PMA for a novel hemostatic device, “Arista AH” (P050038), composed of polysaccharide particles derived from potato starch. The Summary of Safety and Effectiveness (“SSE”) for this product states that it is “a unique absorbable hemostatic agent” and that “it exhibits a faster absorption time (approximately 24 to 48 hours) compared to other absorbable hemostatic agents that absorb in 3 to 8 weeks.”<sup>14</sup> FDA approval of Arista was based on a 288-patient “prospective, multi-center, multi-specialty, randomized, non-inferiority, controlled” clinical study, *id.* at 8, as well as an extensive battery of preclinical studies covering multiple animal models. The data from the clinical study showed that median time to hemostasis for Arista varied according to surgical specialty, and was statistically different from the control arm – another PMA-approved absorbable hemostat. *Id.* at 10. The PMA for Arista would have also needed to contain detailed manufacturing information.

Imagine, however, that the Arista product was submitted after publication of a reclassification order codifying FDA’s over-broad definition. In the Draft Guidance, FDA has proposed requiring only a brief, summary description of device materials and certain performance characteristics without requesting any information on the manufacturing process. In addition, the Draft Guidance seeks minimal or no clinical data, and far less preclinical information than was submitted in the Arista PMA. It is troubling that FDA is

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<sup>14</sup> Arista AH SSE at 3 (emphasis added) *available at* <http://www.fda.gov/cdrh/pdf5/p050038c.pdf>.

proposing a regulatory mechanism that would clear a novel product like Arista through the 510(k) process absent such critical data. It is equally troubling to think that FDA would clear future 510(k)s for products with compositions similar to Arista when the agency does not have the extensive safety and efficacy information for Arista that it has for the other, established materials cited in the 2003 Panel Memo, and there would be only a limited history of use. The overly broad definition would allow new materials on the market via a 510(k) notification with limited data, and would then allow additional 510(k) notifications with minimal data, despite the lack of history of use.

Ethicon submits that the proposed regulatory identification should 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 PMA process. For example, FDA should require that the device be composed of materials that have been demonstrated to be safe and effective, and list these materials. FDA should also require that a detailed description of the manufacturing process be included in any 510(k) notification. If, at a later point, FDA determines that it has sufficient safety and efficacy information on newer materials and processes that are reviewed through the PMA process, the agency could at that time propose to amend the reclassification category to include those materials.

At the 2003 Panel meeting, FDA drew an analogy between the proposed reclassification of absorbable hemostats and its prior reclassification of absorbable suture materials. This analogy fails, however, because the regulatory classification and product codes for reclassified sutures were initially highly specific to each material type (e.g., polypropylene sutures). Only after many years of regulation in these categories did FDA revise the classification to "absorbable sutures" and "non-absorbable sutures." Using this approach, FDA allowed for reduced regulatory burden on like products, but retained tight control over the scope of the categories until extensive experience could be gained on managing these products under Class II regulations. If FDA proceeds with the reclassification of absorbable hemostats, it needs to, at a minimum, incorporate the same specificity into its approach that it did with respect to sutures in describing the eligible product categories.

**B. The Definition of the Reclassified Category Should Identify the Requisite Mechanism(s) of Action for Inclusion**

FDA's proposed language defining the category of products to be reclassified does not indicate the criteria or methods for determining whether the device "accelerates the clotting process of blood during surgical procedures." For example, does FDA deem it necessary that absorbable hemostats have an inherent effect on coagulation? Is it sufficient to show that a product decreases bleeding time in selected animal models? The answers determine, for example, whether absorbable polymerizing sealants (not for use on blood vessel anastomosis sites) are in this class. Biologically inactive sealants may produce intraoperative hemostasis without forming durable clots.<sup>15</sup> Moreover, in advising the 2003 Panel that bone wax "is not considered an absorbable hemostatic agent," 2003 Panel Tr. at 42, FDA suggested that products which stop bleeding only by tamponade would not meet the definition of an absorbable hemostat. Ethicon recommends that the phrase "accelerates the clotting process of blood during surgical procedures" be modified to specify the required mechanism(s) of action for inclusion in the category. Such clarification is especially essential to determine the inclusion or exclusion of products incorporating thrombin, an issue discussed below.

**C. The Definition Should Clarify that the Classification and Regulatory Pathway for Combination Products, e.g., Those Incorporating Licensed Thrombin, Will Be Determined on a Case-By-Case Basis**

FDA's position during the 2002 Panel meeting was that absorbable hemostatic devices containing thrombin would not be eligible for reclassification, but continue to require PMA review:

Since we can't predict what new products are coming, we can only address products that have come through the PMA process. The only ones that have come through the PMA process that include anything besides the absorbable hemostatic device are two products which we have approved, which include licensed bovine thrombin.

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<sup>15</sup> See, e.g., MDR Report # 2954761-2006-00001 (Jan. 10, 2006) (Baxter Floseal).

[T]he agency is proposing that the absorbable hemostatic agents and dressing devices that do not contain bovine thrombin may be reclassified into a lower classification.

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Again, we cannot predict what products are coming in the future so we cannot include them in this reclassification. Those that do include the licensed bovine thrombin, we continue to require PMA.

2002 Panel Tr. at 116-18. In contrast, the introduction to FDA's Draft Guidance states that "[t]he [absorbable hemostatic] device may include a licensed thrombin." The agency has neither explained nor justified this shift in thinking in the proposed rulemaking or Draft Guidance.

In addition, while the Draft Guidance correctly notes that "combinations of a biologic or drug component with an absorbable hemostatic device" may require a PMA or be subject to additional regulatory controls applicable to the biological or drug component, it incorrectly presupposes – citing two prior FDA jurisdictional determinations – that all combinations of licensed thrombin with an absorbable hemostatic device would be reviewed under a 510(k).<sup>16</sup> However, as the preface to FDA's on-line list of jurisdictional determinations makes clear:

these capsular descriptions describe prior FDA RFD decisions only and are not policy statements. . . . Jurisdictional determinations are often influenced by subtle distinctions in a product's composition,

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<sup>16</sup> See Draft Guidance at 2:

Although FDA jurisdiction over combination products is determined by the product's primary mode of action, to date, for combinations of licensed thrombin and an absorbable hemostatic device, the device component has been deemed responsible for the product's primary mode of action with CDRH being assigned the lead for premarket review and regulation. Thus, combinations of licensed thrombin and an absorbable hemostatic device would be reviewed under 510(k) under the proposed rule.

mode(s) of action, intended use and related factors, which are not fully reflected in the capsular descriptions. It is possible that a product that fits within one of the general capsular descriptions provided below might actually receive a different jurisdictional assignment, based on the consideration of factors not reflected in the brief capsular description provided.<sup>17</sup>

Consequently, FDA cannot conclude, based on two jurisdictional determinations, that all combinations of an absorbable hemostat and thrombin can be cleared through the 510(k) process. The lead FDA center and regulatory review pathway for a combination product is determined by the Office of Combination Products based on the specific product's primary mode of action. These determinations necessarily are made on a product-by-product basis. Indeed, the regulatory classification of two identical products may be different because they make different claims. Although FDA has, in the past, issued certain "categorical" determinations for combination products within its Intercenter Agreements, to date, FDA has not issued any categorical determination for the combination of a licensed thrombin and an absorbable hemostat. Accordingly, FDA should clarify in the regulatory definition of the category, and in the Draft Guidance, that the classification and regulatory pathway for any absorbable hemostat incorporating a drug or biologic component, including thrombin, will be determined on a case-by-case basis according to the procedures set forth in the agency's Final Rule defining "primary mode of action." 70 Fed. Reg. 49,848 (Aug. 25, 2005).

#### **IV. The Draft Guidance and Proposed Special Controls Are Not Adequate to Ensure the Safety and Efficacy of Absorbable Hemostatic Devices**

##### **A. Sections 2 & 3: Abbreviated 510(k)**

Sections 2 and 3 of the Draft Guidance suggest that FDA believes many or even most 510(k)s for absorbable hemostat devices may be cleared as abbreviated 510(k)s.<sup>18</sup>

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<sup>17</sup> See FDA Jurisdictional Determinations, *available at* <http://www.fda.gov/oc/combination/determinations.html> (emphasis added).

<sup>18</sup> See, e.g., Draft Guidance at 5: "As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance document."

While Ethicon concurs that this is a “least burdensome” approach, the Company strongly disagrees that an abbreviated 510(k) will ever be appropriate. In light of the significant risks such devices pose, and the critical role of performance characteristics, Ethicon believes that, if the agency decides to proceed with reclassification, traditional 510(k)s containing complete reports of all methods, data, acceptance criteria and conclusions from required testing are necessary to ensure the equivalent safety and efficacy of such devices. Moreover, at the 2003 Panel meeting, FDA described in detail the types of data it would expect to see in a 510(k). The agency did not suggest that it would entertain an abbreviated 510(k), and the Panel did not endorse this type of truncated submission. On the contrary, in its presentation to the Panel, FDA stated: “the third section, which is the content and format of an abbreviated 510(k) submission, is a boilerplate section which only talks about Abbreviated 510(k)s and really wouldn’t apply to this type of 510(k).” 2003 Panel Tr. at 38 (emphasis added). FDA has provided no explanation for why it told the 2003 Panel abbreviated 510(k)s “wouldn’t apply” and then included this option in the Draft Guidance.<sup>19</sup>

FDA should clarify in the Draft Guidance that an abbreviated 510(k) will not be sufficient for clearance of an absorbable hemostatic device.

#### **B. Section 4: Scope**

In the Draft Guidance, the agency has made some attempts to clarify the scope of its proposed classification by identifying the product codes that have been assigned to this category, and by noting that the category “does not include products intended to control bleeding at femoral artery puncture sites (vascular hemostasis device, product code MGB) or for blood vessel anastomosis sites (polymerizing sealant, product code NBE),” or “devices for temporary occlusion of blood vessels (vascular clamp, product code DXC).” Draft Guidance at 6. There is no suggestion, however, that these clarifications will be included in the classification regulation itself, and thus Ethicon continues to believe that the proposed identification is too broad. As explained above, the Company is concerned that such inclusive, non-specific language could be used to encompass new products whose material composition and mechanism of action are not well-known, and which require closer FDA scrutiny than will be afforded through the 510(k) review process. A company

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<sup>19</sup> Saying that it is “boilerplate” is not a sufficient response. If, as FDA correctly told the 2003 Panel, abbreviated 510(k)s are not an option, the Draft Guidance should not invite the submission of abbreviated 510(k)s.

whose novel product falls within the literal wording of the classification regulation could argue that it is entitled to 510(k) review, and that the language of the regulation – not the guidance document – is controlling. FDA should foreclose this argument by better identifying the class in the regulatory definition itself.

Even the clarifications given in Section 4 of the Draft Guidance do not do enough to establish the appropriate boundaries of the category. For one, they do not distinguish between absorbable hemostats composed of new materials, and absorbable hemostats made of materials that are well-known to the agency. In addition, although the regulatory definition states that an absorbable hemostatic device is a device that “produce[s] hemostasis by accelerating the clotting process of blood,” FDA has not specified any test methodology or criteria to determine by what mechanism the device “accelerates the clotting process of blood,” or how to provide information on the device’s mechanism of action.

### **C. Section 5: Risks to Health**

In comparing the proposed Draft Guidance to the special controls presented to the 2003 Panel, Ethicon notes that an important and previously identified risk has been omitted. Specifically, the Draft Guidance does not include in the table of Risks to Health “Concomitant antiplatelet drug therapy, systemic heparinization and cardiopulmonary bypass may increase risk for hemostatic agent failure.” See 2003 Panel Memo at 11. FDA has provided no basis for deleting this risk factor. This risk category should be restored, and should also include the effects of common underlying conditions such as aging and malnutrition. Hemostatic agents may work very differently when certain risk factors are present, and may not be generic for the entire class of products. As one 2003 Panel member observed:

To echo what [was] said, really more from the perspective of newer agents that may be coming to the marketplace, while the previously identified risks look at inflammation, edema, wound dehiscence, generally speaking foreign body reaction and inflammation are only part of the wound healing cascade.

And as some of these strategies might be used in impaired hosts or oncologic applications, future products may need to look at their influence in some of these special states, which may not be generic.

2003 Panel Tr. at 61-62.

In the special controls outline presented to the 2003 panel, FDA suggested that the “concomitant therapy” risk category could be mitigated through animal studies and through labeling. Ethicon disagrees. A search of the published literature readily identifies many articles which question the correlation of animal studies to human experience. In two very recently published, peer-reviewed articles, the authors compared the results of animal studies to the results of human trials evaluating the same product and conditions. The authors of both studies concluded that animal studies often fail to predict human clinical experience. See Hackam, DG, Redelmeier, DA, Translation of Research Evidence from Animals to Humans. JAMA 2006; 296: 1731-32 (Oct. 2006) (research letter); Perel, P, Roberts I, Sena E, Wheble, P, Briscoe, C, Sandercock, P, MacLeod, M, Mignini, LF, Jayaram, P, Khan, K, Comparison of treatment effects between animal experiments and clinical trials; systematic review. BMJ 2007; 334; 197-originally published online 15 Dec 2006; doi:10.1136/bmj.39048.407928.BE *available at* <http://www.bmj.com/cgi/reprint/334/7586/197.pdf>.

Ethicon submits that animal models cannot adequately predict human clinical experience for absorbable hemostats – especially with regard to concomitant therapies and common underlying clinical conditions. Animal testing cannot replicate or reliably predict the impact of these variables. Thus the company believes that at least some clinical data should be required for relevant, expected patient populations and disease states, including the effects of concomitant drugs on hemostatic agent performance. Such studies should evaluate the time to hemostasis, re-bleeding rates, hematoma formation, reoperation rates, immunological response to the product and any concurrently administered coagulants, foreign body reaction, infection, and systemic effects on coagulation. Given the significant number of patients who now take concomitant medications or have underlying diseases or conditions that can affect hemostasis, this risk needs to be addressed explicitly and adequately.

**D. Section 6: Material and Performance Characteristics**

In the materials provided to the 2003 Panel, FDA acknowledged that the manufacture of absorbable hemostatic devices “can be complex.” 2003 Panel Memo. at 9. In its 2003 outline of special controls, the agency recognized that “any modification from standard techniques could [a]ffect time to hemostasis, absorption properties or other important characteristic[s] of the device.” *Id.* at 12. For these reasons, it proposed to require that in a 510(k) for an absorbable hemostatic device, the applicant describe and compare its manufacturing process to standard methods, and that any innovations or deviations from such methods be supported with justifying data. As FDA explained to the 2003 Panel,

Section 6 is a very detailed section which discusses the material and the performance characterization . . . . There would also be manufacturing information which would take into account the types of information . . . about Surgicel, where the pH and the degradation of the material and all of those types of things would be monitored through careful studies and would need to be submitted in a 510(k) to let us see, you know, that that information is understood.

2003 Panel Tr. at 38-39.

In the current Draft Guidance, without explanation or justification, FDA has dropped the requirement for information concerning the manufacturing process for such devices. For the very reasons FDA cited to the Panel in 2003, Ethicon submits that data on the manufacturing process for an absorbable hemostat is critical to the assurance of safety and efficacy for these devices. Unlike the PMA review process, there is no pre-approval inspection with a 510(k). Nor are postmarket changes in the manufacturing process for a 510(k) device reviewed by FDA. Ethicon recognizes that the agency may not withhold 510(k) clearance of a device based on factors such as compliance with good manufacturing practices (“GMPs”), which do not relate to substantial equivalence. *See* 21 U.S.C. § 360c(f)(5). However, the manufacturing process for an absorbable hemostat is directly relevant to the determination of substantial equivalence. As the agency has acknowledged, the manufacturing process for an absorbable hemostat affects its performance characteristics. Thus, without information on the manufacturing process, the analysis of substantial equivalence would be incomplete. Ethicon believes that detailed manufacturing information should be required in any 510(k) for an absorbable hemostatic device.

**E. Section 7: Animal Testing**

Ethicon agrees that animal testing should include arteriolar, venous, and capillary bleeding from various tissues and organs. The company further suggests that the spleen, liver, and vascular retroperitoneal tissues be specifically referenced in the Draft Guidance because these are relevant and clinically challenging uses of absorbable hemostats.

Ethicon also concurs that animal studies should evaluate the time to hemostasis, time to resorption, and any complications related to resorption, as well as complications such as infection, hematoma, coagulopathies, and increased wound healing time. We also believe, however, that additional, critical endpoints need to be evaluated in animal studies, e.g., 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 because of the increased pressure that may result in compression injury and permanent sequellae. Immunologic response is another endpoint that should be studied in animal and clinical models due to the known immunological reactivity of components such as collagen and thrombin. Animal studies for immune sensitization should be conducted with the proposed product alone, and in conjunction with thrombin, if the product contains or is labeled for use with thrombin.

Ethicon further recommends that the Draft Guidance include a statement in Section 7 indicating that animal studies must comply with the Good Laboratory Practice (“GLP”) regulations, 21 C.F.R. Part 58, and that applicants must certify GLP compliance.

**F. Section 8: Clinical Studies**

This section states:

While, in general, clinical studies may not be needed for most absorbable hemostatic devices, FDA may recommend that you collect clinical data for an absorbable hemostatic device with:

- indications for use dissimilar from legally marketed absorbable hemostatic device of the same type
- designs dissimilar from designs previously cleared under a premarket notification

- new technology, i.e., technology different from that used in legally marketed predicates.

Ethicon disagrees with this tentativeness of this statement and believes this language should be revised to state, affirmatively, that in each of those circumstances, FDA will normally require clinical studies.

It is apparent from the 2003 Panel transcript that, in issuing their recommendation for reclassification, the voting members understood that clinical studies would be a key element of special controls for reclassified absorbable hemostats. In its presentation to the Panel, FDA stated:

[S]ection 8 deals with clinical testing, and there's a long list of the types of information that we would be looking for there. . . . It says "A clinical study should be designed to compare the safety and effectiveness of the new device to a legally marketed predicate device. In most cases such comparisons should be made between absorbable hemostatic agents manufactured from similar materials with similar indications for use." So if somebody were manufacturing a device made of regenerated oxidized cellulose, considering that there's only one on the market in the United States, we would expect to see clinical data comparing that new product to the predicate product, which in that case would be Surgicel. Also, a study should be conducted at enough institutions to assure that the observations made regarding the safety and effectiveness of the devices will be significant in spite of technical and procedural differences likely to be encountered when the device is marketed.

2003 Panel Tr. at 40-41. Panel members favorably commented following this presentation: "I think that with the guidelines that we discussed I feel very comfortable with the sort of parameters that were listed for a guidance document," *id.* at 47; "I think that the proposed reclassification is not unreasonable, but with the special controls guidance document. I think that answered a lot of the concerns I had with respect to ongoing safety for new products that come into the field that resemble or are not exactly the same," *id.* at 55; "I agree that I think with these special controls as outlined I feel better about the reclassification to the Class II in this situation," *id.* at 56; and "I think that the guidelines that have been suggested, I think they address the concerns that have been talked about today." *Id.* at 58. Thus, the Panel's recommendation was heavily influenced by FDA's

representations that clinical data would be required. Those strong statements by FDA, which allayed the Panel's concerns, are in sharp contrast to the current language of "may recommend."

While Ethicon recognizes FDA's charge to apply the "least burdensome" approach, the Company submits that clinical studies are vital to the determination of substantial equivalence for absorbable hemostatic devices. Clinical studies should be required except if an applicant presents an alternative approach supported by a scientifically valid rationale and corroborating data.

**G. Section 11: Labeling (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 labeled indications unless data are submitted to establish equivalent safety and efficacy for such uses compared to a predicate that is also labeled for such uses. For example, panel members stated:

I think that out of the blocks the intended use should be the general intended use that was the kind described for Surgifoam with an exclusion for neurological ophthalmic and neurological, unless data is collected specifically to take those exclusions out.

2003 Panel Tr. at 58, and:

[W]ith respect to the intended use issues, I do think the differences at different sites need to be carefully explicated and that as new devices come up that there be the requirement to address those at the individual sites where specific problems have been recognized.

Id. at 55. In addition, FDA's 2003 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." 2003 Panel Memo at 15. In contrast, FDA's current draft guidance says only that "[i]f your device is labeled for any indications in surgical specialties, i.e., beyond general surgery, we may recommend that you conduct additional studies to assess the performance of your device when used as indicated . . . ." Section 8, at 12.

Given the unique risks that are posed by hemostatic agents in neurological, ophthalmic and urologic use, Ethicon believes that the submission of directly relevant supporting data is needed to address these highly foreseeable off-label uses. For this reason, we concur with the recommendations of 2003 Panel members that FDA's special controls for absorbable hemostats should require an indications statement which explicitly excludes any specialty uses for which the device has not been evaluated. FDA has authority to require such a labeling statement under 21 U.S.C. §360c(i)(1)(E), and has invoked this provision on many occasions.

Ethicon also notes, however, that even if an absorbable hemostat is labeled for general use with explicit exclusions, given how hemostatic agents are sourced and used, it is likely that hemostatic agents not evaluated or proven for specialty uses, will, nevertheless, be used for specialized off-label indications. This practice puts patients at risk.<sup>20</sup> An alternative to the problem of potentially hazardous off-label use of a "general use" hemostat would be to require 510(k) applicants for hemostatic agents to submit data on the most likely uses, such as neurosurgery, cardiovascular, vascular, orthopedic (spine), and ENT surgery. In its November 23, 2005 letter to FDA, Ethicon outlined the relevant concerns which it believes should be addressed in clinical and animal studies of these uses. Unless FDA requires that these data be provided, 510(k)-cleared absorbable hemostats will be used in these critical procedures without ever having been tested for those clinical applications.

Ethicon also notes that the "general use" approach to indications labeling proposed in the Draft Guidance may have the unwanted effect of discouraging innovation. By permitting general use labeling without even mandating exclusions in the labeling for the most foreseeable off-label uses, there will be little incentive to manufacturers to evaluate their devices for any specialized indications. Performing extensive and costly studies to gain a specific intended use would confer, at most, a negligible commercial advantage.

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<sup>20</sup> Decisions about which brand of a high volume product to use, especially in the surgical suite, are often made by hospital staff and not the surgeon. Cost plays a significant role in such decisions. If reclassification occurs, and FDA does not implement appropriate measures, 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.

## V. Conclusion

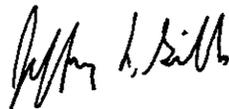
For the reasons discussed above, Ethicon concludes that FDA's proposed regulatory definition and special controls for absorbable hemostatic agents are inadequate to provide the required "reasonable assurance of safety and effectiveness" for these significant risk devices, and the Company opposes reclassification. In addition, based on the significant omissions and deficiencies in the agency's rulemaking notice and related public dockets, and the critical changes between what was presented to the 2003 Panel and FDA's proposals, the Company believes that FDA must, before proceeding with reclassification, correct and reissue the proposal for informed public comment. FDA should also meet or consult publicly with an appropriate range of experts and stakeholders concerning changes to its proposed special controls draft guidance.

Earlier this month, the agency proposed to deny a request for reclassification of non-invasive bone growth stimulators. 72 Fed. Reg. 1951 (Jan. 17, 2007). It is instructive to compare FDA's position and reasoning on the reclassification of these devices with its position and reasoning here. Specifically, FDA's notice concerning non-invasive bone growth stimulators indicates that upon review of the petition, the Orthopedic and Rehabilitation Devices Panel found that the petitioner's proposed special controls were adequate to address the vast majority of identified risks – e.g., electric shock; burn; skin irritation; adverse interaction with electrical implants; adverse interaction with internal/external fixation devices; and biological risks such as carcinogenicity and genotoxicity, but that the proposed controls were not adequate to address a single risk – the risk of inconsistent or ineffective treatment. *Id.* at 1953. FDA concurred with the Panel's recommendation. *Id.* Thus, on the basis of this one risk which FDA said was inadequately mitigated, the agency proposed to deny the reclassification request.

The unmitigated risk cited by FDA for non-invasive bone growth stimulators – ineffective or inconsistent treatment – is hardly life-threatening. In the worst case scenario, a patient with a non-union fracture or incomplete lumbar fusion would, after ineffective treatment, continue to have a non-union fracture or incomplete fusion requiring treatment by other means. While not trivial, this outcome will not be fatal. In marked contrast, a patient who is treated with an ineffective absorbable hemostat could suffer a life-threatening hemorrhage, compression injury, or immunologic response to foreign proteins. It is inconsistent for FDA to advocate the reclassification of absorbable hemostatic devices – where the adequacy of proposed controls to prevent multiple types of life-threatening risks is at best questionable – when the agency is proposing to deny reclassification of a non-invasive device whose failure would have far less dire consequences.

Before FDA can proceed with the reclassification of absorbable hemostats, there must be special controls which are adequate to provide reasonable assurance of the safety and efficacy of these devices. The proposed regulatory identification and special controls do not meet this threshold.

Respectfully submitted,



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JNG/JBD/rd