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Food and Drug Administration
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Re: 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, I am submitting comments to FDA's docket 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. These are the comments we have thus far and we may have more refined arguments if our Request for Extension is granted by the FDA.

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 well as extensive manufacturing and other controls that make this class of products safe and effective. Ferrosan respectfully submits these comments to the

2006N-0362 C2

Proposed Reclassification and the Draft Special Controls document that is part of the reclassification effort.

Executive Summary

Ferrosan has five major issues to address in its review of and comment upon the Proposed Reclassification. First, the process in promulgating the Proposed Reclassification was flawed. Fundamental to any democratic system is due process, i.e. the opportunity to know and understand the basis of the Agency's decision making and to know it is the product of a fair and representative process. The Proposed Reclassification process was lacking in some serious ways. Among Ferrosan's concerns are that the full administrative record considered by the Advisory Panel's has not been made available to the public. FDA also did not include many relevant experts, representative of users of these products, on either the 2002 and 2003 Advisory Panels. Therefore, the Advisory Panels lacked the proper representation needed to assess the use of these products in some additional and important surgical uses. Lastly, CDRH has usurped the role of the Office of Combination Products (OCP) by attempting to define the "primary mode of action" of certain combination products. The Congress and FDA have vested this authority in OCP. It is best to have the jurisdiction, authority and, most importantly, the interpretation of combination product issues in one place within FDA.

Second, the proposed special controls guidance document does not capture or adequately address the concerns of the Advisory Panels. FDA simply has not listened to the concerns of its Advisory Panels or industry. The 2003 Advisory Panel did not see the actual special controls document that is in draft form today. There were some representations made or at least expectations set regarding the content of the proposed special controls that are not reflected in the actual draft guidance document. Among these concerns is the fact the product was not supposed to be cleared via an Abbreviated 510(k). The Advisory Panels considered the definition of "absorbable hemostatic agent" too vague and broad and consistently requested that it be narrowed. Yet, the definition remains unchanged in the draft guidance and it still is too broad. The special controls guidance was to be specific and to impose requirements that would ensure the process was an adequate substitute for a PMA. For example, the Advisory Panels were also left with the impression clinical trial(s) would be required and they are not.

Third, down classifying can be a slippery slope. The process does not ensure that products coming to the market are safe and effective. In its laudable attempt to put "least burdensome" principles into effect, the Agency has clearly compromised too much. To transition from a PMA system of approval to an Abbreviated 510(k) system of clearance using vague and largely undefined special controls leaves too much to chance and too much manufacturer discretion and interpretation in the process. It also leaves FDA with too little data upon which to conclude there is reasonable assurance of safety and effectiveness. We discuss below how these loosened regulatory standards can result in clearances for products over which the Agency has little real understanding and little control or oversight capability. The science and medicine behind these

products simply suggests that there is much more going on with these products than is recognized by the bare bones Draft Special Controls Guidance Document produced by the Agency.

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. The logical fallacy here 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.

Finally, the Draft Special Controls certainly should not cover new products containing thrombin, other biologics, drugs or novel materials and/or constructions. 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. Yet the Agency seems to interpret the word "new" differently than its Advisory Panels. 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.

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.

Analysis

I. The Proposed Reclassification Process has been Procedurally Flawed

A. The complete administrative record was not open to the public.

The process followed by the Agency was well intentioned but has failed in some very important ways that we believe are legally challengeable. The first is the full administrative record has not been available to those who desire to comment upon the process. The Agency has, for example, failed to make publicly available all the documents relied upon by the Advisory Panel that it assembled in 2003 to consider the Proposed Reclassification and Draft Special Controls. Nor did the Agency add any documents considered, if any, during the ensuing three year period following the 2003 Advisory Panel meeting. This includes over three years of Medical Device Reports. Ironically, the FDA did not even discuss in its rulemaking the most recent PMA approved and 510(k)s cleared. Surely FDA's thinking, which lead to these approvals and clearances are relevant to this rulemaking. Those documents and thoughts are important for industry to review and comment upon in making its assessment as to the adequacy of the information before the Advisory Panel and to correlate with the recommendations that came out of their meeting. We know from FDA's own comments that the materials provided to the 2003 Advisory Panel formed the basis for their recommendations. **See 71 Fed. Reg. at 63730.** Yet many of those documents were never made available to the public.

This lack of openness is a disservice not only to the public, but is an inappropriate way for the Agency to proceed. It is fundamental to due process that the public know the basis upon which the Agency's decision was made. That cannot be done by failing to share with the public the evidence that the Agency and its Advisory Panel relied upon. It is also a bit presumptuous to imply, in failing to share the information, that the public—especially the industry that manufactures these products and who may know the most about them—does not need all the information that formed the basis for the Agency's decision. Both industry and the public-at-large do have something to contribute to this regulatory dialogue. To meaningfully participate, we need all of the information considered by the Agency and any reports created by the Agency which expose its thought processes, analysis and conclusions.

We know that Ethicon has made a Request for Extension of the Comment Periods for Dockets 2006N-0363 (71 Fed. Reg. 63728 (Oct. 31, 2006) and 2006D-0363 (71 Fed. Reg. (Oct. 31, 2006) in a letter dated December 21, 2006 (written by the law firm of Hyman, Phelps) based in part upon the information that has not been made available to the public. We concur with the concerns expressed in that letter and respectfully request that the Agency provide an extension of the respective comment periods for this reason as well.

B. FDA did not include many relevant experts in the Advisory Panel.

In addition to flaws in the administrative record, the Agency did not include many appropriate specialists in the process, i.e. those who use a significant portion of the absorbable hemostatic agents sold in this country. For example, the use of these products can be found in the fields of trauma, vascular, transplant, cardiac, urology, neurosurgery and pathology, none of which are covered by the labeling for the product. To exclude these experts from the Advisory Panel was a fundamental flaw and could hardly be expected to produce the best work product for the Agency.

There are wide and disparate uses to which these products are put and they can account for serious differences of opinion on the performance characteristics of these products. The 2003 Advisory Panel had one general surgeon, two oncology surgeons and a professor of plastic surgery and a thoracic surgeon. The 2002 Advisory Panel had three professors of plastic surgery, one dermatologist and one specialist in obstetrics and gynecology. The FDA cannot pretend that new products cleared under a 510(k) will not be used more expansively than their indicated uses. We know that over time products will be used off-label and yet none will have clinical information supporting the cleared use much less these expanded uses.

C. The Office of Combination Products should have jurisdiction over combination product issues

FDA's Office of Combination Products (OCP) was established on December 24, 2002 as a result of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). The "Background" section to the Final Rule states that OCP makes determinations on:

> (1) The regulatory identity of a product as a drug, device, or biologic, or combination product; (2) the agency component that will have jurisdiction for any drug, device, or biological product where such jurisdiction is unclear or in dispute; and (3) the primary mode of action and assignment of a lead center for a combination product. **68 Fed. Reg. at 37076.**

The law gives the OCP broad responsibilities including "updating agreements, guidance documents or practices specific to the assignment of combination products." **See "Overview of the Office of Combination Products" at http://www.fda.gov/oc/combination/overview.html.** It is ironic that in September 2006 OCP published a proposed Notice in which OCP declared its intention to follow-up on this responsibility by reviewing agreements, documents or practices to ensure consistency in making

primary mode of action (PMOA) determinations. See **71 Fed. Reg. 56988-56991.** In the Proposed Reclassification and Draft Special Controls, CDRH has usurped the role of the Office of Combination Products by attempting to define the PMOA of certain combination products. The Congress and FDA have vested this authority in OCP. It is best to have the jurisdiction, authority and most importantly the interpretation of combination product issues in one place within FDA. It is less confusing to industry, it ensures consistency in rulemaking and decision making and it takes individual Center agendas out of play and into the Commissioner's Office. We respectfully request that combination product issues be left to OCP. To the extent the Proposed Reclassification and Draft Special Controls usurp, interfere with or predetermine combination product issues, it is inappropriate and outside of CDRH's prerogative and authority.

II. The Proposed Special Controls Guidance Document Does not Capture What the Advisory Panels Discussed

The Draft Special Controls seriously departs from what was shared and discussed with the Advisory Panel in 2002 and 2003. We are very concerned at how lacking in detail is the proposed Special Controls and how it differs from what the Agency shared and discussed with the Advisory Panel and the public attending that meeting. If these products are reclassified, the Draft Special Controls are the only real requirements standing between products coming to the market and the consuming public, and they are seriously lacking specificity and meaningful content.

A. It all started with the 2002 Advisory Panel.

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.

There were other comments made that were representative of the discussion and the concerns the 2002 Advisory Panel had, such as how would the reclassification work as new technologies came to the market. Other comments surrounded the complexity of the technology and its manufacture. Finally, others revolved around a concern that the definition of the product is too broad and vague. Here are some representative examples of the discussion from the 2002 Advisory Panel meeting:

> 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. **Id. at 123.**
>
> ...
>
> Dr. McCauley: I agree with the two comments. I think the two points that I kind of get stuck on, and the first really relates to variability in the structure and nature of these products and I think if we, indeed, classify them to Class II products then we have to have something that is very specific, not necessarily for each product but for each subgroup of products that comes through with similar structure. **Id. at 124.**
>
> ...
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> 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.**
>
> ...
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> Dr. Newburger: I guess I'm having trouble conceiving the application of these new standards to new products because it is not clear to me what these standards are. These do have different mechanisms of action they are used in different situations. I am concerned since these are used in critical situations intraoperatively that the slightest variation could have really much more profound impact than we think. So, I am wondering how clear the guidelines really would be....I am concerned that it wouldn't be detailed enough and I am in favor of keeping it in Class III. **Id. 128 at and 146.**
>
> ...
>
> Dr. Miller: I guess the specter of putting something in a bleeding wound and have it not clot for 15 minutes or ever clot, that terrifies me. These people have gotten my attention, that there is enough sophistication in the process that that is

possible. So, that has shaken my certainty a little bit in theses things. Maybe there is a lot more to making this effective device that I realized. And I agree with the comments about the guidance document and maybe we should all see that before we move on. **Id. at 175.**

...

Dr Dubler: I am just not sure if that is a question that we should move from III to II unless it were quite certain and unless industry agreed that, in fact, the shift from III to II would permit the maintenance of quality, I would be reluctant to make that shift. So, I would urge the FDA to establish some collaborative process in which they and industry would agree on the impact of the specific controls, and if that were agreed upon then I wouldn't oppose a shift from III to II. But simply to examine in the natural course of things what is in category III, with the idea that regulation should be limited as a matter of legislative intent, seems to me interesting but not dispositive.

Dr. Whalen: Forgive me but I am a surgeon and think in very simple terms. You are against reclassifying at the present time?

Dr. Dubler: I am against reclassifying at the present time. **Id. at 140.**

The 2002 Advisory Panel made it abundantly clear to the Agency how important it was that they not vote in favor of reclassification until they saw the actual content of the special controls. In underscoring this point, the Chairman, Dr. Whalen, summarized a section of the discussion for Dr. Witten from the Agency as follows:

Dr. Whalen: Dr. Witten, in regards to FDA's first question, I think it is very clear that there is not a strong consensus among the panel as to whether or not there should or should not be reclassification, and it will be interesting to see, when we get to the reclassification document, how that goes down. Part of the biggest reason that I perceive from the thread of discussion we have just had on this first question is ***what makes people reticent to wish reclassify is the potential enormity of what would be perceived as an adequate description for a document in this regard.*** With that less than an entirely clear answer, does that satisfy FDA on the first question?

Dr. Witten: Yes, thank you. (Emphasis added). **Id. at 148.**

The Chairman referred to the "potential enormity," i.e. the importance of having a detailed special controls document. Yet when the newly empanelled 2003 Advisory Panel assembled to consider the special controls, they were not given a specific document as desired by the 2002 Advisory Panel. Instead, they were given an example, an outline, of what "categorically" might be found in a final special controls document. It was devoid of specificity, the very thing requested by the 2002 Advisory Panel. In effect, all the 2003 Advisory Panel voted on was the categories that should be addressed in a special controls document. Here is an additional example from the 2003 Advisory Panel meeting:

> Dr. Doyle: I think that most of the things that I have to say have been said, too. I think the thing that struck me most as a consumer rep. is the fact that the guidelines, I think, have to be very clear that because of the differences in the materials of which these are made, if you've seen one, you've seen one. ***And I think it's very important that the guidelines are specific***, and they do seem to be covering the various types of material, particularly, of course, those made from animal, tissues from animal origin. **See 2003 Advisory Panel Transcript at 65.** (Emphasis added).

Our request is that Agency dwell on the serious tenor of the above comments and recount the concerns being expressed by their own consultants empanelled to provide FDA with expert advice. They demonstrate a deep concern over the content and specificity of any proposed special controls.

B. The 2003 Advisory Panel Was Only Shown an Example Outline of a Special Controls Guidance—It Was Not Shown the Eventual Draft Special Controls

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 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.

C. There Were Some Representations Made to the Panel that Were Not Followed-Up On by the Agency.

1. These products were not supposed to be cleared via an Abbreviated 510(k).

The Agency represented several things to the panel that never came to fruition/ completion in the Proposed Reclassification and Draft Special Controls. For example, the first was that in going through the sutures special controls document, the Agency proposed that new products could be cleared via an Abbreviated 510(k), but that would not apply to absorbable hemostatic agents. In discussing this matter with the panel, Dr. Krause 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)***." **See 2003 Advisory Panel Transcript at 43.** (Emphasis added). This comment left an impression with the panel that the Agency did not think an Abbreviated 510(k) would be appropriate for this type of product. Ironically, however, the Agency is now proposing that these products could and should be cleared by an Abbreviated 510(k). The inappropriateness of an Abbreviated 510(k) as a regulatory pathway is elaborated upon later in these comments.

2. **The Agency left the Panel with the impression clinical trials would be required**

All throughout the discussion, the Agency left the Advisory Panel and industry with the additional impression that, even if these products were to be down classified, a special controls document would require that a clinical trial would be required for clearance. Indeed, the 2002 Advisory Panel discussed the need for clinical trials. It was an underlying assumption of the discussion. For example, here are a few of the comments made by the 2002 Advisory Panel:

> Dr. Demets: I am puzzled about something that has been said regarding the Class IIs. If this was reclassified as Class II and a new product comes along that you compare to the predicate, and there were 30-50 patient studies as compared to 300 patient studies, what puzzled me about that is that you can compare a new product to an existing product with say 50 patients for the sake of argument, and you know a lot less about that new product. In fact, the way we think about it in drugs is we call it control creep. That is, you keep approving products with slightly inferior results and pretty soon you are down to almost nothing. So, I am sitting here, puzzling how this is not getting into some type of trap.
>
> You asked me whether we lose by this process. To me, so far, I am thinking we are losing rigor in the definitiveness of the new product being as good as or even perhaps better than what is out there if it winds up with smaller trials. **See 2002 Advisory Panel Transcript at 134-135.**

Dr. Demets' comment presupposes that a clinical trial will be required for clearance of these products. His comments centered around what the size the clinical trial should be, not the fact of whether one should be required or not. That is an underlying assumption upon which his comment is based. Dr. Choti's comment also assumed clinical data would be required as well:

> 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.**

At another point in the meeting, Dr. Krause of FDA went on to describe what should be in a guidance document. If the Agency meant to inform the Advisory Panel that clinical trials would not be mandatory, it certainly did not state that clearly. One certainly would have been left with the impression that clinical trials would be required given the discussion. For example, at the 2003 Advisory Panel meeting Judy O'Grady, Senior Vice President of Regulatory Quality and Clinical Affairs for Integra LifeSciences Corporation, set forth industry's expectation that clinical trials should/would be required for product clearance. Yet no one at FDA clarified that may not be the case after reclassification. In this portion of the transcript, she described in detail what should be found in a future special controls guidance and required for clearance of a product. This became an underlying assumption for the rest of the meeting which, if incorrect, should have been clarified by the Agency:

> Ms. O'Grady: Clinical experience. There should be a summary of any clinical experience. The sponsor should demonstrate that the hemostatic agent will perform as safely and effectively as another legally marketed hemostatic agent.
>
> Clinical data for hemostatic agents composed of materials for which have not been previously used as implantable, absorbable hemostatic agents should be provided from a multi-center clinical trial.
>
> Clinical data should be obtained for high risk surgical procedures where postoperative bleeding adverse events are especially critical, such as neurosurgery, ophthalmic surgery, and others as indicated.
>
> Clinical data should demonstrate that hemostatic agent performs similarly when compared to another legally marketed hemostatic agent.
>
> Clinical studies should evaluate if indicated time to hemostasis, days of adherence, ease of handling, and critical, which would be postoperative, evaluations of postoperative bleeding, infection, hematoma formation, wound dehiscence and any adverse events. **See 2003 Advisory Panel Transcript at 35-36.**

In explaining to the 2003 Advisory Panel what would be required for clearance under the yet-to-be-published special controls guidance, Dr. Krause from FDA represented the following:

> Finally, Section 8 deals with clinical testing, and there's a long list of the types of information that we would be looking for there. I'll just go through a little bit of it.
>
> 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 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 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. And that section goes on gives basically that type of advice. **See 2003 Advisory Panel Transcript at 46.**

If the FDA intended to couch or put conditions upon the issue of whether clinical studies would be required or not, it should have been clearer in doing so. As it stands today, neither the Proposed Reclassification notice in the Federal Register, nor the Draft Special Controls require clinical studies to be performed for new products. The FDA's seeming change of position occurred in the Draft Special Controls where the Agency makes this comment about clinical studies:

> In accordance with the Least Burdensome provisions of the act, FDA will rely upon well-designed bench testing (i.e., material and performance characteristics) and/or animal testing ***rather than requiring clinical studies*** for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. **See Special Controls Guidance document at 10.** (Emphasis added).

So, not only is the Agency ***not*** going to require clinical studies for this important category of products, it actually creates a regulatory presumption that clinical trials should not be required. There should be an absolute requirement that clinical trials must be conducted for thrombin and other biologics or drugs and novel materials and/or constructions. Instead, the Agency has said FDA will rely on well-designed benchmarking and/or animal studies "unless there is a specific justification for using clinical information...." It already appears that FDA is making room for newer generation products to be cleared without clinical data. Clearly, the expectation of the Advisory Panels and industry was that this guidance would be limited in scope to the current generation of absorbable hemostatic agents. The words in the Draft Special Controls belie that fact because they contemplate clearances of products with new indications, different designs and with new technology that may or may not need information developed from clinical trials:

> While, in general, clinical trials may not be needed for most absorbable hemostatic devices, FDA ***may*** recommend that you collect clinical data for an absorbable hemostatic device with:
>
> a. indications for use dissimilar from legally marketed absorbable hemostatic device of the same type
> b. designs dissimilar from designs from previously cleared under a premarket notification

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

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. **See Draft Special Controls at 10.** (Emphasis added).

The question is whether new technologies will really ever be required to file a PMA or are the crafty exceptions created by FDA so huge as to allow a vast array of new unproven technologies on to the market without filing a PMA and without clinical information in humans. One of the subtle ironies in the Draft Special Controls is that, while clinical trials are not needed to get clearance, if a company chooses to do a trial the devices are considered "significant risk" devices for which there must be an IDE filed with and reviewed by the FDA. This makes no sense at all.

D. Some Concerns of the Panel were Not Addressed

1. The Vague and Broad Definition of "Absorbable Hemostatic Agent" has been a Consistent Concern of the Advisory Panels Not Addressed in the Proposal

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).
>
> ...

> 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).

Even Dr. Krause and others at FDA recognized the definition was vague, even intentionally so. During the 2003 Advisory Panel he stated as follows:

> That's a pretty nebulous and general description of hemostatic agents, but I think it's intentionally so, so that products that fit that general description can be looked at for the use as a hemostatic agent. **See 2003 Advisory Panel Transcript at 39.**

We understand the need for regulatory flexibility and the desire to avoid periodically promulgating a new regulation to redefine an "absorbable hemostatic agent." That, however, is no excuse or substitute argument for making the definition intentionally overbroad so that the definition could accommodate products that have no place in the same category of product and the regulatory scheme that approves them. 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.

The logical fallacy here 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. 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. Abbreviated 510(k) with a undefined and loose special controls guidance).

One does not have to look far to see the pitfalls of the Agency's broad definition. The Arista absorbable hemostatic device was approved in 2006, and contains a change in device material to purified plant starch that is prepared by a proprietary process. It is appropriate that extensive regulatory review associated with a PMA was applied to this product, and furthermore that PMA regulations will cover any manufacturing change. The real concern is that any new manufacturer can seek an Abbreviated 510(k) clearance for a supposedly similar device based on summary comparability data. Yet the safety history of this material, does not exist. It is the presumed background safety of the predicate product which justifies reclassification with special controls. Yet, if the products are sufficiently different from one another, that presumption is misplaced. Similar logic can be applied to absorbable hemostatic devices containing thrombin. The FloSeal gelatin and thrombin device was approved in December 1999 and the CoStasis collagen and thrombin device was approved in June 2000. There has been insufficient time for the Agency to rely on a safety history of these two combination products to allow future thrombin combination products to gain approval through an Abbreviated 510(k).

For example, a product named ThrombiGel™ was cleared by FDA in 2005 as topical hemostatic agent used as trauma dressing for the control of surface bleeding from vascular access sites, etc. Would there be anything preventing that manufacturer from attempting to get another 510(k) for this product for use as an absorbable hemostatic agent? Even without a 510(k) what if the manufacture attempted to sell it off-label or a physician just chose to use the product in a more critical unapproved application? These are the kinds of questions and issues created when the path to market is too simplistic and not well-defined. We really will not fully understand the products coming to the market.

To repeat a quote of Dr. Krause from the 2003 Advisory Panel:

> So if somebody were manufacturing a device made of regenerated oxidized cellulose, considering 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. **See 2003 Advisory Panel Transcript at 46.**

If the Agency's position is that devices with little or no safety history should not be included in the Class II reclassification, why not say so? Using the Agency's own database, it should be easy to limit the definition to the absorbable hemostatic devices that are appropriate for reclassification now.

2. **<u>The Advisory Panel requested detail in the manufacturing controls</u>**

The Advisory Panels made so many comments about manufacturing controls that it is hard to capture them all here. But to underscore how the 2003 Advisory Panel was left with the impression that there would be robust controls, we need look no further than the comments of FDA's own Dr. Krause:

> Dr: Krause: Section 6 is a very detailed section which discusses the material and the performance characterization, and I don't want to go through that in great detail. That's in the handout that had sent you and the one that we posted up on the Web, but I think the industry representatives did a really good jog of pointing out the types of criteria that would go into that section....There would also be manufacturing information which would take into account the types of information that Dr. Paulson was talking about with Surgicel, where the pH and the degradation of the material and all 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. **See 2003 Advisory Panel Transcript at 44-45.**

When one then turns to the comments of the industry representatives to whom Dr. Krause referred, it is clear that the Advisory Panel was told about significant manufacturing controls. **See 2003 Advisory Panel Transcript at 14-38**. In fact, Dr. O'Grady, Vice President of Regulatory Quality and Clinical Affairs for Integra LifeSciences Corporation, discussed sterilization, pyrogenicity testing, expiration testing and manufacturing controls. As an example she stated:

> Pyrogenicity testing. The pyrogen level of the final sterile device should be less thatn .06 endotoxin units per mL, and this is specifically for any neurosurgical use or in contact with cerebral spinal fluid.
>
> Product expiration testing, data should support the expiration date for the product and should be submitted, and stability studies should monitor the critical performance parameters of the device to insure it will perform safe and effectively over the lifetime of the product.
>
> Manufacturing should comply with the FDA quality system regulation, including design controls. Submission should contain information on the device reagents and processing, device specifications, product release specifications, product

> release testing, residual levels of manufacturing agents, such as any leachables, residual levels of heavy metals, pyrogen levels, packaging, sterility. **See 2003 Advisory Panel Transcript at 36-37.**

So, these are the comments to which Dr. Krause was referring when he said "I think the industry representatives did a really good job of pointing out the types of criteria that would go into that section." Nonetheless, while he lead the Advisory Panel to believe they did good job describing what should go into manufacturing controls, they do not bear any resemblance to what ended up in the Draft Special Controls.

Dr. Leitch provides a representative and succinct example of the concern the Advisory Panel members had regarding manufacturing issue in material performance and characterization.

> Dr. Leitch: And so for me that seems to me to be the biggest concern that I have outside of some of these other issues [use in a neurological site] of manufacturing performance which I think ought to be encompassed in the guidelines. **See 2003 Advisory Panel Transcript at 68.**

3. The Advisory Panel requested more controls for special uses

When asked what additional information should be in the guidance, the 2003 Advisory Panel was clear in requesting specific requirements for devices that are used for different surgical procedures, as the following documents:

> Dr. Leitch: And then with 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 these at the individual sites where specific problems have been recognized. **See 2003 Advisory Panel Transcript at 63.**
>
> ...
>
> Dr. Choti: I think there are some variability in the special controls with each device. I think that as far as the intended use and descriptive material, I do think that Ann suggested that it needs to be site specific where it's applied and also with each different device there may be some variability based on how different it is and what some of the information, clinical or animal data, suggests as to what descriptive materials. So that should be defined based on the material, but I think that if that's clearly specified in the special controls, I think that it's reasonable to move ahead with that. **See 2003 Advisory Panel Transcript at 63-64.**

Reviewing the draft guidance, we find that this concern of the Advisory Panel was not explicitly addressed as requested. It is not clear how uses at different surgical sites will be addressed, especially given the Abbreviated 501(k) route. Based on Dr. Choti's statement, without such details, the Advisory Panel would question whether it was reasonable to proceed with the draft guidance as proposed.

III. The Slippery Slope of Down Regulation

The Agency's proposed reclassification will not be limited as it might seem to just the down classification from Class III to Class II products. The reclassification as proposed by FDA, as it will play out in reality, will result in loosening the standards in many ways. This becomes a slippery slope which will result in standards well below that intended by the Advisory Panels in 2002 and 2003, as well as that intended by industry. The combined effect of the loosening efforts will result in future products qualifying for 510(k) status that are not at all contemplated today.

A. Moving from a PMA to an "Abbreviated" 510(k) was not contemplated by the Advisory Panels or Industry.

The first way in which the proposed reclassification is loosened is to allow these products to be cleared via an Abbreviated 510(k) instead of a Traditional 510(k). This makes the down classification even more dramatic. The FDA went from asking the panel to debate whether the product should be down classified at all, to hearing a response from its own Advisory Panel that it should be done only with a robust special controls document. From that discussion, FDA ended up proposing that an "Abbreviated" 510(k) would be sufficient for a clearance. FDA knows full well that the level of scrutiny given in a PMA compared with an Abbreviated 510(k) are worlds apart. It is fundamental to any reclassification that there is still a reasonable assurance of safety and effectiveness. With 510(k) products this is accomplished through the use of regulatory surrogates or fictions that allow one to conclude you have products which are as safe and effective as the predicates. The 510(k) product must be shown to be substantially equivalent to a predicate device.

The problem with the proposed Agency approach is that it assumes that one can easily make the assumption of substantial equivalence with a minimum of core data. In a PMA, a comprehensive effort is exerted commensurate with a device that is considered "a significant risk device" by the Agency. **See Draft Special Controls at page 11.** For a PMA separate regulatory scientists from each of the core disciplines are involved in the review. Extensive documentation and proof must be submitted for all essential aspects of the device that contribute to its safety and efficacy. With a Traditional 510(k) the regulatory regime essentially "trusts" the manufacturer to properly develop and interpret its own data. The 510(k) "system" eliminates the in-depth study, data submission and review. The Agency review team is reduced to a single reviewer who primarily reviews report summaries. As the manufacturer prepares these summaries, it must be assumed that the summaries are biased in favor of the product. Since the supporting data are not submitted with a 510(k) as with a PMA, the reviewer cannot make an unbiased judgment of substantial equivalence with the predicate device.

The 510(k) approach is supposed to make acceptable compromises from the PMA system based upon the level of perceived risk to allow for administrative efficiency. The Draft Special Controls describes an Abbreviated 510(k) in this way:

> In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special control guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this guidance document, as well as any additional risks specific to your device. **See Draft Special Controls at 3.**

The summary report alluded to above, in turn, only requires the following categories to be addressed in an Abbreviated 510(k). Using the FDA's own language this is what a summary report must contain:

> Description of the device and its intended use
>
> Description of device design requirements
>
> Identification of the risk analysis method
>
> Discussion of the device characteristics
>
> Description of the performance aspects—In this section FDA states "If you follow a suggested test method, you may cite the method rather than describing it." FDA also states that for each test, "you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, or (2) describe the acceptance criteria that you will apply to your test results."
>
> Reliance on standards—This section only requires that if any part of a design or testing relies on a standard, the company need only provide either "a statement that testing will be conducted and meet the specified acceptance criteria before the device is marketed" or " a declaration of conformity to the standards." **See Draft Special Controls at 4-5.**

This list of required elements is appalling when juxtaposed with the requirements historically demanded for these products. These required elements are unbelievably scant when considering this product will be used within a body cavity and reside there until absorbed or unless or until something untoward happens with the product.

The problem is that all manufacturers have to do is "describe" risk issues, performance or other things in an Abbreviated 510(k) or "cite" tests or methods or use "summary" reports. The FDA also relies on "statements" or "certifications" of compliance with standards, etc. It is an exercise in abstraction. Product sponsors often do interpret data much more favorably than the FDA often does. That is usually not much of an issue with lower risk, non-implantable products. But with higher risk, implantable products too much discretion, interpretation and trust can be misplaced. Many companies who manufacture 510(k) products do not have the mindset or quality systems in place to truly ensure a quality product is developed, studied and reliably

reproduced. Yet the FDA's proposal here is entirely dependent upon those assumptions.

What is even worse is that the FDA did not stop at proposing that a Traditional 510(k) would be appropriate. FDA went even further to determine that an Abbreviated 510(k) would be appropriate. Under an Abbreviated 510(k), the Agency is even more reliant upon the proper interpretation, skill and good faith of a manufacturer because many of the data submissions are found in summary reports with none of the underlying raw data for FDA to examine on its own.

What is worse yet is that one 510(k) product begets another so there is regulatory "creep." Pretty soon the standards have been watered-down well below the level that even FDA will tolerate, but it is inevitable. This concern was possibly best captured by Dr. Demets at the 2002 Advisory Panel meeting:

> Dr. Demets: I am puzzled about something that has been said regarding the Class IIs. If this was reclassified as Class II and a new product comes along that you compare to the predicate, and there were 30-50 patient studies as compared to 300 patient studies, what puzzled me about that is that you can compare a new product to an existing product with say 50 patients for the sake of argument, and you know a lot less about that new product. ***In fact, the way we think about it in drugs is we call it control creep. That is, you keep approving products with slightly inferior results and pretty soon you are down to almost nothing. So, I am sitting here, puzzling how this is not getting into some type of trap.***
>
> You asked me whether we lose by this process. To me, so far, ***I am thinking we are losing rigor in the definitiveness of the new product being as good as or even perhaps better than what is out there*** if it winds up with smaller trials. **See 2002 Advisory Panel Transcript at 134-135.** (Emphasis added).

FDA will confront some interesting challenges from new companies seeking clearance of their absorbable hemostatic products. For example, it is conceivable to have a first time manufacturer of absorbable hemostatic agents who has only manufactured Class I products from a country without a solid regulatory regime or heritage. This company could provide to FDA summary reports, including their own interpretation of the results, and certify all sorts of data for FDA and come to market without ever having the actual study report (much less the raw data) reviewed or its plant subjected to a pre-approval inspection. The company will be allowed to "promise" the product will meet certain standards without having to provide any real proof of it. Dr. Chang, speaking at the 2002 Advisory Panel had a similar concern. He stated as follows:

> Dr. Chang: My other question, and I don't know if there is an answer, is what about the monitoring? What about companies that submit an address in Thailand or an address in Tibet? I mean, some place where it is not easy to have a site visit, how easily would they get a 510(k) through FDA for marketing in the U.S.? **See 2002 Advisory Panel Transcript at 127-128.**

The irony is that a company submitting an Abbreviated 510(k) will not be interrogated about its manufacturing process. It will not even have to submit data for review. It will just describe the process. There will be no pre-approval inspection. There will be no submission to the Agency when changes are made and it will be up to the manufacturer's interpretation to decide when a manufacturing change affects safety or effectiveness such that a new 510(k) may be required. So a product once cleared could be significantly changed without any regulatory oversight. This is why the FDA's regulatory drift, its surprisingly apathetic position, is so alarming.

It 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, 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 (required by a loosely defined special controls document) and unfettered changes to the product post clearance. It is, in short, an abdication of FDA's responsibility.

B. The Advisory Panels Contemplated More Scientific and Regulatory Rigor in the Special Controls

The second way in which reclassification will be loosened in a way not contemplated by the Advisory Panels or industry is that the proposed special controls document is not nearly as medically or scientifically robust as what was discussed in the Advisory Panel meetings. As discussed above, the Advisory Panels were reluctant to reclassify unless there was specific and detailed special control document in place that would ensure future products were properly characterized and of the same quality as the previous generation of products. As is discussed above the special controls documents are deficient in several respects, the most important of which is that the FDA will not require clinical trials. This is not as it was represented to the Advisory Panels'. It certainly does not meet with industry's expectations.

IV. Public Comment on the Draft Guidance

It is unfortunate that the industry was willing to compromise with the Agency and accept reclassification upon the condition that the special controls would ensure a minimum level of product characterization, performance and manufacturing and quality controls. The industry did not get the special controls it contemplated. This is an industry that has invested a great deal of time and expense to develop, study, manufacture and maintain a quality product. Product changes have been made through similar robust processes. Under FDA's proposals new entrants will come on the market with a fraction of the investment, time commitment and evidence needed to establish a reasonable assurance of safety and effectiveness.

That the proposed guidance for new entrants has been made purposefully vague and broad ranging seems unwise and contrary to scientific opinion. Even if the Agency felt itself justified to ignore some of the recommendations of the Advisory Committees, the Draft Special Controls is unclear and too lenient for this device class that has the potential for use in life-threatening conditions. We are concerned that the lack of appropriate regulatory documentation and review will add undue risk to the public for this device class.

A. The Rationale for the Draft Guidance is Flawed

The Agency's rationale for proposing a change in regulation of absorbable hemostatic devices to Class II with special controls is based on the history of safe and effective use of these devices and the scarcity of adverse event reports in the medical literature and the FDA's Medical Device Reporting System. It is not by accident that the currently marketed absorbable hemostatic devices have great safety records. It is precisely because they have undergone the rigor of clinical trial testing and filing a PMA with all of the detail that requires, including pre-approval inspections. The manufacturing process was honed for submission and perfected with years of quality production and attention to detail.

Surveying the history of safety of so broad a class of material is a daunting task. Only one product, an absorbable porcine sponge (Gelfoam), has been available since 1945; this product was approved in 1983. A sponge made of regenerated oxidized cellulose (Surgicel) was approved in 1960, and a bovine collagen device (Avitene) in 1976. The remainder of the products in this class was approved after 1980. Absorbable hemostatic devices containing thrombin were only recently approved in 1999 and thereafter. Most recently, an absorbable hemostatic device made from purified plant starch was approved in 2006. Even disregarding the accepted fact that the Medical Device Reporting System is qualitative since it focuses on unexpected adverse events and tends to ignore expected adverse events, there has been little elapsed time for the Agency to gather safety documentation on most device types.

Again, it is laudable that the Agency is taking the mandate to apply the "least burdensome" approach seriously. However, for absorbable hemostatic devices, it seems clear that the Agency has over-interpreted its limited safety and efficacy database in stating that "there is sufficient information to establish special controls to provide such assurance [of the safety and effectiveness of the device]." **See 71 Fed. Reg. at 6370.**

B. The Draft Guidance is Flawed

Scope: Definition too broad. The Agency's definition of absorbable hemostatic agents is vague and problematic and too broad. The Federal Register states "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." **See 71 Fed Reg. at 63279.** This is a broad class that encompases any product coded LMF or LMG and includes devices made from animal sources (porcine gelatin and bovine

collagen) and from cellulose (oxidized cellulose and regenerated oxidized cellulose). Although polymeric sealants and future novel hemostatic materials are not currently included in this device list, it is conceivable that these products could be allowed under the proposed reclassification if they receive LMF or LMG codes because the Draft Special Controls document is deficient in not including specific tests and criteria for gauging if a device is accelerating the clotting process.

Scope: Mechanism of Action. Lacking from the draft guidance is any request for mechanism of action documentation for combination products, nor is there any reference to guidance from the Office of Combination Products. At the least, the applicant should be required to demonstrate that the device and the biologic each have hemostatic activity in animal models, and that the biologic's action is secondary to that of the device. Again, without such a requirement, the scope of the reclassification is too broad. FDA's position on this has been inconsistent. It has, for example, stated that bone wax will not be included in the definition of an absorbable hemostatic agent because its mechanism of action is different (physical tamponade versus chemically or biologically accelerating clotting). Yet the Agency does not provide a requirement to determine what the mechanism of action is and how do you identify and measure it. The inquiry is easier to determine in the case of bone wax, but much more subtle and difficult with other products such as tissue sealants.

Risks to Health. The risk analysis mitigation plan, a critical part of the reclassification guidance, suffers from the same vagueness as the rest of the guidance. General references to materials and performance characteristics, animal testing, boiocompatibility, and even human testing are made, but with no clear directive on how each identified risk will be reviewed and found to be appropriately mitigated, given the limited information that will be submitted as part of a Traditional 510(k) or Abbreviated 510(k). Of particular concern is how new materials, new constructions, and new combination products will be assessed given the proposed standard of substantial equivalence. One questions why CDRH cannot draft more specific guidance documents like those created by CDER for the pharmaceutical industry.

Material and Performance Characteristics: Materials. A significant shortcoming of the proposed Draft Special Controls is in the lack of details for Material Specifications in Section 6. The special controls covers collagen or animal-derived material from bovine sources. However, it is unclear why gelatin from bovine and porcine sources is not mentioned considering the extensive use of this material in absorbable hemostatic devices. Gelatin is chemically denatured collagen and is recognized to have different properties and different risks of transmission of communicable disease agents. To address these concerns the FDA even prepared a guidance document entitled "FDA Guidance for Industry on Sourcing and Processing Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy in FDA-Regulated Products for Human Use" (October 10, 1997). This issue is still relevant today. In the recently released Federal Register FDA has published a "Proposed Rule on the Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Ruminants" (January 12, 2007). It is clear that the use of gelatin requires different sourcing and processing requirements than those cited in the draft reclassification

guidance for collagen, but the Draft Special Controls is unclear how gelatin is to be regulated. It seems the Agency has not merged its thinking on these different fronts into the Proposed Reclassification and Draft Special Controls.

Material and Performance Characteristics: Manufacturing Controls. Products cleared under the Proposed Reclassification can and will be markedly different from those that were approved through the PMA process. FDA's proposal will ensure the FDA does not truly know the characteristics and performance of the products it will clear and it will know even less over time as changes are made to these products or manufacturing processes. The current draft guidance is lacking in manufacturing controls on new products. Abandoning the pre-approval inspection and the review of manufacturing changes places an unwarranted and trusting reliance on industry to self-regulate and self-police. How will a lack of regulatory controls eliminate or prevent unintended effects? Consider that in the proposed guidance, the Agency will not learn anything about the manufacturing process during product review. After clearance of the submission, the manufacturer is free to make change after change without regulatory oversight. It is easy to see how a new manufacturing process can evolve that looks nothing like the process that the product clearance was based upon. This possibility does not seem acceptable considering the biological materials involved and the potential life-threatening uses of the product.

Another very important manufacturing control is to rigorously monitor for endotoxin levels. FDA has historically imposed stringent criteria for endotoxin levels. This is a particularly important factor knowing these products are used with the brain, heart and spine. This was a major concern of the Advisory Panel members in both 2002 and 2003. The United States Pharmacopoeia has a chapter that discusses acceptable levels of bacterial endotoxins in sterile and nonpyrogenic medical devices that come in contact with the cardiovascular system, the lymphatic system, or cerebrospinal fluid. **See USPC Official, Chapter 161 (2006).** The Draft Special Controls must provide more specificity in this regard.

Material and Performance Characteristics: Substantial Equivalence of Materials. The proposed Abbreviated 510(k) regulatory route requires only that the applicant identify and describe the Material and Performance Characteristics of the absorbable hemostatic agents to include material specifications product characterization, final product specification, and shelf life. Providing information based on "substantial equivalence" however, is significantly less rigorous than providing laboratory data to establish each material or performance characteristic. With new absorbable hemostatic agents using new and unique manufacturing processes and raw materials, it does not seem appropriate to rely on substantially equivalence to judge the acceptability of material and performance characteristics. For example, how would the Agency have approved the new purified plant starch material of Arista if that product were submitted without clinical documentation as an Abbreviated 510(k)? We would be concerned if the Agency used regenerated oxidized collagen or gelatin as a reference for substantial equivalence.

Animal Testing. The guidance allows the reliance upon "well-designed" bench testing and/or animal testing rather than requiring clinical studies for new absorbable hemostatic agents unless there is specific justification for asking for clinical information to support a determination of substantial equivalence. The guidance states that clinical studies will not be needed for most absorbable hemostatic agent devices. This is highly presumptuous as the guidance makes no recommendations of the type or extent of animal testing necessary or on the criteria for substantial equivalence that would be applied in lieu of clinical testing. Also lacking is any consideration of the animal testing necessary of devices intended for multiple surgical applications. Most seriously, the Draft Special Controls makes no mention of how a suitable reference will be chosen for demonstration of substantial equivalence, as required for a 510(k) submission. There is the risk that a recently cleared device could serve as the predicate device for another submission, and so on. If each change is modest from the previous device and incremental, the result could be the unintended introduction of new materials and new technologies over time.

Clinical Studies. It is ironic that this section gives specific requirements for an acceptable clinical study, with more details than in the previous sections, yet the Agency states in this section that "clinical studies may not be needed for most absorbable hemostatic devices." Of concern is the lack of criteria that the Agency will use to determine when clinical testing is appropriate. We believe that clinical data are not necessary for existing products with known materials and incremental changes to them. Nor are they needed for products with existing materials in new combinations. The manufacturing processes and output are known to FDA and these modest changes should not require clinical data. Animal or even toxicological data, in some limited circumstances, may be appropriate. But where the manufacturer is unknown to FDA, because they have never manufactured an absorbable hemostat before, or the manufacturer is known but the material and/or construction is new, then clinical trials should be required. Additionally, when thrombin or other biologics or drugs are added, clinical trials should be required.

B. Lessening the Regulatory Requirement to a Traditional 510(k) or Abbreviated 510(k) is Unwise

It is an inappropriate risk to public health to allow the approval of absorbable hemostatic devices via the Traditional 510(k) or Abbreviated 510(k) route. As stated earlier in these comments, the Agency review team for a Traditional 510(k) or an Abbreviated 510(k) is reduced to a single reviewer who primarily reviews report summaries. As the manufacturer prepares these summaries, it must be assumed that the summaries are biased in favor of the product. Since the supporting data are not submitted with a 510(k) as with a PMA, the reviewer cannot make an informed judgment of substantial equivalence with the predicate device. It will be biased by the inherent bias of the manufacturer who has drafted the summary. Furthermore, the surrendering of post-marketing oversight by giving up post-approval "changes being effected" review and yearly post-approval reports via the proposed 510(k) regulatory route is not prudent. Of concern are the compromises in the documentation and review of the materials, manufacturing, and preclinical animal data that occur in the proposed Class II special

controls guidance. Currently with a PMA, the applicant must address biocompatibility, irritation, sensitization, hemocompatability and systemic toxicity issues with animal studies. The Animal Testing section of the proposed Draft Special Controls is vague and may allow an applicant to submit with little or no animal data. The Agency has identified risks with absorbable hemostatic agents of uncontrolled bleeding, hematoma, infection, foreign body reactions, immunological reactions, adhesion formation, failure to be absorbed, and interference with methylmethacrylate adhesives that need to be mitigated with animal testing. Yet the proposed guidance does not provide any roadmap or assurances that these risks will be appropriately mitigated.

Currently, the Agency relies on each applicant to conduct an appropriate animal testing program. It would be of benefit to the public health if the Agency would include in a proposed guidance what specific animal tests are required to be conducted for each risk mitigation plan. Such guidance would have the benefit of an industry-wide standardization and would provide the Agency with a database that would allow more scientifically based judgments on the safety of future product submissions.

There is a risk to public health with unduly relying solely on animal testing as animal studies focus on acute tests (time to hemostatis) but do not provide information on post-operative behavior or concomitant medications or disease states, information that can only be studied in humans. The Agency recognizes that an absorbable hemostatic agent is a significant risk device as defined in 21 CFR 812.3(m)(4). As such, at least one clinical study as outlined in the proposed guidance, should be required to be completed and reviewed by the Agency prior to clearance for thrombin or other biologics and drugs and novel materials and/or constructions..

C. <u>If FDA can deny reclassification for non-invasive bone growth stimulators, it should be especially cautious with these products</u>

One of the great ironies in developing these comments is that very recently the Agency denied the reclassification of non-invasive bone growth stimulators. Here is a category of products for which there is certainly less risk than for absorbable hemostatic agents, yet the Agency concluded that certain risks, i.e. electric shock, burn, skin irritation, adverse ineraction with electrical implants, adverse interaction with internal/external fixation devise and biologic risks were adequately addressed. But the FDA stated that the proposed reclassification failed to address the risk of inconsistent of ineffective treatment. **See 72 Fed. Reg. at 1953.** This risk pales in comparison to the risks that are not mitigated in FDA's own Proposed Reclassification. Surely FDA sees the inconsistency in this position. FDA must put more detail in the Draft Special Controls to mitigate these risks.

V. <u>The Special Controls Certainly Should Not Cover New Products Containing Thrombin or other Biologics, Drugs or Novel Materials and/or Constructions</u>

The Agency's approach to "new" products is too cavalier. New products, i.e. those combined with drugs, biologics or using novel materials and/or constructions, should not

be reclassified from Class III to Class II. 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. Yet the Agency seems to interpret the word "new" differently than its Advisory Panels. 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.

It is clear that an absorbable hemostatic agent may include a licensed thrombin. However, absorbable hemostatic products that include biological products or drug components are combination products as defined in 21 CFR 3.2(e). When the device component is responsible for the primary mode of action of the absorbable hemostatic agent, it is assigned to CDRH for premarket review and regulation. However, the Draft Special Controls is defective in not including specific tests and criteria for gauging the primary mechanism of action. A manufacturer need only show a summary of the hemostatic effects of the proposed device in preclinical testing for an Abbreviated 510(k), and is not required to test the individual components to demonstrate how each component (gelatin/collagen and thrombin) is contributing to efficacy. Of equal concern are inactive carriers or polymeric sealants mixed with thrombin that are functioning as thrombin delivery systems but can be regulated as an absorbable hemostatic agent.

What is concerning is that CDRH seems to think a "a thrombin, is a thrombin, is a thrombin." This is not true. On the CDER-side of the world, FDA has still not found a way to bring generic biologics to market by showing they are bioequivalent to the innovator. Yet CDRH is proposing to declare substantial equivalence with no human data at all with products that can vary widely in materials construction and, most importantly for a biologic, in the manufacturing process. With biologics the drug is a byproduct of its manufacturing process and different manufacturing processes can produce different biologics. CDRH is far too conclusive in its position that one thrombin product is the same as another thrombin product with very little data to characterize potential differences.

CBER has issued a guidance document entitled "Guidance for Industry on Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use" (May 1999). It is clear in this document that clinical testing is required for approving fibrin sealant products, and that extra care in testing is needed for products with multiple components contributing to efficacy. For the use of thrombin with absorbable hemostatic devices, most of the cited safety history is based on applications where the thrombin is added to the device during use. As stated in the guidance cited above, there is a risk of relying on this history as "locally prepared fibrin sealants are not standardized or consistent." Since the real value of an absorbable hemostatic device containing thrombin is both standardization and consistency, these essential factors need to be demonstrated in humans.

VI. 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.

Ferrosan has addressed five major issues to address in its review of and comment upon the Proposed Reclassification. First, the process in promulgating the Proposed Reclassification was flawed. Among Ferrosan's concerns are that the full administrative record considered by the Advisory Panel's has not been made available to the public. FDA also did not include many relevant experts, representative of users of these products, on either the 2002 and 2003 Advisory Panels. Lastly, CDRH has usurped the role of the Office of Combination Products (OCP) by attempting to define the "primary mode of action" of certain combination products. The Congress and FDA have vested this authority in OCP. It is best to have the jurisdiction, authority and most importantly the interpretation of combination product issues in one place within FDA.

Second, the proposed special controls guidance document does not capture or adequately address the concerns the either Advisory Panel. Third, down classifying can be a slippery slope. The process does not ensure that products coming to the market are safe and effective. 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, the Draft Special Controls certainly should not cover new products containing thrombin, other biologics, drugs or novel materials and/or constructions. The Agency's approach to "new" products is too cavalier. New products, by their very nature, are different and therefore must remain subject to Class III approval mechanisms. 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.

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.

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

Sincerely,

Mark E. DuVal
Counsel to Ferrosan