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Division of Dockets Management Branch (HFA – 305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

June 5, 2007

Re: Extended Comment Period—Additional Comments to Proposed Reclassification and Draft Class II Special Controls Guidance Document: Absorbable Hemostatic Agents

Dockets No. 2006N-0362 and 2006D-0363
General and Plastic Surgery Devices; Reclassification of Absorbable Hemostatic Device 21 CFR Part 878 (the "Proposed Reclassification" and "Draft Special Controls")

Dear Sir or Madam:

Introduction

On behalf of my client Ferrosan A/S, Sydmarken 5, DK-2860 Soeborg, in response to the extension granted by the Agency regarding the above-referenced proposed reclassification of absorbable hemostatic agents (Proposed Reclassification) and the accompanying Special Controls Guidance Document (Draft Special Controls) being proposed by the Agency, I am submitting a second set of comments to FDA's docket. We thank FDA for granting our Request for Extension and that of Ethicon's.

Ferrosan is a Danish company that develops and manufactures innovative products for the medical device industry, specifically the hemostatic device marketplace. Its current products are Surgifoam™ Absorbable Gelatin Sponge, U.S.P. PMA #990004 (owned by Ferrosan) and Surgifoam™ Absorbable Gelatin Powder, U.S.P. and Surgiflo Hemostatic Matrix, all of which are distributed in the United States by Ethicon, a Division of Johnson & Johnson ("Ethicon"). Ferrosan is developing future generation products for sale in the United States and has a significant stake in the regulatory regime that nurtures or retards investment in this arena. Surgifoam™ is a product approved by FDA through a PMA after extensive investment in vitro, in vivo, animal and human clinical testing as

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well as extensive manufacturing and other controls that make this class of products safe and effective. Ferrosan respectfully submits this second set of comments to the Proposed Reclassification and the Draft Special Controls document that is part of the reclassification effort.

Our goal is to work with the Agency to achieve reclassification in a manner which honors the input of FDA's own Advisory Panels, recognizes the concerns of industry and does not leave the Agency vulnerable to challenge. It is far better to conduct this process properly than to engage in protracted arguments over process and substance.

Executive Summary

Ferrosan submits the following additional views in support of its original comments to Proposed Reclassification and Draft Special Controls guidance document.

First, to repeat our last comment, the process in promulgating the Proposed Reclassification was seriously flawed. The complete administrative record is still unavailable to the parties and the Agency did not involve relevant medical experts to discuss the uses and regulation of these products.

Second, the FDA has not produced the Special Controls guidance document envisaged by its Advisory Panels. Our initial comments share in great length, by exhaustively quoting panel members from the transcripts, that FDA promised one special controls document and delivered another.

Third, 510(k) labeling and promotion is notoriously subject to unintended, unwanted expansion. Products that are cleared under a 510(k) for a general indication are often promoted for specific uses not endorsed by the FDA. That will most certainly occur due to the manner in which FDA proposes to reclassify these products.

Fourth, even if the Agency felt justified in ignoring some of the recommendations of the Advisory Panels, the proposed reclassification guidance is vague and too lenient for this device class that has the potential for use in life-threatening conditions.

Finally, FDA's overall approach here is a "dumbing down" of the standards for product approval to an intolerable level. It is unacceptable to accept reclassification with special controls that are loosely defined and not rigorous and subject to a system, an Abbreviated 510(k), that essentially allows a manufacturer to say "trust me" and requires only a very cursory and superficial review of a limited amount of data (without clinical data required) and unfettered changes to the product post clearance.

Analysis

First, to repeat our last comment, the process in promulgating the Proposed Reclassification was seriously flawed.

Although the Agency has extended the comment period, the complete administrative record is still not available to the public. We cannot effectively comment without the full administrative record being available. Today the full administrative record only contains the two transcripts of the 2002 and 2003 Advisory Panel meetings. It is our position, as set forth further below that the transcripts of these proceedings unequivocally support our arguments and position. This is true despite the fact that the FDA did not have all of the relevant experts on hand to deliberate these issues. Notably, there were no neurosurgical experts who constitute a very large user population and in uses that are very critical and for which the products can be misapplied. Indeed, the FDA in 2004 issued it own warning notice on April 2, 2004, entitled "FDA Public Health Notification: Paralysis From Absorbable Hemostatic Agent." This warning addressed adverse events in "bony or neural spaces." Suffice it to say, the Agency has not had input from the many relevant and important medical specialties who use these products (and can misuse use them) in some very serious ways.

For both of these reasons---the unavailability of the public record and failing to involve relevant medical specialists--and more as set forth in our original comment, we believe the process in promulgating the Proposed Reclassification has been seriously flawed and cannot go unchallenged.

Second, the FDA has not produced the Special Controls guidance document envisaged by its Advisory Panels. Our initial comments share in great length, by exhaustively quoting panel members from the transcripts, that FDA promised one special controls document and delivered another.

The Draft Special Controls do not at all capture the discussion and concerns expressed by the 2002 or 2003 Advisory Panel members. The document actually shared with the 2003 Advisory Panel was not the Draft Special Controls we are commenting upon today. Rather, it was another special controls for sutures which provided a "template" if you will for what might be contained in a special controls guidance for absorbable hemostatic agents. While the Agency seemed to listen attentively to all that its Advisory Panel members had to say regarding the content of a special controls guidance, one can honestly say that the actual content of the special controls document looks nothing like the discussion that took place.

To provide context, this debate began with the 2002 Advisory Panel at which the panel voted to table the discussion of the Proposed Reclassification. The issue was tabled because the controversy surrounded whether to vote for reclassification or not. Many panel members felt that these products are very complex in their manufacture and performance and placement in the body. There was strong sentiment expressed that reclassification should not occur but for a strong and comprehensive set of special

controls. Many members of the panel felt uncomfortable voting for reclassification without seeing the specifics of the special controls that would be proposed. It is undisputed that the panel felt so strongly about this that they agreed to table the matter requesting the Agency to develop and let them comment upon the special controls. Dr. Whalen, the Chairman of the 2002 Advisory Panel, in closing the panel meeting summed up the sentiment of the panel with these words:

> Dr. Witten, your advisory committee has voted 4-3 to table this action. If I can take the prerogative of the chair to add to that, ***I believe it is because they would like to see sufficient amplication of what a guidance document would be before taking any action for reclassifying the hemostatic agents.*** **See 2002 Advisory Panel Transcript at 176-177.** (Emphasis added).

The key here is the words "sufficient amplication." Both the 2002 and 2003 Advisory Panels made it abundantly clear what their concerns were, as evidenced by the meeting transcripts, but they seem to have been largely ignored by the Agency. Dr. Doyle a member of the 2002 Advisory Panel summoned up the sentiment of the group with this comment:

> Dr. Doyle: I have the sense of buying a pig in a poke. I would like to see the guidelines too. I feel much the same ways as the others. I think it is sort of the chicken and the egg, and I would feel more comfortable, before we reclassified, if we knew what is going to be in place [meaning special controls]. **Id. at 141.**

Despite the call by the 2002 Advisory Panel for specificity in a special controls guidance document that would address their concerns, the 2003 Advisory Panel was only provided with an example to serve as an outline of what a special controls document might look like. The Agency provided the panelists with an example. The Agency used the proposed special controls for sutures entitled "Class II Special Controls Guidance Document: Surgical Sutures; Draft Guidance for Industry and FDA." The document was not at all specific to absorbable hemostatic agents. Indeed, Dr. Krause called it a "kind of a guide" and parts of it "boilerplate" (**see 2003 Advisory Panel Transcript at 42 and 43, 46, 47.**), suggesting it was to show the Advisory Panel categorically, not specifically, what would be found in a future special controls guidance document for absorbable hemostatic agents.

The 2003 Advisory Panel thought they were opining only upon the "categories" to be contained in a special controls document. The 2003 Advisory Panel did not believe at all that it was endorsing the content of a specific special controls document. In fact, there is a disconnect between what the 2002 and 2003 Advisory Panels' expected out of the content of the special controls document that was discussed and the one FDA eventually produced. There were some representations made and expectations set by the FDA regarding the content of the proposed special controls that are not reflected in the actual draft guidance document. The content of the Draft Special Controls is disappointing and reflects poorly on the credibility of the Agency.

Third, even if the Agency felt justified in ignoring some of the recommendations of the Advisory Panels, the proposed reclassification guidance is vague and too lenient for this device class that has the potential for use in life-threatening conditions.

Members of both the 2002 and 2003 Advisory Panels consistently expressed concern to FDA that the definition of absorbable hemostatic agent was too vague and broad. Ferrosan shares this concern and it has been set forth in writing to the FDA by Ethicon in the past. The concern is that products not contemplated by or eligible for a 510(k) clearance might fall under the umbrella of a vague and broad definition. Dr. Choti whose tenure spanned both Advisory Panels was one of the most articulate and vocal members on this issue. Throughout Dr. Choti's membership on both panels, he repeatedly voiced concern that the proposed reclassification was too vague. He felt that the proposed definition did not anticipate how seemingly small changes to products could mean that the product should fall outside the definition and be ineligible for clearance under a 510(k). Some of the comments made in the two Advisory Panels are captured below. They were echoed many times by his colleagues throughout both Advisory Panel meetings in 2002 and 2003.

> Dr. Choti: The one issue is that these products are grouped together. The processing is different. The products are different. Some are bovine; some are porcine; some are cellulose and the manufacturing processes are different. ***Perhaps the definition that we have come up with, which is absorbable hemostatic product, is somewhat non-specific.*** So, I think it is important that new similar products as they are developed need to be carefully regulated if they are to be placed in this class. That would be one concern, that these are not really all the same devices. **See 2002 Advisory Panel Transcript at 123.** (Emphasis added).
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> ...
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> The two concerns I have, as I have expressed initially, is that I think part of the guidelines should somehow state the product itself, that is, whether it is a gelatin sponge. ***The way it is currently defined, absorbable hemostatic product, in itself is quite non-specific and if it is a totally new material, then it certainly needs to be tested and approved.*** But if a product is very similar or is manufactured similarly, then I think the biocompatibility, animal studies, some clinical data is fairly straightforward. **See 2002 Advisory Panel Transcript at 147.** (Emphasis added).

After seeing the Agency's proposed outline for the special controls guidance document in the 2003 Advisory Panel meeting, and in the midst of the debate, Dr. Choti reiterated concerns he had raised at the 2002 Advisory Panel meeting:

> Dr. Choti: This question I brought up last time [meaning the 2002 Advisory Panel] perhaps to address to Dave [Krause] is just still ***I think the definition or identification is still somewhat nebulous***, and Dave, you mentioned that there's kind of a reason to keep it vague, and I think that makes sense, but 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 sealants which have a different role, the Tissiel (phonetic) 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? **See 2003 Advisory Panel Transcript at 59-60.** (Emphasis added).

The point is that the Agency has debated for years whether to allow reclassification at all and then it proposes a definition of an absorbable hemostatic agent that is so expansive and inclusive as to include (or potentially include) products that are well outside the category of products with which FDA developed its comfort level. The definition indeed is overly broad. The proposed definition must acknowledge and capture the difference between products with known materials, constructions, performance characteristics and manufacturing controls from those where the experience base does not exist. Products with thrombin, other biologics or drugs or novel materials and/or constructions are unknown to the Agency at this time for lack of an experience base and should fall outside the definition. What will prevent a general nasal pack which has received a 510(k) or a tissue sealant for pulmonary use or vascular anastomosis from falling within this definition? It is inconceivable that the FDA could go from such tight regulatory controls (i.e. a PMA) to such a loose and almost nonchalant approach to these products (i.e. an Abbreviated 510(k) with a loose special controls guidance).

Fourth, 510(k) labeling and promotion is notoriously subject to unintended, unwanted expansion.

FDA, despite all the inadequacies of the 510(k) clearance system and the lack of clinical evidence, takes solace that the products will not be labeled for uses broader than that for which they are cleared. The problem is that products cleared for a general indication are often promoted for specific uses not endorsed by the FDA. That will most certainly occur due to the manner in which FDA proposes to reclassify these products. So a product cleared for general surgical use will be promoted and used in some very specific applications for which the Agency might want data but it will not be provided by the company. Take the example of ablation devices being used for atrial fibrillation or biliary duct stents used in the peripheral and coronary vasculature without specific approval/clearance in those settings. The FDA knows today that it is setting itself up for this sort of problem. It is even unclear, for example, whether FDA will be able to prevent the use of tissue sealants from use as an absorbable hemostatic agent. That is why it is so critically important to have some amount of human safety and effectiveness

data for 510(k) clearance of these products, because they will be used in a broader range of uses than those for which they are officially labeled.

Finally, FDA's overall approach here is a "dumbing down" of the standards for product approval to an intolerable level.

It is one thing to accept reclassification moving to a Traditional 510(k) with a tight product classification definition and a rigorous set of special controls. It is quite another to accept reclassification with special controls that are loosely defined and not rigorous and subject to a system, i.e. an Abbreviated 510(k), that essentially allows a manufacturer to say "trust me" and requires only a very cursory and superficial review of a limited amount of data (without clinical data required) and unfettered changes to the product post clearance. It is, in short, an abdication of FDA's responsibility.

In addition, the Agency's approach to "new" products is too cavalier. These products will introduce significant differences that are clearly not encompassed by the experience base which gives way to reclassification. New products such as these, by their very nature, are different and therefore must remain subject to Class III approval mechanisms. Thrombin-based products are no exception to this concern. The Advisory Panels wanted to accommodate more regulatory simplicity for products that were truly the "same as" or "similar to" products in defining "substantially equivalent." Neither the Advisory Panel or industry contemplated, or anticipated, that the Agency's proposal would be so accepting of new materials, constructions and the addition of thrombin. Nor did they expect any of this would be possible without some clinical trials being conducted.

Recommendation

We advocate first against reclassification under the circumstances because FDA did not follow its own procedures and because we believe the proposed definition and special controls are inadequate. As such, we fully believe this regulatory move is premature. If, however, a number of changes are made to ensure the public health is protected, then reclassification may be appropriate. Specifically, the definition of the applicable class must be more restrictive. Without that the class of products potentially qualifying for clearance will be too broad to ensure that the spirit of the Advisory Panels' comments are addressed. In addition, the Draft Special Controls must contain substantially more substantive content than FDA has provided to date. We respectfully request that the Agency redraft the special controls guidance to address the comments that have been submitted by the public and then empanel another Advisory Panel so that this panel can review the actual special controls document proposed by the Agency. We predict a new Advisory Panel will not agree with the some of the content that is noticeably lacking or even missing from the previous two panel discussions. Some of the missing contents are dramatic departures from the discussions that took place in 2002 and 2003.

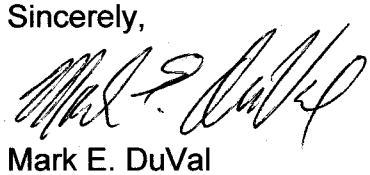
If the FDA resists redrafting the special controls and holding a public Advisory Panel meeting it should, at a minimum, send to its Advisory Panel members the Draft Special Controls and the public comments filed with this Proposed Reclassification and Draft Special Controls, and ask for their final comments. If the Advisory Panel members object to the Draft Special Controls, as we suspect, then the Agency should feel compelled to then re-submit for public comment a new special controls document that addresses their thoughtful, expert comments. While this latter approach would be unfortunate, because it would eliminate the actual public debate that ensues when experts and the public deliberate, it would at least allow the Advisory Panel members an opportunity to comment. The Agency may not like the feedback it receives because it may be inconsistent with the Draft Special Controls they have constructed, but it would be in the best interest of the public.

Conclusion

Absorbable hemostatic devices are currently and should remain categorized as Class III, requiring valid scientific evidence to establish safety and efficacy prior to approval. This classification is appropriate because absorbable hemostatic devices are life sustaining, life supporting, and substantially important to preventing impairment of human health. Although the Least Burdensome Approach mandate of CDRH is clear and reasonable, application to absorbable hemostatic devices at this time is premature. The continued requirement of Class III PMA is appropriate to safeguard the public health. Reclassification is appropriate only if the definition is restrictive and the special controls are detailed. An examination of current requirements for a PMA and the proposed requirements for the Draft Special Controls for absorbable hemostatic devices shows the possibility of many critical information gaps in regulatory review and oversight that will increase the risk to the public. This is especially true of combination products adding thrombin or other biologics or drugs.

Should you have any questions or need additional information, do not hesitate to contact me.

Sincerely,



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