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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

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May 31, 2019
8:00 a.m.

Gaithersburg Holiday Inn, Grand Ballroom
2 Montgomery Village Avenue
Gaithersburg, MD 20879

PANEL MEMBERS:

| | |
|---|---|
| FRANK R. LEWIS, JR., M.D. | Chair |
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| TERRY HICKS, M.D. | Temporary Non-Voting Member |
| MATTHEW BLOOM, M.D. | Temporary Non-Voting Member |
| ALEXANDER KRUPNICK, M.D. | Temporary Non-Voting Member |
| WALTER PORIES, M.D. | Temporary Non-Voting Member |
| WILLIAM MEURER, M.D. | Temporary Non-Voting Member |
| ELLIOT LEVY, M.D. | Temporary Non-Voting Member |
| LYNN A. PAWELSKI, M.B.A. | Industry Representative |
| RACHEL S. BRUMMERT, M.S. | Consumer Representative |
| PHILIP POSNER, Ph.D. | Patient Representative |
| PATRICIO GARCIA, M.P.H., CDR, USPHS | Designated Federal Officer |



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M E E T I N G

(8:06 a.m.)

DR. LEWIS: Good morning. I want to call the General and Plastic Surgery Devices Panel to order for this session related to hemostatic agents.

I'm Dr. Frank Lewis, the Chair of the Panel. My clinical experience, I'm a trauma surgeon and have been -- was the executive director of the board for some time until my retirement about a year ago.

I would like to, in a moment, ask the Panel to introduce themselves. A couple of housekeeping items.

I note for the record that the members present constitute a quorum as required by federal law. I would like to add that the Panel participating in the meeting today has received formal training in FDA device law and regulations.

For today's agenda, the Committee will discuss and make recommendations regarding the reclassification of absorbable hemostatic agents. These devices are considered transitional devices since they were in commercial distribution as of May 28th, 1976, when the Medical Devices Amendments became effective. The FDA has therefore had jurisdiction over these as devices rather than drugs for 43 years.

Before we begin, I want to ask our distinguished Panel members and the FDA staff as well to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. Let's begin at the center of the table with Ms. Pawelski.

MS. PAWELSKI: Lynn Pawelski. I'm the Vice President of Global Regulatory Affairs for Baxter Healthcare, and I'm the Industry Representative on the Panel.

DR. POSNER: I'm Phil Posner. I'm the Patient Representative on the Panel. I'm a retired medical scientist, and the last time I looked at these, I was using Gelfoam in 1971 as my controlling agent.

MS. BRUMMERT: Rachel Brummert. I'm with Charlotte-Mecklenburg Police Department, and I'm the Consumer Representative today.

DR. PORIES: I'm Walter Pories. I'm Professor of Surgery and Biochemistry at East Carolina University and Director of the Diabetes Research Metabolic Group.

DR. HICKS: I'm Terry Hicks. I'm the Associate Chair of the Department of Colon and Rectal Surgery at the Ochsner Clinic and for the last 37 years have been an academic teaching surgeon at the Ochsner Clinic.

CDR GARCIA: Commander Patricio Garcia. I am the Designated Federal Officer for this meeting.

DR. BLOOM: Matthew Bloom. I'm a trauma and general surgeon from Cedars-Sinai, Los Angeles.

DR. MILLER: Michael Miller. I'm a plastic surgeon, and I am in private practice in Denver. I've been there for 2 months, but for many years I was the Chair of Plastic Surgery at Ohio State University, and I retain a clinical appointment at Ohio State.

DR. KRUPNICK: I'm Sasha Krupnick. I'm a thoracic surgeon at the University of Virginia.

DR. MEURER: Will Meurer. I'm Associate Professor of Emergency Medicine and Neurology at the University of Michigan.

DR. LEVY: Elliot Levy. I'm an interventional radiologist and staff clinician at the NIH.

DR. KRAUSE: Good morning. Thank you all for being here and helping us out on this issue. My name is David Krause. I'm a cell biologist by training. I'm the Deputy Director of the Office of Surgical and Infection Control Devices, and I'm also the Acting Director of the Division of Infection Control and Plastic Surgery Devices.

DR. LEWIS: Thank you, all. I want to remind the audience, if you have not already done so, to please sign the attendance sheets, which are on the table just outside the door,

at some point this morning.

I now recognize Commander Patricio Garcia, the Designated Federal Officer for this meeting, who will make some introductory remarks.

CDR GARCIA: Thank you, Dr. Lewis, and good morning, everyone. I will now read the Conflict of Interest Statement, particular matter of general applicability.

The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them,

including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the reclassification of certain absorbable hemostatic agents from Class III to Class II with special controls.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Lynn Pawelski is serving as the Industry Representative, acting on behalf of all related industry. She is employed by Baxter Healthcare, Incorporated.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationship that they may have with any firm at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Thank you.

Before I turn this meeting back over to Dr. Lewis, I would like to make a few general

announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Ms. Stephanie Caccomo.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. Artair Mallett at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Thank you very much. Dr. Lewis.

DR. LEWIS: We would now like to turn to remarks from the FDA, and we'll ask Dr. Adam Pierce to take the podium and provide introductory remarks and a device description for the issues that we'll be dealing with today.

Dr. Pierce.

DR. PIERCE: Good morning, I'm Adam Pierce, a biologist at the FDA.

We are here to discuss the reclassification of absorbable collagen-based hemostatic devices with the Panel. FDA is requesting the Committee's input on the reclassification of

absorbable collagen-based hemostatic devices from Class III to Class II. For the purposes of this presentation, we may also refer to these devices as collagen-based hemostats, collagen-based devices, or collagen hemostats. These devices currently have an assigned product code LMF.

Today we are not considering reclassification of absorbable non-collagen-based hemostatic devices or absorbable collagen-based hemostatic devices containing added biologics.

I will begin the presentation with an introduction to specifically describe the devices included in this discussion. After an introduction, we will hear from industry representatives, possibly. Then FDA presentations will follow, to include individual presentations on the clinical considerations of these devices, current postmarket surveillance information, proposed reclassification to Class II and associated special controls. After FDA presentations, we will hold an Open Public Hearing. At the end, FDA will ask specific questions to the Committee regarding the reclassification of absorbable collagen-based hemostatic devices.

Please note that there will be time allotted at the end of each individual presentation to allow for clarifying questions from the Committee.

FDA would like the Committee to review and discuss available scientific evidence regarding the safety and effectiveness of absorbable collagen-based hemostatic devices. FDA would like your input on the appropriate classification of the device type as Class III or Class II. When discussing your input and recommendations, please consider the following items:

- Identify risks to health presented by this device type;
- Determine if general and special controls are sufficient to ensure device safety and effectiveness;

- Determine the sufficiency of the special controls presented by FDA; and
- Clarify if additional special controls are needed.

This next presentation is intended to provide the necessary background information on the definition and description of currently marketed absorbable collagen-based hemostatic devices. This information may facilitate your understanding of the current regulation and how the proposed special controls are sufficient to ensure device safety and effectiveness.

Absorbable collagen-based hemostatic devices are currently regulated as Class III devices under the following definition: "An absorbable hemostatic agent or dressing is a device intended to produce hemostasis by accelerating the clotting process of blood. It is absorbable."

Currently there are three product codes used to distinguish between differences in material and technology. Absorbable collagen-based hemostatic agents are assigned the product code LMF. Absorbable collagen-based hemostatic agents with thrombin are assigned PMX product code. Absorbable non-collagen-based hemostatic agents are assigned product code LMG.

To properly delineate absorbable devices -- to properly delineate absorbable hemostatic devices and their intended uses, the FDA has proposed to revise the existing device identification in the classification regulation to absorbable hemostatic device and create two subcategories to distinguish between absorbable collagen-based hemostatic devices and absorbable collagen-based hemostatic devices containing added biologics or absorbable non-collagen-based hemostatic devices.

Under this proposal, devices currently grouped under product code LMF would fall within subcategory absorbable collagen-based hemostatic devices, while devices under product codes PMX and LMG would fall within subcategories absorbable collagen-based

hemostatic devices containing added biologics and absorbable non-collagen-based hemostatic devices.

As stated earlier, FDA is requesting the Committee's input on reclassification of absorbable collagen-based hemostatic devices from Class III to Class II. Today we are not considering the reclassification of absorbable collagen-based hemostatic devices containing added biologics or absorbable non-collagen-based hemostatic devices.

The currently approved absorbable hemostatic devices can be categorized into six general categories regarding the material composition:

- Gelatin
- Microfibrillar collagen
- Oxidized cellulose
- Regenerated oxidized cellulose
- Plant-based polysaccharides
- Combination products

The currently approved absorbable collagen-based hemostatic devices are composed of either gelatin or collagen.

Gelatin is a crude extract derived from animal tissues, typically, the animal hides or tendons. The resulting extract is a heterogeneous mixture of water-soluble animal proteins, including collagen protein.

Collagen is a purified extract derived from the same animal tissues as gelatin. The extensive purification steps result in a homogeneous mixture of water-insoluble animal protein that is predominantly composed of collagen, and it is most commonly extracted as a triple helical structure that can make up multiple types of collagen. Collagen Types I and IV are the most commonly used in medical devices.

The gelatin material or purified collagen can be further processed into a finished

device that are ultimately a gelatin sponge or a microfibrillar collagen sheet, respectively. The gelatin sponge is processed into a finished form, as essentially a block of gelatin with a porous structure. Porcine sources are used for the manufacture of a gelatin sponge. The manufacturing of gelatin sponges has a long history dating back to when the method was first introduced in 1945.

For a finished device composed of microfibrillar collagen, the purified raw material can be further processed into a woven or non-woven sheet that is the finished device. Sheet forms of microfibrillar collagen are most commonly used for absorbable hemostatic devices. The microfibrillar collagen is typically derived from mammalian sources, with porcine or bovine sources being the most common. Similar to gelatin sponges, microfibrillar collagen has a long history of manufacturing dating back to 1936.

It is important to note that both types of these devices induce hemostasis through its mechanical action by the absorption of blood. When the blood is absorbed, the platelets aggregate to initiate the clotting cascade and subsequent hemostasis.

It is also important to note that these devices are currently reviewed within the scope of the recent 2019 FDA guidance entitled "Medical Devices Containing Materials Derived from Animal Sources," which implements guidelines necessary to mitigate the risks associated with the use of animal-derived material in medical devices.

There are currently nine approved devices that can be defined as absorbable collagen-based hemostatic devices, which include Gelfoam, Avitene, Collastat, Superstat, Instat, Helistat, Hemopad, Actifoam, and Surgifoam.

The indications for use statement generally identifies the condition and patient population for which the device is to be used. Here are some representative examples from currently approved devices. The representative examples from the currently approved devices include: "The device is recommended for use in surgical procedures (other than

neurosurgical, urological and ophthalmological surgery) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical."

Alternatively, the indications may state that "The device is used dry or saturated with sterile chloride solution, is indicated in surgical procedures as a hemostatic device, when control of capillary, venous, or arteriolar bleeding by pressure, ligature, and other conventional procedures is either ineffective or impractical."

The specific examples presented above are not necessarily representative of all the approved indications for use and claims but are provided to illustrate the relatively narrow range of approved statements.

FDA recognizes that science and clinical practice have evolved, and indications for use that have been approved for hemostatic devices may not adequately capture all of their intended uses.

I'd like to have this time allotted for your questions to clarify any of your understanding of the material that I just presented.

DR. LEWIS: I have two questions. The first is that in the Executive Summary we were provided, there was no explanation of why the FDA is recommending reclassification of the collagen-based hemostats but is not recommending and specifically wants to retain in Class III the non-collagen-based hemostats, which have, in essence, exactly the same indications, they have the same purposes, they affect hemostasis by different mechanisms, but in both cases the common element is activation of the normal clotting cascade. That would seem to create a dichotomy between two products which basically a quite similar. Why is that the case?

DR. PIERCE: Yeah. So, we did consider that, and looking at what is approved, we do not have an extensive experience in review of some technologies as well as it's currently evolving. So, we had to look at who was manufacturing what. So, when you have a single

manufacturer of a device, we're not sure that another manufacturer can actually manufacture that device.

DR. LEWIS: Okay.

DR. PIERCE: They're different technologies.

DR. LEWIS: The second question is you've cited six or eight products that are made under different names by different companies. In the Executive Summary, we were provided a description of only two PMAs which have been reviewed by the FDA, one in 1995 for a product called Hemostagene and the other in 1999 for a product called Surgifoam Sponge. We were not given any data or any discussion regarding other PMAs. Have all of those other products required PMAs, and do they exist or were they brought into market under the approval of the first two?

DR. PIERCE: Right. So, a little bit of both. So, the PMA numbers you see here that start with a P, they had a PMA associated with them. The devices Gelfoam and Avitene you see here with the N associated with them were initially regulated as drugs pre-1976 and were transitioned to CDRH. So, you could say we have a PMA equivalent, I'd guess you'd say; a drug application would be equivalent to a PMA.

DR. LEWIS: And is there any data related to those --

DR. PIERCE: Yes.

DR. LEWIS: -- in terms of safety and efficacy?

DR. PIERCE: Yes.

DR. LEWIS: We weren't presented with any of that. Do you have any --

DR. PIERCE: Yeah. So, a lot of that data is confidential, but it does consist of preclinical and/or clinical data.

DR. LEWIS: Okay. And actually, a third question: In the history we were provided, there were panels identical to this one which were convened in 2002, 2003, and 2006. The

panels in 2003 and 2006, as I understand it, both recommended at the time that these devices be down-classified to Class II, and no subsequent action was taken by the FDA in regard to that. Can you explain why?

DR. PIERCE: Yeah. I do have a presentation later also reiterating all the points that we're discussing right now, but mainly it was due to administrative reasons for the delay, but I do walk through that recent regulatory history that leads up to now and how that has evolved, administratively speaking.

DR. LEWIS: Okay.

Are there other questions? Yes.

DR. MEURER: Will Meurer.

Thank you for the presentation. I know I'm supposed to know this, but could you refresh our memories? I sort of understand the differences between Class II and Class III devices for their initial approval, going through different processes. What is different about their post-approval life cycles? What's different about being a Class III versus a Class II when you're in a post-approval state?

DR. PIERCE: Right. There is a few different things, but that's determined during the review of the PMA, so some devices may require different post-approval requirements than others. But, generally speaking, you won't have annual reporting and the premarket review process is shortened. I cover some other things at a future presentation, too, where I'll identify that.

(Off microphone comment.)

DR. PIERCE: Thank you.

DR. LEWIS: We will now have a presentation from an industry representative. Dr. Richard Kocharian, representing Ethicon, will make some remarks.

Dr. Kocharian.

DR. KOCHARIAN: Thank you. Good morning. I'm Richard Kocharian, and I'm Senior Medical Director for Biosurgery and Wound Closure platforms at Ethicon.

DR. LEWIS: Could you speak up just a bit louder, please?

DR. KOCHARIAN: Sure. I'm Richard Kocharian, and I'm Senior Franchise Medical Director for Biosurgery and Wound Closure platforms at Ethicon. I'm a general surgeon by practice, 15 years, and the last 15 years with industry. I am also a medical monitor and safety lead on hemostasis clinical trials run by Ethicon.

I first would like to thank the Panel members and FDA representatives for this opportunity to speak at today's meeting, and thanks also to Dr. Pierce for the presentation on proposed reclassification of products listed under LMF. We greatly appreciate the Agency's continual commitment to patient safety and would like to thank you for taking into consideration the previous comments provided during the 2014-15 strategic initiatives.

While we appreciate the list of special controls presented from the Agency and are looking forward to the discussion this afternoon, we do want to reinforce that products in this category are absorbable hemostats. They may remain in the body and are not always meant to be removed once hemostasis is achieved.

Additionally, some of the absorbable hemostats in this category can be coupled with active biologics -- has their effectiveness. While products may not be co-packaged with biologic agents, they are still allowed to be used in conjunction with a biologic agent for approved labeling.

Due to the complexity of the composition of these products, and potentially used in combination with biologics, we believe that strict controls are warranted to ensure their safety and effectiveness for the intended use.

The PMA process allows for an extensive review and, more importantly, oversight and control during the life cycle of these devices, which could be lost through the 510(k)

process.

The animal data may be appropriate to demonstrate effectiveness of the product; however, if a new device has different base chemistry or the source of the raw material is different than what has been previously approved, I would like to emphasize that human clinical data would support the assurance of safety in patients.

The PMA process also guarantees preapproval facility inspection to ensure adherence to good manufacturing practice guidelines in order to maintain consistent product characteristics. Slight manufacturing modifications can shift these parameters, which could potentially impact the device interactions with active biologics, hence their effectiveness and safety.

And, in conclusion, we would like to thank the Agency for including special manufacturing controls in their recommendation; however, we would like to recommend to keep products that are absorbable collagen-based devices as Class III.

Once again, thank you very much for the time and this opportunity to present our perspective.

DR. LEWIS: So, you are recommending that no change be made, that these continue as Class III devices in order to have closer oversight?

DR. KOCHARIAN: That's our position, yes.

DR. LEWIS: Okay. Are there other questions from the Panel for the speaker?

(No response.)

DR. LEWIS: Thank you very much.

DR. KOCHARIAN: Thank you.

DR. LEWIS: We will now hear a series of presentations from the FDA related to the absorbable collagen-based hemostats. Presentations will be made by Dr. George Gibeily, who will present on clinical considerations; Ms. Karen Nast will present on postmarket

surveillance; and Dr. Adam Pierce will present on the FDA's proposal for reclassification and special controls. We'll begin with Dr. Gibeily.

DR. GIBEILY: Dr. Lewis, Panel members, distinguished guests, my name is George Gibeily. I'm an FDA medical officer and general surgeon in the Center for Devices and Radiological Health.

Today we'll discuss why FDA believes that down-classification of absorbable hemostats, collagen hemostats, is appropriate, beginning with a discussion on traditional methods of hemostasis, a brief device description, current premarket approval process, unique issues with minimally invasive surgery, a literature review that shows some of the typical risks as well as risks of unusual case reports, as well as off-label uses, concluding with a rationale for down-classification.

Traditional methods of hemostasis include suture ligature of blood vessels after achieving proximal and distal control; clipping/stapling of vessels; use of energy-based devices such as mono- and bipolar cautery; focused and harmonic high-frequency ultrasound devices as well as laser.

The geometry and physical characteristics of the hemostat go into play as to where you're going to use it, typically. For example, energy-based devices may be used in large surface area bleeding, not uncommon with solid organ resection.

When conventional methods fail or are ineffective or impractical for minimal, mild, and moderate bleeding, absorbable collagen hemostats may be used and have been shown to prevent extended bleeding, decrease surgical morbidity related to blood loss, and decreased transfusion requirements with the admonition from industry, use what you need and remove the excess.

So, Dr. Pierce has already talked about the device description on the two main types of collage hemostats, the porcine and the bovine hemostats. I'd like to highlight the fact

that both hemostats provide a surface on which clot can form. They absorb water, not blood, to concentrate platelets and clotting factors. And they swell to create a physical barrier to bleeding. They do not chemically initiate the clotting cascade.

So, collagen hemostats in 1945 were typically used in their sponge form. They could be removed or left in place. Today, collagen hemostats are produced as woven pads, flour and powder, powder to be sprayed on dry or mixed with saline to be applied as a paste using an applicator. These hemostats become part of the clot and cannot easily be removed without rebleeding, and so they're frequently left in the organ space. It may take 2 to 3 months to absorb.

The powder and flour forms of these hemostats require applicators of different lengths for open versus laparoscopic surgery or thoracoscopic surgery. The applicators help deliver the hemostats to confined spaces which aren't easily compressed and are propelled by syringe-like devices or bellows.

The theoretical risks associated with these applicators include spillage or residual device from applicator shaft outside the target bleeding site, unpredictable unit dosing of the hemostat due to the residual in the applicator or inconsistent force placed on the bellows or the syringe. The propulse of air can theoretically force a device into low pressure venous channels and create the risk of thromboembolism.

These hemostats are intended primarily for mild -- minimal, mild, and moderate bleeding correlating with -- visually with oozing, pooling, and flowing. The rates of bleeding can be measured gravimetrically in video libraries created from in vivo examples to train raters for enrolling future target bleeding sites in animal and clinical studies. The inter- and intra-rater reliability is measured, determining severity of bleeding for enrollment, with the greatest correlation being for determination of hemostasis and bleeding too severe to enroll, that is, the streaming and the gushing type of bleeding, audible hemorrhage. You

shouldn't be using those hemostats for that.

A typical PMA review involves reviewing performance studies, evaluating device swelling, device delivery, device material properties such as adhesiveness and cohesiveness. This is especially important with powdered hemostats. These tests determine the ease of hemostat dislodgment, which is especially pertinent for a gravity-challenged bleeding site, such as the inverted gallbladder bed and the liver.

Our PMA reviews also include preclinical animal studies conducted on a variety of bleeding sites. These studies are usually performed on target bleeding sites to be indicated in the labeling and include organ bleeding such as liver, soft tissue bleeding, cardiovascular, and orthopedic extremity. The studies conducted are used to evaluate the effectiveness of hemostasis but also the severity of adhesion formation in the chronic animal studies.

Clinical studies use the best available control to evaluate such endpoints as time to hemostasis and time of preparation, rebleeding compared to the control, and the follow-up is usually about 90 days. These patients, though, may be consented for up to 5 years if the subject hemostat is used in oncologic surgery to assess the impact on oncologic prognosis.

Some unique concerns regarding the application, especially of powdered hemostats in the laparoscopic operative field, include the restrictive access that the operative field imposes to the target bleeding site; limited cone of vision; magnification of the bleeding site which may confound the point of hemostasis; and lack of haptic feedback, making it more difficult to apply uniform pressure once the device has been applied.

Irrigation fluid used to remove the excess hemostat can sometimes compromise exposure of the operative field, can actually spread the hemostat beyond the target bleeding site into the remote recesses of the abdomen, perhaps increasing the risk of adhesion and/or abscess formation.

Additionally, I might add, pneumo-peritoneum itself applied to the target bleeding

site can give you a false impression of hemostasis, possibly even increasing the risk of thromboembolism and/or rebleeding with desufflation of the abdomen. Dispersion of the hemostat onto the anatomic site of dissection can also confound the anatomy, making the dissection more treacherous.

So, we ask sponsors who intend to indicate the subject hemostat for minimally invasive surgery to provide in vivo testing and a minimally invasive surgical model to inform labeling and with mitigations for these potential problems.

So, we performed -- oh, that's out of order, I apologize. I'm not sure how that happened. Okay, literature review. We did a literature review and -- extending from the panel in 2003 to December of 2018. The searches were limited to studies conducted in humans and in English. Duplicated references were removed. There are 919 reports retrieved; 626 were excluded if they weren't done in the U.S. on absorbable collagen hemostatic devices. These hemostats are frequently combined with biologics, so it made it more difficult to get -- to sort out some of these studies and did not present -- if the studies didn't give results on safety they, too, were excluded.

So, FDA ended up reviewing, out of the 626, 293 articles in greater detail, full-text articles, and of those, 280 were excluded. Basically, what we found from these articles, we didn't find any unusual complications that occurred. There was in one study, a vascular study, a rebleeding at 10 minutes for a 22% incidence of rebleeding. They all were controlled. There was no postoperative bleeding. Twenty-six percent of these patients required blood transfusions, possibly because they were on antiplatelet medications. There was a laparoscopic partial nephrectomy study also presented with a 4.8% transfusion requirement. And then two case series were interesting because there were nine cases of residual device and mimic tumors after removal of the primary cancer.

On-label adverse events reported including -- included bleeding and foreign body

reaction, hematoma, infection, and adhesion formation. These are known to be related to the hemostat, but there was some real unusual case reports as well. Typically, these hemostats, when placed in a confined space next to a nerve, do swell and can cause nerve compression and nerve neuropraxia, nerve injury. But what we found was sometimes these collagen hemostats were causing severe granulomatous inflammatory reactions marked by eosinophilia that caused a delayed nerve dysfunction. Whether that's because of swelling related to the inflammation or other injurious factors, we don't know.

There were also reports of stenosis. These are case reports of stenosis of small vessel anastomoses, one case of a distal coronary anastomosis that was stenosed and attributed to the inflammatory response of the hemostat. It was also applied in a couple cases to the retroperitoneum where the fibrosis caused urethral obstruction.

And the hemostats have also been known to clog drains resulting in seroma, hematoma, abscess, skin necrosis, and in the chest, airway compression and superior vena cava syndrome.

There was one case of a fatal embolism when the hemostat was applied to a removed bone skewer. It met the bleeding criteria of moderate. They applied the hemostat, and it immediately embolized and caused intraoperative death to the patient, who was not resuscitatable. Placed in the intracranial cavity. Reports of acute diffuse encephalomyelitis. Embolization of the collagen, believe it or not, into the CSF circulation causing obstruction of the aqueducts and hydrocephalus.

And then, finally, pseudo-mass formation on imaging has become a real diagnostic issue, and we're seeing this in the MDRs. Because of the slowly absorbable characteristics of these hemostats, 2 to 3 months, sometimes longer, on imaging patients they do appear sometimes to be a recurrent high-grade tumor or abscess because they, too, have a hypervascular rim typical of these conditions, and this had led occasionally to additional

imaging, prolonged hospital stay, additional invasive procedures, and even reoperation in these patients.

These hemostats can trap air for long periods of time, and around aorta graft, as you all know, that can indicate graft infection, which has a 40% mortality. Grafts are allowed to have air around them for up to 6 weeks. These hemostats have been known to retain air longer than that and become a diagnostic issue in these patients.

Also, early small bile high-grade obstruction related to -- this hemostat was seen in C-section cases and one after hysterectomy IVC injury. They presented with high-grade obstruction. On reoperation, nodular inflamed densities were at the point of obstruction on histology. They turned out to be the hemostat.

So, in addition, FDA acknowledges that many of the adverse events we're seeing in the MDRs and in the literature are due to off-label uses of these hemostats, and so I want to just present a couple of these here because they are pertinent to what we're seeing.

Examples of off-label uses include the hemostats used as antibiotic carriers at the site of surgery, as carriers of chemotherapeutic agents and even pain medications. They're used as sealants for surgical access tracts as in pituitary hypophysectomy to prevent CSF leaks, as well as sealants for lung biopsy and liver biopsy to prevent, you know, air leaks and bile leaks, respectively. Used as embolic agents intraluminally in blood vessels. It's saved me several times in general surgery. I was happy to have our invasive radiologist around to use it, but it is, in fact, an off-label use.

And most recently and interestingly, it's been used as a barrier to detect bowel during thermo-ablation of liver tumors by adding a water-soluble contrast to the hemostat. It's injected under imaging guidance to protect, for example, the hepatic flexure from a liver tumor in the right lobe of the liver. So, these are concerns, but we don't regulate off-label uses of hemostats.

In summary, I'd like to say that since we have not seen new PMAs in over 20 years, and we understand collagen hemostats and can develop special controls, including clinical studies to assure safety and effectiveness. It seems reasonable to down-classify these hemostats if used as intended. Panel members, please keep in mind, however, that these devices are being used differently today compared to 1945, so please consider all available evidence, including these differences, when you vote on the appropriate risk classification of absorbable collagen hemostats.

Clarifying questions?

DR. LEWIS: I'd like to begin with a question, actually, then we'll turn to the Panel members, and I'm basing my question on the written material we were provided in the Executive Summary. And so, I've got some skepticism regarding this, but in the literature review we were presented, the FDA, after using MEDLINE and Embase, identified 919 articles that were published for what appear to be scientifically valid reasons. They excluded all but 13 of those reports --

DR. GIBEILY: Right.

DR. LEWIS: -- from consideration because they were not scientifically rigorous. Of the 13, only 4 were included as use of the agents in accepted indications. The others were off-label uses, basically. Of the four studies, one that you cited here was a randomized controlled study, therefore theoretically Class I; however, it included only 23 patients, and as you indicated, the subgroup analysis included only 1 and 5 patients in two different groups.

DR. GIBEILY: Right.

DR. LEWIS: So that study is actually scientifically completely invalid --

DR. GIBEILY: Right.

DR. LEWIS: -- because of small numbers, and it's worthless in demonstrating

anything, either complications or efficacy. The second study that was cited was a retrospective cohort study, numbers unspecified. By definition, it includes no controls, therefore no data regarding efficacy, and we really don't know about the complications. The last two studies were case control studies. Again, numbers were not provided, but by definition there are no controls. So, in the entire world's literature, nearly a thousand cases, we end up with zero literature that demonstrates either efficacy or safety of these agents. It's therefore difficult for me -- and you've cited a number of one-off, very significant complications. It's difficult for me to see how any of this justifies down-classification.

DR. GIBEILY: Yeah. You know, we do have a number of well-controlled PMA studies that we review that have not been published, and we look at safety and efficacy very carefully in those studies, and the PMAs that have been approved, have been approved based on those safety and efficacy studies that did not show up in the literature.

So, I have been conflicted, to be honest, and that's why we're presenting this to you all. I can say from what I have reviewed in some of our PMAs submitted, that we look very carefully at the safety, we use the best possible control that's already on the market, and we compare the subject hemostat to that best possible control, looking at endpoints such as hemostasis at 6 minutes, 3 minutes, and 10 minutes, looking for non-inferiority initially and then superiority, as well as safety endpoints, and they meet those criteria. And so the hemostats that are on market right now have gone through a very rigorous PMA process review.

DR. LEWIS: Well, again, there may well be other evidence than what we were presented, but what was present in the Executive Summary cited only two PMAs.

DR. GIBEILY: Right.

DR. LEWIS: One was submitted in 1995, the other in 1999. One was for

Hemostagene and the other was for Surgifoam Sponge. The first study was a 300-patient clinical study of general gynecologic, cardiovascular, and cardiac and vascular patients.

DR. GIBEILY: Right.

DR. LEWIS: However, the conclusion of that study, "The performance of the Hemostagene Sponge was not statistically different from the control sponge."

DR. GIBEILY: Right.

DR. LEWIS: The second PMA submitted in 1999, relative to the Surgifoam Sponge, reached a conclusion, again, "The performance of the Surgifoam Sponge was not statistically different from the control sponge."

DR. GIBEILY: Again, in these studies we look first for non-inferiority, and if they can show non-inferiority and they meet the safety endpoints, then they can then go on to demonstrate superiority. So, we start with a feasibility study, which is usually single-armed, and then go to a controlled study looking for non-inferiority.

DR. LEWIS: But, in essence, what the Panel is left with -- I mean, we haven't obviously seen any of these other studies that might demonstrate efficacy, but what we're left with is no evidence whatsoever for efficacy in the published PMAs that we received nor in the medical literature. It's really --

DR. KRAUSE: So, can I clarify? The PMAs you're talking about, those -- the sponges, the Hemostagene and the Spongostan were compared to approved hemostatic agents that were already considered safe and effective. So, the conclusion that they were not worse or, you know, not better basically says they were as safe and as effective as the previously approved products. So, in other words, they were compared to a product that was already approved for that use, and so the comparison was it's either as good, which was enough, or it's better, and in that case, they turned out to be just as good. So, I think, you know, that is evidence that those devices were safe and effective.

DR. LEWIS: Okay. I guess the final point that bothers me very significantly about this is that all of those old studies in the '90s were done with conventional anticoagulants, heparin and Coumadin basically, in any patients who were using them. The advent of the newer antithrombotic agents, basically Xarelto and a host of others, are really products of the last decade primarily, and therefore the antithrombotic products that patients can be expected to be utilizing, for whom these sponges will often be used in order to control bleeding in a surgical field, are basically confronting a completely different mechanism from the classical anticoagulants, and as far as I can gather from the reported results, we have zero studies evaluating the effectiveness of these in patients who are taking these newer and much more potent agents.

DR. KRAUSE: Yeah.

DR. LEWIS: So how do you -- how do you demonstrate efficacy of these devices in regard to this newer generation of anticoagulants?

DR. KRAUSE: So, the products that we would clear, once we've down-classified these, we would expect companies to do studies to show that they can -- if they wanted to label the product for use on patients who are anticoagulated, we would expect them to provide us with those data.

DR. LEWIS: But that would imply a PMA, which is Class III.

DR. KRAUSE: Well, no, we could -- we can collect clinical data in a 510(k).

DR. LEWIS: But you don't do that premarket.

DR. KRAUSE: We do.

DR. LEWIS: That's not -- okay.

DR. KRAUSE: Well, there are plenty of 510(k)s where we have requested and obtained clinical studies. There is no prohibition for us to collect clinical data in a 510(k). We do it often, yeah.

DR. LEWIS: Yes.

DR. MEURER: Will Meurer.

So, I guess if I understand it correctly, you know, the current studies would be your more contemporary studies, and we'll count the '90s as that. You know, the control is what was previously approved.

DR. GIBEILY: Correct.

DR. MEURER: So then if you take that back and back and back and back, that means the study -- it's basically all based on the study from 1945. Could you tell us a little bit about like what kind of control was used, I guess, in that sort of seminal study in 1945, because then that's really sort of the basis by which all these others are being compared. Can we trust that they're safe and effective compared to what they tested in 1945?

DR. GIBEILY: I mean, I don't know that study in particular, but I suspect it was compared to gauze sponges.

DR. KRAUSE: So, we can get into a really long discussion, but I'm going to give you a little FDA history. Effectiveness for drugs was not required until 1961 or 1962, so some of those older products that were approved by the Center for Drugs back in the '40s and '30s and before only required evidence that the product was safe. There were no requirements for effectiveness until the Kefauver Act in 1962, and after that, effectiveness became a requirement.

So Avitene did have a study, they did have safety and effectiveness compared to Gelfoam, which was done -- the study was done in the middle '60s or so, and everything subsequent to that, all the products were either compared to Gelfoam or Avitene or anything that was subsequently approved and so on and so forth.

DR. LEWIS: Dr. Pories.

DR. PORIES: You know, speaking as a consumer and as a potential patient, I'm

troubled by the fact that this Committee, which is supposed to make some decisions, has not been privy to the data. I mean, we've been told first that certain data is confidential and other data is -- well, we aren't sure of the data. But as we're sitting here, we don't have any information except the one you cited, which is really scientifically inadequate.

DR. KRAUSE: So, apologies that we didn't provide you with the links, but all of the approved PMAs since CDRH has been regulating these products are available, the summary of safety and effectiveness data are available on the FDA website. We probably should have provided you with the links, but all of those PMAs, the data are available on the FDA website.

DR. POSNER: Phil Posner.

Listening to what you just said about doing clinical trials and seeing what can happen, as a very naive person, I have to ask you what is the difference between Class II and Class III, of having to apply for a 510 versus PMA if you're going to ask them to do all the things that they would be doing in a PMA anyway? And so what advantage is there of down-classification to the patient, to the FDA, and to industry to change this? Because it sounds like all the things we asked, there's no difference between the two.

DR. KRAUSE: So, there are major differences. A PMA requires that the manufacturer provide annual reports every year. It requires that every change to the device, no matter how slight, requires a PMA supplement. All of those types of changes. It also reduces competition in the marketplace because less companies get involved in manufacturing these types of devices because they have to do a full-blown PMA to get in, whereas if we down-classify to Class II, other manufacturers can make products similar.

And if someone makes, let's say -- you know, the Gelfoam has a monograph in the USP. So, if somebody wanted to make Gelfoam -- something similar to Gelfoam, they could do so by making a product that meets the USP requirements, the monograph in the USP,

they would provide us with a 510(k) to show that their product is identical to Gelfoam that's on the market, and we would clear them for the same indications. However, if they wanted to expand on that indication, if they wanted to use that same product, if they wanted to put something in the labeling that we have not previously cleared for Gelfoam, we would either ask for animal data or human clinical data to show that they could actually do that, and we could do that in a 510(k). So, the other part of that is when a company wanted to change the source of, you know, where they buy the collagen or where they obtain various components of how they make their device, in a PMA you would need to submit something for every one of those steps whereas in a 510(k) you do not.

DR. POSNER: So, to go back to the question about the newer anticoagulants, the ones that were approved as a Class III would have to do the studies with the newer anticoagulants to be used. But if they're a Class II, they wouldn't have to do that unless someone was paying attention. If someone were asleep at the switch, they could slip one in without having to do those studies.

DR. LEWIS: Did you want to respond?

DR. KRAUSE: I'm sorry, I missed that.

DR. POSNER: The question with the newer anticoagulants, if it were approved under a Class III classification, they would have to do the studies automatically to cover the new anticoagulants. If they were approved under Class II, they would only have to do those studies if someone at the FDA required it. So, it means that we are assuming that the FDA will be totally vigilant under a Class II and catch the fact that they need to do a different set of studies for the newer anticoagulants.

DR. KRAUSE: You know, I don't know how to answer that. Certainly, we are vigilant, and we keep our eyes open and we read very carefully everything that's submitted, and if a company says that their product can be used with any anticoagulant, we would make them

prove it. And that would be in a 510(k) or a PMA.

DR. POSNER: But if it came on the market and one of the surgeons decided to use it, saying anticoagulants and assuming it was the same as all of the other ones that were out there and the new ones were in there, it's a difficult situation for safety, and as a patient, I'd worry about that, particularly someone who's on one of the newer anticoagulants.

DR. KRAUSE: So, currently, we don't regulate medical practice, and someone can do that anyway, whether they have a PMA or a 510(k), any legally available product, a surgeon or a physician can use any way they see fit. So, changing the classification wouldn't change off-label use.

Becky Nipper wanted to say something for the FDA.

MS. NIPPER: Hi. Becky Nipper, FDA.

I just wanted to explain a little bit. The reason that we haven't shared all of the PMA data that we have, it's actually a legal reason. We're bound by what they call the 6-year rule, which allows us to leverage and share data that is more than 6 years old but was after the 6-year rule went into effect, which was in 1997. So, basically, we have that window of data, PMA data, that we're allowed to share and that we're allowed to leverage as part of our reclassification, but kind of outside of that window and going back farther, we are legally not allowed to do that. So that's why you're not seeing all of those prior studies.

DR. LEWIS: But you have to realize that it places us in a very difficult position because, basically, the three sources of information which you provided us, which were existing literature, MDRs, and PMAs, that's all we received. Not a single one of those provides any evidence whatsoever for the efficacy of these devices under conventional anticoagulation, let alone under the newer anticoagulants. So, you're asking us to make a decision relative to safety and efficacy based on no objective data, and in fact, the only one we've heard from, an industry representative, recommends no change.

Since no other industry representatives are here, and we have to interpret that as a lack of interest on their part about the changes, the changes and the creation of a dichotomy between the collagen-based and the non-collagen-based hemostats, when they're both intended for exactly the same thing and are physically pretty much identical products, makes no sense to me. It's not clear at all to me, at least, what the impetus is for a down-classification since there's absolutely zero evidence that it's warranted.

MS. NIPPER: Understood. I just wanted to share the legal reason why we can only share a subset of the data from the PMAs. You know, the rest of the discussion is why we're here today.

DR. LEWIS: Yeah, but do you understand, do you understand the position that puts us in? I mean, you're --

MS. NIPPER: Understood.

DR. LEWIS: You're basically saying accept this on faith. That's really not our job.

DR. KRAUSE: So, again, all of the PMAs that are approved, and they were -- the last one for collagen was approved in early 2000 and it had a P99 number. All of the data for those are on the FDA website; they're in the summaries of safety and effectiveness data, and so those exist. What Ms. Nipper is talking about is all the specific data that are in the PMA, we can't release that, but what's in the summary of safety and effectiveness pretty much covers the clinical trial in total. All the adverse events, all of the, you know, issues that came up, they're all in the summary of safety and effectiveness, the entire clinical study. For all those PMAs that you saw listed up there, they all exist in the summary. So those summaries are available.

DR. MEURER: Bill Meurer.

So, I guess the effectiveness, though, if it's always being compared to like the old-school Gelfoam, at least on the website I can't find the summary of the clinical trial from

1945 that was comparing that to gauze, right? And I think that's the basis, this versus nothing. A lot of collagen versus collagen studies are only going to tell us so much, but collagen versus no collagen, I guess -- I mean, maybe I'm bad at looking at the website. I mean I'm trying, I'm trying to find that.

DR. KRAUSE: Right. So, again, as I mentioned, there was no requirement for effectiveness before 1962, so there was no clinical trial showing that Gelfoam was effective in 1945.

DR. MEURER: Okay. Then if this was still in the division of drugs, this would have been -- this stuff would have been pulled off the market like the antipyrine eardrops. I love to give my kids the stuff, their earaches. I mean, I guess you can't speak for the division of drugs but --

DR. KRAUSE: Well, I can answer that. So, after the law was changed in 1962, the Center for Drugs did call for new drug applications for all medical products that they felt needed to have data to support their effectiveness, and so there were some studies done. I think because of the long history of Gelfoam, the effective use, they never called for a new drug application for Gelfoam, so that never came in because there was -- there were -- you know, again, this gets very complicated, but there were many products on the market like, for example, Pepto-Bismol, there's never been a study for Pepto-Bismol.

But what Drugs decided was that because of the long history of the effective use of these products, that as long as they didn't change the labeling or change what it was to be used for, things along those lines, they could survive basically or grandfather it in based on their history. But if Pepto-Bismol said, you know, this treats sore throats, then they would be required to do a study.

DR. LEWIS: Yes, sir. Dr. Miller.

DR. MILLER: Yeah, Mike Miller here.

I'm a little concerned that we're getting into a theoretical discussion here that's losing some practical thinking here. These have been used for almost 70 years, I mean, they -- and I personally have witnessed their effectiveness. You know, they stop bleeding if they're used appropriately. So, this question whether we've proven that they're effective is a little bit of -- I think we're taking our eye off the ball a little bit. I mean, we also don't have studies which prove you just stop bleeding, period. I mean, you know, are we sure we should do that? I mean, where's the study that shows we need to stop bleeding? Maybe we don't have to stop it. You know, this is -- I think these have been around a long time, I think the -- requiring a PMA is really a barrier to entry to other products and other -- another industry, you know, people who may want to get involved in this. I don't think it's necessary. I think if you can show that what your product is, is like these existing products that have been around for almost 70 years, I'm good with that.

And then it's up to the surgeon to use their judgment as to whether they should use it in somebody with new anticoagulants or -- I mean, the profession has some responsibility here to learn to how to use these things appropriately, and we don't need to cede all that to the FDA. I mean, this is something that we can do as responsible surgeons. So, I'm very comfortable with just downgrading this.

I was on this Panel years ago, if I remember correctly. I mean, I remember a discussion like this. It seems like I remember it. It's been a long time, though, and my memory is fading on a lot of stuff, but this is -- I think we should -- I approve of the idea of downgrading it.

DR. LEWIS: Dr. Ashar.

DR. ASHAR: Hi. Yes, Binita Ashar, U.S. Food and Drug Administration.

I wanted to clarify for the Panel a little bit about the 510(k) process because I understand the concern related to great innovation occurring with respect to

anticoagulants that are being used in the marketplace and are very different today than the ones that were used previously in the initial collagen hemostat device studies.

So, if a manufacturer came to FDA and specifically wanted to market their device for use in anticoagulated subjects, FDA would hold them accountable because we would consider that claim to be part of their intended use, part of their indications for use. We would look at all of the labeling to understand the intended use of the device. And then if we determine that that was, you know, a substantially equivalent intended use, we would move down the 510(k) flowchart and request performance testing data specifically in patients that they wish to use their device with, anticoagulated with Xarelto, for example, or whatever the anticoagulant was, so that we would have clinical studies that would demonstrate safe and effective use of that product in those specific target populations. So, I just wanted to give this Panel that background that we are looking to keep pace with innovation.

The 510(k) process, in this capacity, is designed to do exactly that. So, the company could not market for these specific uses without providing data. And this Panel has the opportunity to flag this as an issue of concern and to propose other sorts of things related, perhaps, to the studies you would like to see in these specific target populations, for example, or any other safeguards, you know, allowing us to carefully and thoughtfully review these during the 510(k) review process. Thank you.

DR. LEWIS: Thank you.

DR. MILLER: Dr. Lewis.

DR. LEWIS: Yes, Dr. Miller.

DR. MILLER: I have a question to our FDA representative, quickly. Would requiring a demonstration of efficacy with the newer anticoagulants, would that be considered a special control that would be appropriate for a Class II or is that --

DR. ASHAR: I think that it would -- you know, you certainly could propose it as a special control, I think, you know, especially it would have to mitigate a particular patient risk, so you would have to identify the risk that -- you know, associated with the anticoagulants. So, thinking this through, the risk would be bleeding or lack of effectiveness, and the special control would be clinical studies potentially in these populations. You could propose it that way. There's many ways to accomplish this. Also, the natural review process could also take care of it because this would be a new population, an expansion of the indication, which would warrant a demonstration of safe and effective use in that population, whereby a study would possibly naturally be accomplished anyways. But the concern is understood from this Panel. If you have specific recommendations about how the study should be conducted, about the level of evidence that would be necessary to get those specific claims for those specific populations, that sort of information would be very helpful to us. Rather than the actual mechanics of the process, we would appreciate the scientific input that this Committee provides.

DR. KRAUSE: Let me just say we have had companies that have a cleared 510(k) for a certain wound dressing, which is a Class II device, who have come to us and have wanted to indicate their product for use on anticoagulated patients, and we required them to provide us with a clinical study in a 510(k) so that they could get that indication. So, the fact that we would make these products Class II would not change the fact that we could collect clinical data for any new claim that we think warrants the use of a clinical study.

DR. LEWIS: Dr. Posner.

DR. POSNER: Yeah, I'm just an uneducated patient, but just off the top of my head, I think about a company coming in and improving the adhesiveness of the anticoagulant, particularly the powder, and I'm then assuming that because we didn't think of listing that as something that you need to look out for, that somebody in FDA is going to think about

sensing that you need to look out for, and if I can think of that, there must be a whole bunch of other pharmacokinetics and different physical changes that can be added to the new product that, unless somebody picks up on it, won't be asked to be tested, and I worry about that, whereas if it stays in Class III, it would automatically be tested, because of the side effects we talk about, they hang around for how much time? They hang around --

DR. GIBEILY: Two to three months.

DR. POSNER: -- for too long.

DR. GIBEILY: Yeah.

DR. POSNER: But if somebody comes up with a new product that actually seals quicker, it might also hang around for a longer time, and if you don't ask to study that, then we don't have the clinical data to see whether we do get the other side effects. And I'm just saying -- I won't talk for my colleagues, but I'm not bright enough to think of all the things that we ought to list as special things that ought to be looked at.

DR. LEWIS: Dr. Hicks.

DR. HICKS: Yeah, if I could just back up a step. I don't think I got my arms around the idea of you're rolling along with a classification of III, and all of a sudden now we need to go to II. In your office and behind the scenes, behind the curtain, what's the real impetus for this?

DR. KRAUSE: So, I think Dr. Pierce is going to get into it a little bit, but back in 2002 we looked at all the information that was available, and we said, you know, these products have been around forever. We've had so many PMAs, we've done this -- we've done the same, you know, basic clinical study multiple times, and we think these devices are a good candidate for down-classification. So, we brought it to this Panel, and the Panel said, well, what are the special controls? And we said, oh, well, you know, we'd like you to give us some advice and they said, well, we'd like to know what you think the special controls

should be, so they tabled the discussion and so that -- you know, we brought it back in 2003.

This time we brought the special controls, the Panel took a look at it, and they said, yeah, these have been used forever, they're safe, nobody's had problems with these, there are very few adverse events. Most of the surgeons at the table said, you know what, we've used these for years, they're safe and effective, we think the special controls that you are recommending are adequate, and they voted unanimously to down-classify. There were various impediments over the years, and I really don't want to get into that, but it had nothing to do with the fact that we -- you know, we still wanted to down-classify.

But then in -- I'm not sure when it was exactly, but fairly recently there was a genuine large effort at the Center to figure out what products we could put under less -- you know, less restrictive regulation, you know, the least burdensome idea of how much, you know, regulation is necessary for products to be used safely and effectively. The FDA -- I mean CDRH, everybody in CDRH went through all of the devices that they regulated and came up with a list that could be down-classified, and this was one of those that was put on that list, the LMF products. So that's the latest impetus for trying to get these down-classified again.

To the question that Dr. Posner --

DR. HICKS: Wait a second. I want to follow up.

DR. KRAUSE: Let me just say, to the question Dr. Posner posed about changes to the device that we can't anticipate, FDA deals with that every day, and when we try to down-classify something, we can only down-classify what we've seen, okay? When something comes in, there's a process that we go through, and you know, I don't want to go through the whole process, but we go through various steps, and if something in the device has changed, let's say first, the indication, to the point where we think it's a new intended use,

we can kick it out of the 510(k) process, and we can raise that product for the new indication to a higher level. We can make it -- you know, we can make it a PMA, or we can look at it in the terms of, yeah, we think it's still Class II, but it doesn't fit this regulation anymore, and we can write a new Class II regulation. And then the next step is when we look at it as if we think the technology has changed significantly, we can make that assessment again, and we can kick it out if we think we're coming up with different questions that we've never asked about that type of product before. We can kick it out of the review process for 510(k), we can move it again to either a PMA or we can write a new Class II regulation. So, there are ways that we can address that. It's not that, you know -- we have to anticipate there's going to be changes to products over the years, and that's going to happen. But when we do reclassification, we can only reclassify what exists. We can't anticipate. And, you know, you're ahead of the curve, you're looking way down the road, which is a good thing, but we can't anticipate what's going to happen and so keep things in Class III because we think, well, you know, somewhere down the line somebody's going to come up with this different product.

That's difficult to do because we could do that for every product. We could say, you know, these things are going to change so much over the years, we better keep them in Class III. That's not the way we look at things. We look at what's the information we have today, what is the history, what are we seeing in MDR reports, what are we seeing in multiple different -- you know, the literature, everywhere that we look around, and then we decide, or a company could, or an individual could submit. We receive many petitions saying down-classify these to Class II. So, these things happen, and so, again, we can't anticipate what's going to happen. We only can react to what's current information.

DR. LEWIS: Yes, Dr. Levy.

DR. HICKS: Can I just finish my question? I'm concerned about this, too. So, they're

concerned enough to go from II to III. We don't have much data, and we're going to go III to II. In the interim from the last time that a panel looked at this issue and going forward, has this come up before where they pointed out about lack of good scientific data?

DR. KRAUSE: So, I could go look at the transcript from 2003, but I don't think that came up. I think the Panel was satisfied that the data that were available were fine.

DR. LEWIS: Dr. Meurer.

DR. MEURER: Will Meurer.

So, to maybe summarize, the primary public health and regulatory benefit to down-classifying is that if we assume that there might be better things that companies, and sponsors could make; they would have more of an incentive to do so if it was classified as II versus III because the PMA process represents a more substantial barrier.

DR. LEWIS: Seeing no further questions, thank you, Dr. Gibeily. We'll call Ms. Karen Nast to the podium for her presentation.

MS. NAST: Hello, I'm Karen Nast from the Division of General Surgery Devices in CDRH. I'm going to provide an overview of the MDR data available for absorbable collagen-based hemostatic devices.

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including underreporting, data quality issues like the potential submission of incomplete, inaccurate, untimely, unverified, or biased data.

Limitations of the MDR regulation: A lack of MDRs does not necessarily mean there are no problems. It is not possible to definitively determine a causal relationship between an event and device based on MDR data alone.

And, finally, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential underreporting of events and lack of information about the total number of devices.

This graph shows the number of MDRs received each year for absorbable collagen-based hemostatic devices. FDA received a total 165 MDRs between July 24th, 2003, and December 31st, 2018. July 24th, 2003, was chosen as the start date for this analysis in order to capture MDRs received since the date of FDA's last panel meeting conducted to discuss reclassification of absorbable hemostatic devices, and that was held on July 24th, 2003.

In comparison to the number of adverse event reports, absorbable hemostatic devices are used in millions of surgeries each year. For example, in 2012 alone, absorbable hemostatic devices were used in 6.9 million surgical procedures, according to a market report conducted by Life Science Intelligence in 2013.

The MDR database was searched between July 24th, 2003, and December 31st, 2018. There were 8 deaths, 117 injuries, and 40 malfunctions. The deaths included several cases of off-label use. Most of these reports were submitted by the manufacturer.

The most commonly reported device problems include off-label use, packaging issues and failure to be absorbed, poor adhesion and poor absorbency. Off-label use includes reports of arterial embolization and sclerotherapy. The most commonly reported patient problems include infection, allergic reaction, foreign body reaction, paralysis, hematoma, acute renal failure, hydrocephalus, numbness/tingling, nerve compression, seizure, and loss of bowel or bladder control.

Thank you. I'll take any questions.

DR. LEWIS: Are there any questions at all from the Panel?

(No response.)

DR. LEWIS: I gather that the central thrust of your testimony is that while the complications that are reported are really over a 15½-year period, and so they average only about 10 per year, and compared with the total usage during that time, that's in essence an

inconsequential number, since it was cited in our summary that these devices, in 2012, were used about six million times. And so, if we talk about if the MDRs were even underreported by a factor of 10, the incidence would still be quite low. So, I gather the central thrust of your testimony is that although the complications are severe, they're rare. Would that be correct?

MS. NAST: That is true. We receive very few MDRs for these devices.

DR. LEWIS: Okay, thank you.

MS. NAST: Thank you.

DR. LEWIS: I'll now call on Dr. Adam Pierce to present the FDA proposal for reclassification and special controls.

CDR GARCIA: He stepped out. Just give me a minute.

DR. LEWIS: Huh?

CDR GARCIA: He stepped out. I'll be right back.

DR. LEWIS: Okay. Apparently, he stepped out and will be back shortly.

UNIDENTIFIED SPEAKER: He'll be right back.

(Pause.)

DR. LEWIS: Dr. Pierce, do you --

DR. PIERCE: Sorry about the bathroom break.

DR. LEWIS: No problem.

DR. PIERCE: Hi, I'm Dr. Adam Pierce on behalf of the FDA. Right now, I will present FDA's proposed approach to reclassification of absorbable collagen-based hemostatic devices. I will present our proposed approach to identify the absorbable collagen-based hemostatic devices with a specific definition of device type and its use and to specifically identify them as Class II devices. Additionally, FDA has drafted special controls that would provide a reasonable assurance of safety and effectiveness for these devices.

Since this reclassification has been proposed to the Panel in the past, it is important to summarize previous reclassification efforts and the conclusions derived from them.

In 2002 FDA convened the Panel to discuss FDA's proposed reclassification of all absorbable hemostatic devices to Class II. Of note, this proposal for reclassification considered all absorbable hemostatic devices under 21 C.F.R. 878.4490 and did not differentiate between collagen-based, non-collagen-based, and collagen-based hemostatic devices with added biologics. The Panel postponed a recommendation until their review of a special controls document could provide a reasonable assurance of safety and effectiveness of these devices as Class II.

In 2003 the Panel reviewed a draft special controls document that was presented by FDA. After review of the special controls, the Panel made a unanimous recommendation to support reclassification of all absorbable hemostatic devices to Class II.

In 2006 FDA proposed an order to reclassify all absorbable hemostatic devices to Class II and published an accompanying draft special controls guidance document. Due to administrative reasons, FDA delayed continued efforts to reclassify these devices until 2014 when these efforts were reinitiated by CDRH's strategic priority entitled "Strike the Right Balance between Premarket and Postmarket Data Collection." This strategic priority initiated a retrospective review of Class III devices to determine whether or not, based on our current understanding of the technology, reclassification may be appropriate.

The results of this retrospective analysis were published in 2015 with a recommendation to reclassify absorbable collagen-based hemostatic devices with the product code LMF. FDA did not recommend reclassification of absorbable collagen-based hemostatic devices containing biologics with product code PMX or non-collagen-based hemostatic devices with product code LMG because FDA does not have extensive experience in the review of these types of devices or because their technologies continue to

evolve.

FDA's current proposal is to reclassify absorbable collagen-based hemostatic devices as Class II with the following identification: "An absorbable collagen-based hemostatic device is a device that is placed in the body during surgery to produce hemostasis by accelerating the clotting process of blood. The device type is predominantly composed of collagen-based materials derived from animal sources and is absorbable."

Based on available evidence, FDA has identified the following potential risks related to the use of absorbable collagen-based hemostatic devices:

- Uncontrolled Bleeding
- Hematoma
- Infection
- Wound Dehiscence
- Foreign Body Reactions
- Immunological Reactions
- Adhesion Formation
- Failure to be Absorbed
- Interference with Methylmethacrylate Adhesives
- Aspiration into Blood Salvage System Filters
- Embolization
- Paralysis/Nerve Damage/Tissue Necrosis
- Disease Transmission and
- Toxicity

We have proposed to mitigate these potential risks with the following measures:

- Material Characterization
- Nonclinical Performance Testing

- Biocompatibility Testing
- Shelf Life
- Sterility
- In Vivo Evaluation and
- Labeling

For each potential risk identified, each mitigation method may be combined with other methods to adequately mitigate each risk. In the Executive Summary provided to the Panel, FDA has included Table Number 2 to clarify how we intend to mitigate each potential risk using one or multiple mitigation methods. Section 9 of the Executive Summary describes how these mitigation methods are incorporated into proposed special controls. To further clarify how these mitigation methods will be implemented as part of the proposed special controls, FDA would like to briefly describe each proposed mitigation approach.

An absorbable collagen-based hemostatic device is dependent on its material characteristics to ensure device safety and effectiveness. As part of FDA's proposed special controls, material characterization should include material source information to mitigate the risk of disease transmission from animal-derived materials. The processing of these types of devices typically use hazardous reagents such as cross-linkers that can affect the safety and effectiveness of the finished device. Therefore, it is important to ensure that the cross-linking density is provided, that material processing information detailing all manufacturing agents and residual amounts of processing reagents are quantified.

Device-related particulates may inadvertently enter blood vessels to cause embolism and may enter into blood salvage systems where they can cause clogging of blood transfusion filters. Device-related particulates may also significantly impact the ability of the device to achieve hemostasis, thereby resulting in uncontrolled bleeding. In order to

mitigate these risks, FDA believes that device-related particulates must be characterized to maintain device safety and ensure adequate device performance.

Collagen-based devices are known to elicit foreign body reactions and immunological reactions. In order to mitigate these risks, FDA believes that collagen characterization information, including elemental analysis and decellularization efficiency determination, must be provided to demonstrate the identity, purity, and quality of the collagen used.

To mitigate the risks of foreign body reaction, immunological reaction, and failure of device absorption, FDA believes that all patient-contacting components of the device must be demonstrated to be biocompatible and that all residual reagents in the final product must be demonstrated to be safe for human exposure. Because the risks of infection and disease transmission can arise from a contaminated device, sterility testing must demonstrate the sterility of patient-contacting components and acceptable levels of endotoxins and material-mediated pyrogens.

Deterioration of the device over its shelf life may also lead to immunological reactions and failure of the device to be absorbed. Device deterioration over time may also lead to inability of the device to achieve hemostasis, thereby resulting in uncontrolled bleeding.

Device swelling must also be controlled throughout the duration of the proposed shelf life in order to mitigate the risks of paralysis, nerve damage, and tissue necrosis.

Additionally, the loss of package integrity over time may lead to compromised sterility causing infection.

Therefore, performance data must support the shelf life of the device by demonstrating continued sterility of the device, package integrity, and device functionality over the identified shelf life. The labeling must specify an expiration date or shelf life based on such performance data.

FDA believes that nonclinical performance testing must be conducted to demonstrate that the device performs as intended under anticipated conditions of use. To mitigate the risks associated with uncontrolled bleeding and hematoma, nonclinical performance testing must include characterization of the in vitro clotting time of the device. Since unintended device effects such as paralysis, nerve damage, or tissue necrosis can occur from device swelling, nonclinical performance testing must characterize the amount of swelling, such as the change in volume or the change in the weight of the device.

Because device performance may be adversely affected by the concomitant use of other devices, and to deliver an absorbable collagen-based hemostatic device to surgical devices, such examples are laparoscopic graspers, applicators, or surgical sealants. Nonclinical performance testing must also be conducted to demonstrate reliability of the delivery system and compatibility of the delivery system with the absorbable collagen-based hemostatic device. In order to demonstrate that the device performs as intended under anticipated conditions, FDA believes that additional nonclinical performance tests need to be conducted.

To mitigate the risk of a failure of absorption, nonclinical performance testing must characterize the absorption of the device under physiologically relevant conditions. To mitigate the risk of device fragments being embolized, the fragmentation rate of the device must be characterized.

In addition, certain nonclinical performance tests that are device specific based on the technology or the indications for use would have to be conducted. For example, for absorbable collagen-based hemostatic devices intended for use on bone surfaces, bench testing must be conducted to demonstrate that the device does not interfere with the bonding strength of methylmethacrylate adhesives.

For devices intended to be used in applications involving blood transfusion systems,

nonclinical performance testing must demonstrate that the device does not impair the proper operation of the blood transfusion system. For example, the device may be passed through a cell salvage system under various filtering conditions to mitigate the risk of aspiration into blood transfusion filters.

To prevent unintended adverse device effects due to improper device use such as uncontrolled bleeding, embolization, and tissue or nerve damage from device swelling, FDA believes that usability testing must demonstrate that the device design and labeling are sufficient for the device to perform as intended. The reliability of the device deployment mechanism and compatibility with devices used in deployment must be evaluated in vivo.

The FDA also believes that in vivo evaluation of the device must be conducted to demonstrate that the device controls bleeding and that the device does not promote adverse or local systemic effects under anticipated use.

In order to properly evaluate bleeding, the in vivo models chosen for the intended application of the hemostatic device must represent the intended use, including the type of bleeding and targeted tissues of bleeding, and a validated bleeding scale must be used for selection and evaluation of bleeding sites to support the intended use.

To demonstrate that the device controls bleeding within a clinically meaningful time and to mitigate the risks associated with uncontrolled bleeding and hematoma, in vivo evaluation must demonstrate its effectiveness of hemostasis at 10 minutes or less, including with respect to time of bleeding cessation, rebleeding potential, blood loss, as well as hematological and clinical chemistry parameters.

To mitigate risks associated with embolism, in vivo evaluation must characterize thromboembolic risk.

To mitigate risks of immunological reaction and foreign body reaction, in vivo evaluation must characterize the immunogenicity of non-mammalian collagens as well as

inflammatory cell response or potential histotoxicities.

To mitigate the risk of failure of absorption, in vivo evaluation must characterize time to complete absorption.

To mitigate several risks including foreign body reaction, infection, immunological reaction, and adhesion formation, in vivo evaluation must include macroscopic and microscopic histology at the implant site and sites distant from the implant site.

Many of the risks associated with absorbable collagen-based hemostatic devices are related to the surgical procedure involving selection or use of the device. FDA believes that appropriate labeling, including specific instructions for proper deployment by users, appropriate warnings, precautions, and limitations needed for the safe use of the device, and information on how the device operates and the typical course of treatment must be provided to mitigate these risks.

For example, the risks of immunological reaction, foreign body reaction, infection, and uncontrolled bleeding may be mitigated by providing appropriate information on patient and/or site selection for use of the device.

The risk of paralysis, nerve damage, and tissue necrosis may be mitigated by providing instructions of deployment of the device in confined spaces and information on the amount of device swelling that is anticipated to occur.

The risk of wound dehiscence may be mitigated by providing a warning that the device may interfere with the healing of wound edges. The risk of aspiration into blood salvage system filters may be mitigated by providing warnings not to utilize the device in conjunction with autotransfusion systems.

In addition, FDA believes that due to the risk of embolism and documented harm when used in such situations, that a contraindication for intravascular application of the device must be provided unless data demonstrates safe use in such situations.

FDA believes that providing a detailed summary of the in vivo evaluation in the labeling, pertinent to use of the device, will further help provide users with adequate information needed to inform proper selection and use of the device.

Finally, for absorbable collagen-based hemostatic devices intended for general surgical use, a hemostatic effectiveness table comparing the ability of the device to achieve hemostasis, such as time to hemostasis, in multiple specialties of surgical procedures must be provided to mitigate the risks associated with bleeding, such as uncontrolled bleeding and hematoma.

After reviewing the available evidence, FDA believes that general and special controls are adequate to mitigate the risks to health and to provide a reasonable assurance of safety and effectiveness of absorbable collagen-based hemostatic devices.

In addition, when considering the evidence available to the FDA, FDA believes the on-label use of absorbable collagen-based hemostatic devices presents no more than a moderate risk to the patient. The reports from the MDRs are minimal in comparison to other implantable devices and suggests that the device-related risks are not changing.

Additionally, FDA believes that the technological characteristics of absorbable collagen-based hemostatic devices have not significantly changed in over 20 years.

FDA believes the potential risks associated with device use can be adequately mitigated through the proposed special controls.

If absorbable hemostatic devices are to be reclassified to Class II, future absorbable collagen-based hemostatic devices will be regulated using a 510(k) pathway instead of a PMA pathway. In other words, future absorbable collagen-based hemostatic devices would be subject to a shortened premarket review process with reduced control of manufacturing without a requirement for annual reporting.

Clinical data would not be needed for every 510(k), although clinical data may still be

requested through the 510(k) process. FDA may request clinical data, for example, when an absorbable collagen-based hemostatic device contains a new technology or a new indication for use, such as a use of the device in a new surgical specialty.

I'd like to take this time to answer any clarifying questions. I'm sure you have a lot.

DR. LEWIS: When you speak about some of these various testing models and you talk about in vivo testing whatever, I assume you mean animal testing; is that right?

DR. PIERCE: That's correct, yes.

DR. LEWIS: Does the FDA do that, or do you require that of the companies?

DR. PIERCE: We require the company to do that.

DR. LEWIS: Okay. Also to recapitulate what's already been discussed at some length is while the hemostatic agents themselves have not changed in 20 years, the anticoagulant environment in which they're expected to perform has changed dramatically, and I guess that's still one of my principal concerns is these more potent anticoagulants might be expected to create a clinical situation which is very difficult to reverse compared with traditional, and so that would seem to be one area where testing is needed to ensure effectiveness.

DR. PIERCE: Yeah. So, FDA is definitely aware of that specific concern. You don't see the MDR data suggesting that it is an evolving risk. And also, I would like to mention all the currently marketed devices that are out there are being used in this setting; however, they're not specifically labeled for use for anticoagulated patients. I'm not aware of any absorbable hemostatic device that tested specifically on anticoagulated patients and are labeled for it. So, unless we have a safety signal, I don't -- you know, I don't foresee a change in how we address it. But I think we interrogated before, it's extremely likely if somebody said I want to be indicated for anticoagulated patients, we would make sure that sufficient performance data is supporting that.

DR. LEWIS: Yeah, but it will come -- I mean, people will rarely use it for that specific indication, but it would be a clinical accompaniment of taking care of a wide variety of patients today. It would simply be a realistic issue.

DR. PIERCE: Yeah. And that issue was considered in the previous clinical studies when the cardiovascular patients were included or cardiothoracic patients. That was always a point of consideration when conducting the clinical trials, and that would always be included as inclusion or exclusion criteria or a revision of the protocol to ensure reversal of, say, heparin or in this case, an antidote for Xarelto.

DR. LEWIS: Questions from the Panel.

Dr. Bloom.

DR. BLOOM: I would just make the comment that when the NOACs, when the new generation of oral anticoagulants came out, the big problem was that we didn't have a reversal agent for them. As clinicians, that was a big problem. But now that we do have agents available to reverse, it's not as much of an issue. Speaking as a trauma surgeon, certainly that was a big problem for us. When I have to operate on a patient that is on one of these new agents, I don't expect I can get the hemostasis unless the agent is reversed, or I give platelets, for example.

To take that a step further, I don't think it should be the burden of the manufacturers of a piece of a collagen that I might put on an oozing surface to prove that it works in the face of these novel anticoagulants. It's part of my practice to reverse as much as possible, whether it's reversal of Coumadin or reversal of heparin or reversal of these normal agents, the collagen itself -- our understanding of the coagulation cascade, which is changing monthly, the group at Denver is changing what we really think we know about it, the effect of collagen activating platelets should be distinct from the linking of thrombin on platelets and forming a platelet plug. I wouldn't make it a function of the collagen

manufacturers to have to show specific efficacy in that condition.

DR. PIERCE: I think you did emphasize that good clinical judgment is going to consider these factors.

DR. GIBEILY: Right. And just to add to that, these studies are not done with the use of anticoagulation or antiplatelet drugs as an exclusion factor. They're not intended to be used in that setting. And just to reiterate, clinical studies are not excluded in the 510(k) process. They are very much a part of the 510(k) process. They are a special control and we do -- we can request clinical studies. And I don't think there'd be a lot of inertia because we're not talking about long-term studies here; we're talking about, you know, does it work or doesn't and in specific situations.

DR. LEWIS: Dr. Posner.

DR. POSNER: Yeah, it was a very nice presentation. A question I have about your phrasing of hemostatic efficacy and the concept that comparing it against the original ones where there was no test of that, knowing what that definition entails and how that might affect the region of efficacy as opposed to thrombus and embolus formation. And I'm sure you guys can do that, but just in my head, for you to define what you mean by efficacy, how it's going to be measured, and since you may not have short-term models on this, whether you might ask for follow-up on these to see whether there is a thrombus or embolus problem 1 year down the road or 6 months down the road or what have you.

DR. PIERCE: Yeah. So that's an important point. We, as a team, developed these special controls around all the non-confidential and confidential information that we have for all the approved devices. So, in terms of hemostatic effectiveness, we leveraged the performance of all the previous approved -- the previously approved devices that we're recommending down-classification, to make sure that the performance is not diminished over time.

(Off microphone comment.)

DR. PIERCE: Correct. So, we wanted to leave that, you know, up to you guys as well as, you know, we have an opinion. Cardiovascular patients, we routinely hear, are not going to be allowed to bleed for 10 minutes. I think that would be -- you could have a whole conversation on that. So, we wanted to make sure that we have an upper boundary, and as you mentioned, lower boundaries can actually have unintended side effects that we monitor in, say, a survival animal study.

DR. LEWIS: Thank you for your presentation. Oh, I'm sorry, we have one more question.

DR. LEVY: Thank you. I'm a little confused. For the special controls, they're designed to -- or they're based upon a demonstration of the following "risks to health for absorbable collagen-based hemostatic devices," and 1a and 1b, uncontrolled bleeding and hematoma, I'm having trouble reconciling that as a risk to health related to the collagen device. That seems more to me like if the device was ineffective, that would be the -- these would be the consequences. I can see unique situations where a hematoma that contains a collagen product might be a unique consideration, but I'm having trouble reconciling at least these two as risks to health associated with the collagen device that would be charged to the companies producing the products. Can you clarify that for me?

DR. PIERCE: Right. So, we considered the scenario where if a device was ineffective, what would happen. You would see an increase in the intraoperative time, you would essentially negate all the benefits of using these devices. So, we're trying to make sure that we have a reasonable assurance of effectiveness. Did I answer your question? So, a lack of effectiveness can be a safety concern. It is not always a safety concern.

DR. LEVY: I think that last point clarified it.

DR. PIERCE: Okay, perfect. Thank you.

DR. GIBEILY: Could I add one more thing? Just to reiterate, these hemostats are intended for minimal, mild, and moderate bleeding. Moderate equates to flowing, which gravimetrically is equivalent to 10 cc a minute. Anything more than that they shouldn't be used for. And we do have a bleeding scale that these hemostats have to meet compared to a control, and if they're used for bleeding beyond that, they're being used off label. Ten cc per minute is the upper level.

DR. LEWIS: Thank you very much for your presentation, Dr. Pierce.

DR. PIERCE: Thank you.

DR. LEWIS: We'll now take a 15-minute break and reconvene at 10:15. And, I would like to announce that we are markedly ahead of schedule, and at 10:15 we will have the open public forum rather than at 1:00. Currently, we know of only one person who wishes to speak at that forum, and so it will not require an hour but a very short period of time, which means we will be able to turn to the FDA questions fairly quickly this morning and potentially finish before lunch. So, I would like to provide you all with some motivation in thinking about that.

(Laughter.)

DR. LEWIS: Because leaving Washington on a Friday afternoon is going to be disaster no matter which way you go, and so it would be dramatically in your interests to convene this session in a concise and expedited manner.

We'll now take a 15-minute break, reconvene at 10:15 with the open public forum. Thank you.

(Off the record at 10:04 a.m.)

(On the record at 10:15 a.m.)

DR. LEWIS: We will reconvene the General and Plastic Surgery Devices Panel, and before we proceed, Dr. Krause wishes to make an announcement.

DR. KRAUSE: Right. I just wanted to clarify one fact. Becky Nipper mentioned that the 6-year rule goes back to 1997. She asked me to correct her mistake, that actually it goes back to November the 28th, 1990. So just to clarify in the record that the date for application of the 6-year rule goes back to files that were submitted to the FDA on or after November 28th, 1990, okay? Thank you.

DR. LEWIS: We'll now proceed with the Open Public Hearing and call to the podium Ms. Stephanie Fox-Rawlings from the National Center for Health Research.

(Off microphone comment.)

DR. LEWIS: I'm sorry. Ms. Rawlings, pardon me. Commander Garcia needs to make a brief announcement first.

CDR GARCIA: Thank you, Dr. Lewis. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you, Dr. Lewis.

DR. LEWIS: Thank you.

Ms. Fox-Rawlings, would you proceed?

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-Rawlings. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We understand the desire to make it easier for new products to get onto the market, but down-classifying collagen-based hemostatic devices would allow similar products to enter the market with much less scrutiny. The collagen-based hemostatic devices currently on the market have been shown to have benefits that outweigh the risks. To ensure that any new versions of these products are safe and effective or as safe and as effective as those already on the market, new products should be tested in clinical trials.

Different formations of collagen-based devices or different sources of collagen may not have the same level of benefit or the same risk profile as currently approved devices. Changes in the delivery system can also affect these profiles. In vivo examination in a small number of animals or humans may not accurately identify these differences. Well-designed clinical trials with appropriate controls and a sufficient number of participants are needed to determine if the benefits of a new product outweigh its risks.

A major problem with the 510(k) pathway which is used for Class II devices is that it does not establish either safety or effectiveness of new devices. This was the conclusion of an Institute of Medicine report back in 2011 and is still a problem today. Most Class II devices are not reviewed by this Advisory Committee, so I will quickly summarize the problem.

Instead of demonstrating that a device is safe and effective in clinical trials, Class II devices must have evidence that they are substantially equivalent to a device already on the market. That might seem reasonable, but the definition of substantial equivalence has been widely criticized in the medical literature and in the media. FDA has allowed Class II devices to be sold even when they vary dramatically from the previous device, such as using different materials and having a different mechanism of action. Special controls are supposed to support claims of safety and effectiveness, but without clinical trials, they are frequently not sufficient.

Even more concerning, devices that have been recalled or removed from the market because they do not work or have unacceptable risk can still serve as a substantially equivalent device for a new Class II device. This means that while current collagen-based hemostatic devices may be safe and effective, this may not be the case for future substantially equivalent devices which could put patients at undue risk for harm.

Changing the classification of these devices could benefit some companies that want to sell these devices, but it may harm patients or their physicians. Patients and their physicians can't make informed treatment decisions without clear, scientific evidence of safety and effectiveness.

There is currently no system in place that includes all or even most adverse events that occur due to collagen-based hemostatic devices or most other devices. The current reporting system relies on voluntary reporting by patients or health professionals and comprise only a small proportion of the adverse events that occur.

The FDA does not have the authority to require postmarket studies of new Class II devices unless evidence arises later that they might be less safe or less effective than expected. This would typically be delayed for years after the product was sold. Meanwhile, thousands of patients could be harmed.

The safety and effectiveness of new devices needs to be established before they are approved. Approval of products without this evidence puts patients at risk for unnecessary harm. Adequate and well-controlled clinical trials are the best way to establish that the benefits outweigh the risks for patients needing collagen-based hemostatic devices.

Thank you.

DR. LEWIS: Questions from the Panel?

Dr. Meurer.

DR. MEURER: Will Meurer.

How would you design a trial to test the safety and effectiveness of a collagen hemostatic device?

DR. FOX-RAWLINGS: I don't think I am completely qualified to answer that because I am not -- I'm afraid I'm not well enough informed about what the good comparisons would be, but it definitely needs to have sufficient numbers, it has to have controls. I think randomization is an important issue in this case because we need to make -- try to eliminate as many biases as possible.

DR. LEWIS: Dr. Fox-Rawlings, I appreciate the points you've made, and obviously, some of that was raised earlier. I think the overwhelming issue here in consideration to the Panel, and I hesitate to speak for other people, but in the data presented, the number of MDRs reported yearly averages between 10 and 11 over a 15-year period. For the year 2012, the usage of these devices was cited to be between six and seven million. Even if we assume that MDRs are underreported tenfold and let's say there would be 100 per year, the ratio of 100 adverse reactions to six million usages clearly still puts the risk to patients at an exceedingly small number, somewhere under 1%. Based on that, why do you cite that there is -- there might be a significant human risk to the approval of these as a Class II device?

DR. FOX-RAWLINGS: I'm not sure I would assume that even a tenfold would not be

an underestimation. These are voluntary, and I do not -- I think many -- I think the reports to FDA are much, much lower than the actual adverse events, and that's in part because if you're using a device, are you going to automatically go and report something just because something happened? Are you going to say, oh, well, it must be the device, or how many people even know to report? For this particular type of device, I can't even estimate what that sort of ratio would be.

I very much take your point, and the concern is more part of -- a large part of our concern is the problems with the 510(k) process that could allow fairly different products that have a very different risk-benefit profile than current devices to be allowed on the market without clinical testing. So, it's not necessarily the devices that are out now or even something that would be very, very, very similar to the current devices. It's more as they change and develop, if they aren't tested with clinical trials, then we may not be able to accurately predict what those benefits and risks ratios are.

DR. LEWIS: Oh. I think the difficulty that we might see is that, based on the citations provided in the literature review that the FDA did, which I assume was complete and conscientious, we've heard in the critical review that over, in essence, a 40-year period there isn't a single study that demonstrates safety and efficacy of these devices; therefore, proposing that that be done is not so simple.

DR. FOX-RAWLINGS: Well, the FDA has said that they have those studies for the PMA. I mean, for a PMA device you have to have clinical trials of some sort, so whether or not they're published in the literature, that is a separate question from whether or not -- I assume the FDA has established that the ones that are on the market have benefits that outweigh the risks, that is part of what the approval process is.

DR. LEWIS: Yeah. Unfortunately, they're keeping it secret from everybody. All right, thank you --

DR. FOX-RAWLINGS: And that's --

DR. LEWIS: -- for your presentation.

DR. FOX-RAWLINGS: Yeah.

DR. LEWIS: It's very clear.

DR. FOX-RAWLINGS: Thank you.

DR. LEWIS: Are there other speakers who wish to speak at this public forum?

(No response.)

DR. LEWIS: Seeing none, we will proceed to the FDA questions. I believe Dr. Pierce is going to present those.

DR. PIERCE: Hi, I'm Dr. Adam Pierce for the FDA. FDA has a series of specific questions to the Panel to provide input into the currently proposed reclassification effort and special controls. Based on the feedback from yesterday, I'm going to summarize the really long questions, so Panel members, you have the entire question in front of you and the rationale.

Question Number 1: FDA has identified the following risks to health for absorbable collagen-based hemostatic devices based on reports in the Medical Device Reporting database, information available to FDA under section 520(h)(4) of the FD&C Act, the published literature, and the recommendations of the 2002 and 2003 Panels. The risks are:

- Uncontrolled Bleeding
- Hematoma
- Infection
- Wound Dehiscence
- Foreign Body Reaction
- Immunological Reaction
- Adhesion Formation

- Failure to be Absorbed
- Interference with Methylmethacrylate Adhesives
- Aspiration into Blood Salvage System Filters
- Embolization
- Paralysis/Nerve Damage/Tissue Necrosis
- Disease Transmission
- Adverse Tissue Reaction and
- Toxicity

a. Please comment on whether you believe FDA has identified a complete and accurate list of risks to health presented by absorbable collagen-based hemostats.

b. Additionally, please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of absorbable collagen-based hemostatic devices.

DR. LEWIS: I would cite first the questions that were raised earlier by Dr. Levy regarding the first two conditions, uncontrolled bleeding and hematoma. It seems to me that uncontrolled bleeding would not actually reflect on the performance of the device so much as its use in an inappropriate situation where there was presumably more arterial or level bleeding, capillary bleeding, and therefore the device couldn't be expected to perform effectively. So, it's hard for me to, like him, to ascribe that to a failure of the device.

Similarly, the presence of a hematoma is a normal physiologic event when there's some oozing between the device and the bleeding surface, and that seems to me not to be any sort of a complication.

So those two I would question. We understood your explanation before, which I appreciate, but I think those two are problematic in terms of really being considered failure

of the devices.

The third thing is down the list, (k) embolization, probably should be highlighted because embolization is the one complication which kills people once you put these things in the circulation either intentionally or otherwise, and they are used by radiologists sometimes to embolize small vessels under controlled circumstances, but usage that might provide for that by using an enclosed space is a distinct hazard and that, perhaps, should be highlighted as being more dangerous to the patient than most other things. So those would be my only comments. I ask for the Panel to basically --

DR. PIERCE: I would like to clarify in regards to hematoma, so we're looking at it in the terms of when it presents itself as a risk to health. So, it may be present, but it may not be clinically significant or lead to any other adverse effects.

DR. LEWIS: Dr. Posner.

DR. POSNER: Just very simply, the previous panels that approved the declassification or moving down to level II, was there anything presented to that group that isn't in the list now, and are there new things that are on this that weren't on the previous one? So just to get an idea, since it was already approved by earlier panels. I wanted to find if there's a comparison.

DR. PIERCE: So, to the best of my knowledge, this list includes everything that the Panel has seen -- oh, I'm sorry, previous panels considered in their information, including the identification of all the risks. We have added risks based on our current understanding of these devices.

DR. LEWIS: Yes, Dr. Bloom.

DR. BLOOM: I'd like the Committee to consider adding possibly one more, which is that the use of these devices can, in the postoperative period, on imaging studies, have the appearance of abscesses or I guess the evidence that it could look like recurrence of tumor.

Certainly, in my experience, every time I put it on the spleen, I get a CT scan, it looks like an abscess is forming because of its air-trapping qualities, and for a clinician not to know that could initiate unnecessary and unwarranted other procedures, so perhaps an indication that it has an unusual appearance on postoperative imaging studies.

DR. PIERCE: I'd like to note that it's currently under foreign body reactions. We identify the last half of it, encapsulated devices can also present as an image artifact mimicking residual or recurrent tumor or abscess resulting in additional diagnostic studies and surgical procedures.

DR. BLOOM: So, noted, thank you.

DR. PIERCE: Thank you.

DR. LEWIS: Dr. Meurer.

DR. MEURER: Will Meurer.

Under Item (k) embolization, one of the serious adverse effects is listed as asterixis. In comparison to some of the other things there, asterixis, to me, would seem more like a symptom of something like hepatic encephalopathy as opposed to a direct consequence of embolization, so I would say that the FDA could consider removing asterixis. And I don't know if we really want to talk about why asterixis is there, but I would say that you may want to examine whether that is needed in that list.

DR. LEWIS: Okay.

Dr. Pories.

DR. PORIES: Pories.

This is sort of curious, but in this age of diversity and cultural sensitivity, the inclusion of pork products or bovine products, somehow the patients need to be made aware, I'm not sure how to do it, but it is a concern to Seventh Day Adventists and Muslims and Orthodox Jews about including these animal products. I'm not sure how to deal with it,

but I think we ought to at least bring it up that this might be a concern.

DR. POSNER: Well, that's true for Christian Scientists who just don't even want the devices, so it's something that needs to be covered. Along that line, diabetics often develop an allergy to porcine insulin and have to switch over to bovine insulin for periods of time, and so again, an awareness of allergies, and I assume that was covered in one of the things that you had as allergies, that you have to test allergies to porcine versus bovine depending upon the individual that you're dealing with.

DR. LEWIS: Yes.

DR. MILLER: It's Mike Miller.

I think I would keep on the list uncontrolled bleeding because it -- although it is up to the surgeon to make a good decision about whether to use this and depend on it to control the bleeding, it seems like a labeling thing, you know, that should be a part of the special controls, because of in terms of having good judgment or when and when not to use it, it needs to be clarified for the surgeon.

DR. LEWIS: Yes, Dr. Meurer.

DR. MEURER: Will Meurer.

I guess the question may be for the FDA would be if there are other sort of similar products that have animal components and given the sort of autonomy of the public for whatever reasons they may want to avoid the use of animal products, whether they have any advice to us as to how this could be brought in, practically speaking. I suppose the cellulose-based alternatives to this might be considered to be used, but again, I wouldn't -- I wouldn't want to presume to question my surgeon in terms of what they want to use. Gelatin is a animal-derived product, so I guess is there any -- does the FDA have any suggestions or recommendations on how physicians and patients should interact about the use of animal-derived products?

DR. PIERCE: So, we're not going to make a specific recommendation on what a surgeon should be telling their patient; we think they should, you know, tell them what's appropriate. This specific issue is taken into consideration when we run clinical trials as well as when we look at device labeling. And in the end, when we talk about who brings it up to their patient, ultimately, the discretion of the surgeon.

DR. LEWIS: Dr. Krause, based on the comments, do you have enough information for Question 1?

DR. KRAUSE: We do, thank you.

DR. LEWIS: Proceed to Question 2.

DR. PIERCE: All right. As defined in 21 C.F.R. 860.7(d)(1), "there is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of an unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

Also defined, "there is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

So, in light of the feedback yesterday, so in context of this reclassification to Class II, please comment on whether, based on available scientific evidence, there is a reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices.

And I would add as Class II.

DR. LEWIS: Questions, comments?

(No response.)

DR. LEWIS: I guess I have real difficulty with this question, and we spoke to this earlier, because as we commented, based on critical review of available science, there really is no published scientific evidence of efficacy or safety in these devices, and in the two PMAs that were cited, both reached a conclusion that there was no difference between the device and control. So, it's a difficult question because based on available scientific evidence, the answer is it's not been shown, which means we're relying essentially on two things which aren't really scientific evidence.

One is that the incidence of reported MDRs and complications relative to the usage of these devices is extremely low, and we're accepting that if we approve this, we're accepting that that's adequate evidence, but it's clearly not a well-controlled scientific study and it's kind of a back-of-the-envelope calculation. And, secondly, in regard to efficacy, we're simply relying on historical anecdotal evidence that people use these things and think they work, but we don't really have scientific studies devoted to that. So, it's kind of a difficult question because, strictly speaking, we don't have scientific evidence, but there are two things out there which tend to -- yes, Ms. Pawelski.

MS. PAWELSKI: With all due respect, Dr. Lewis, I think the evidence in the PMAs does demonstrate efficacy. Non-inferiority studies are a valid demonstration of efficacy. In each of those studies, the products were demonstrated to stop bleeding or achieve hemostasis to a certain extent within 10 minutes. The studies showed that there was no difference between the two, but the two methods were both efficacious. So non-inferiority is valid there. Now, you know, we approve drug products just based on performance versus placebo. Drug products aren't asked necessarily to do comparative efficacy.

DR. LEWIS: Well, the conclusions that I read earlier, the two quotes from both studies were that there was no statistical validity to that.

MS. PAWELSKI: There was no statistical difference between the two treatment groups.

DR. LEWIS: Right.

MS. PAWELSKI: Meaning that they both worked equally, they both worked, they just -- nothing was superior to each other; they were non-inferior. They both were efficacious, but one didn't turn out to be any -- and please, FDA, jump in. One didn't turn out to be any better than the other, but they both worked.

DR. PIERCE: So, for example, you can pick your hemostat on the list of choice, you like it, it's been used a long time. If I come in with a new device and it works just as good with no statistical difference, would you use it? And, hopefully, the answer is yes. I would like to reiterate that these devices are currently on the market, they've been on the market a long time, and as well as when new PMAs came in, albeit a long time ago, as well as some recent PMAs outside this product code, they may have used these devices as a control, so they continue to be analyzed as controls of currently marketed -- or controls representing currently marketed devices. And as we mentioned, we don't have a signal that they're not safe or not effective.

DR. LEWIS: So -- yes, Dr. Miller.

DR. MILLER: Mike Miller.

I appreciate, Dr. Lewis, your -- you're formally correct. I mean we, you know, may lack evidence, but is there a reason to be skeptical of whether these things work or not? I mean, I think that even if the MDRs were underreported by a hundred thousand-fold, it would still be 1% of a problem. So, I think the -- you know, they've been used for so long, they clearly work under the right circumstances, the risk is extremely low if used properly.

I'm very comfortable with these devices and down-classifying them to Class II. I think that's very reasonable and sensible and practical.

DR. LEWIS: Dr. Pories.

DR. PORIES: While I agree with you, I think then this answer has to be rephrased. I think when you say available scientific evidence, at least that means something else to me than experience. So, I think this is a very difficult statement, just as Dr. Lewis indicated, but I think it needs to be rephrased.

DR. MILLER: Can I just respond to that?

DR. LEWIS: Yes, Dr. Miller.

DR. MILLER: I think, again, you're -- if you're putting in the category of scientific evidence, very specific study designs and things like that, I mean, you're -- I can't disagree with you. But, again, I would hearken back to the idea that we have no scientific evidence that you just stop bleeding, period. I mean, according to the -- show me a study, under current scientific criteria, which shows you should bother stopping bleeding. I mean, that study's not practical, and since the beginning of time, we've done this.

DR. PORIES: I agree with you that it works, and I've used it and it works, no question. We're talking here about the language. So, I think if you could say based on long-term experience there's reasonable assurance of safety, that's much more acceptable than the words "scientific evidence."

DR. LEWIS: Are you willing to accept that change in wording, Dr. Pierce, Dr. Krause?

DR. KRAUSE: So valid scientific evidence has a -- let me read the definition of valid scientific evidence that the FDA goes by.

(Off microphone discussion.)

DR. KRAUSE: Okay. Well, this is specific to -- okay. So, here's kind of a partial definition. "Valid scientific evidence is evidence from well-controlled investigations,

partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can be fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device, the safety and effectiveness of which is questionable." And let me give you the -- this is under Part 860 of the C.F.R. Title 21. And it's 860.7, determination of safety and effectiveness.

So, I think experience, as Dr. Miller was pointing out, does count as long as the preponderance of the evidence is that the device works. There are, of course -- you know, the pinnacle is, you know, randomized clinical trials, but that's not the only requirement. And, again, I'd like to reiterate, we have -- since about 1995 or so, there have been multiple PMA -- or earlier, since 1990 or so there have -- or in the middle '80s there have been seven approved PMAs. Again, I don't want to go back to those that were done in the Center for Drugs, but there were those done, the PMAs and the data for those are available if you look up the PMA and you can go to the summary of safety and effectiveness data on the website. It gives those clinical studies and there's -- there's like seven of them. And Adam had the numbers up, somebody can look them up, and there are, you know, 99 -- P99004 and P99009 and P99 -- was it 031 -- are the most recent.

DR. LEWIS: Dr. Posner.

DR. POSNER: Just to point out the obvious. The question says available scientific

evidence, and one of the things that was clarified in this discussion for me is when they said control, until they specify the controls are existing ones that have been on the market and worked for a long period of time. If you just say control, that's against zero. So, you know, I'm satisfied that it's the available evidence, and the studies were control studies against the existing ones that have already been through the PMA process.

DR. LEWIS: Dr. Pierce.

DR. PIERCE: All of the controls were approved devices at the time.

(Off microphone comment.)

DR. PIERCE: Yeah, yeah.

DR. LEWIS: Dr. Meurer.

DR. MEURER: I think we all probably -- we've sort of talked about we've seen this stuff work, but like how, you know, was that scientific evidence. I guess, you know, we didn't -- when we talk about what's available, there's a lot in the medical literature, there's a lot in the FDA website. But I think we could all probably attest that a prerequisite for hemostasis is clot formation, right? That's got to be true. So, I mean, there's -- I'm using a quick search. A good article that compared the agents in terms of their ability to form clots in vitro in the *Journal of Surgical Research*, Volume 66 -- or I'm sorry, Issue 2, pages 100, 208 in 1996. When they took blood and put this stuff in it, the blood clotted pretty quickly. So, I think, you know, in terms of, you know, other than what we have seen with our eyes -- and this is just a very quick search. You know, we probably all could've done more detailed literature searches to kind of get at these issues, but I think there is pretty reasonable assurance of effectiveness in that it makes clots, unique clots, for hemostasis. I'm pretty satisfied with that.

DR. LEWIS: Seeing no further comments, I'd like to call for a vote of the Panel on this question. So, the question is please comment on whether, based on available evidence,

there's a reasonable assurance of safety and effectiveness. Would those who believe that this is a true statement, therefore the answer to the question is yes, please raise your hand?

(Show of hands.)

DR. LEWIS: Those opposed.

(Show of hands.)

DR. LEWIS: Seems to be approved unanimously. Let's move on to Question 3.

DR. PIERCE: So, again, based on the feedback from yesterday, I'm not going to read the entire question but the major bullet points only.

Question Number 3: FDA proposes that the following special controls would adequately mitigate the risks to health and provide reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices:

- Materials characterization of the device must include the following:
  - Material source information
  - Material processing information
  - Cross-linking density
  - Device-related particulates and
  - Collagen characterization information
- Biocompatibility evaluation of the device;
  - Must include the evaluation of all patient-contacting components
  - Residual reagents in the final product must be demonstrated to be safe
- Performance data must demonstrate the sterility of the patient-contacting components
- Performance data must also demonstrate the shelf-life of the device
- Nonclinical performance testing must demonstrate that the device performs as

intended under anticipated conditions of use, and must characterize:

- Swelling
- In vitro clotting time
- Reliability of the delivery system
- Device absorption and
- Device fragmentation

- For devices intended to be used on bone surfaces, nonclinical performance testing must demonstrate that it does not interfere with the bonding strength of methylmethacrylate adhesives
- When these devices are intended to be used involving blood transfusion systems, nonclinical performance testing must demonstrate that the device does not impair proper operation of the blood transfusion system
- In vivo evaluation of the device must include the following:
  - Usability testing and analysis must demonstrate that the device design and labeling are sufficient for the device to perform as intended
  - In vivo performance data must demonstrate that the device controls bleeding and does not promote adverse local or systemic effects under anticipated conditions of use
- The in vivo models chosen for the intended application of the hemostatic device must represent the intended use, including the type of bleeding and targeted tissue of bleeding
- A validated bleeding scale tool for bleeding severity must be used for selection and evaluation of the bleeding sites to support the intended use
  - The following characteristics must also be evaluated:
    - Reliability of the deployment mechanism

- Effectiveness of hemostasis at 10 minutes or less, with the characterization of rebleeding potential, blood loss, and thromboembolic risk
- Immunogenicity
- Inflammatory cell response
- Time to complete absorption
- Macro- and microscopic histology at the implant site and distant to the implant site
- Hematological and clinical chemistry parameters

- Labeling must include:
  - Specific instructions for deployment by users
    - Warnings, precautions, and limitations needed for safe use, including available information such as interference with healing of wound edges
    - Interference with methylmethacrylate adhesives
    - Use with autotransfusion systems
    - There must be a contraindication for intravascular application of the device unless clinical data demonstrating safe use in this area is provided
    - Information on how the device operates and the typical course of treatment
    - A detailed summary of the in vivo evaluation pertinent to the use of the device
    - For devices intended for general surgical use, a hemostatic effectiveness table comparing device performance in multiple specialties of surgical procedures
    - An expiration date for shelf life

Please comment on whether you believe any other special controls are necessary to mitigate the risks to health and provide reasonable assurance of device safety and

effectiveness or whether you disagree with the inclusion of any of the special controls.

In your deliberations, please include a discussion of the following questions:

a. Are different special controls needed for different forms of the device (e.g., sheet form or powder form)?

b. Should a validated bleeding scale be used to demonstrate effectiveness of hemostasis? What should be considered as effective hemostasis?

c. Should effectiveness of hemostasis be evaluated at 10 minutes or less, or at a different time point?

d. Are clinical data necessary to demonstrate device safety and effectiveness for all absorbable collagen-based hemostatic devices?

e. Are there additional special controls that could be implemented to mitigate risks associated with inappropriate device use (e.g., postmarket surveillance)?

DR. LEWIS: Ask for discussion from the Panel regarding these questions.

(Pause.)

DR. LEWIS: So, this is a fairly exhaustive list you've provided to us. I guess the question actually would be if you will be able to effectively demonstrate this from different manufacturers. It seems like an extraordinary amount of testing that you'll be requesting. Have any comments on that?

DR. PIERCE: Yeah. So, all of these issues really are reflective of how we currently review PMAs with the exception of routine clinical data, annual reporting, as well as a shortened premarket process. So, in terms of the rigor of the data, you know, that's always relative, but these are concerns or, you know, lessons that are learned across the board across different product codes.

DR. LEWIS: To take sub-questions in order one at a time, are special controls needed for the different forms of the device, sheet form, powder form. Obviously, the powder

form is more difficult to apply, but assuming it's all of the same material, it would not appear that any other special controls will be necessary for one versus the other. The issues are strictly in the method of application rather than the hemostatic effectiveness, so it's difficult to see how that would be the case, and I don't know that there are any other forms we need to deal with, are there?

Dr. Posner.

DR. POSNER: Well, on the powder, there's a question of dispersion radius, and so a styptic stick is fine, it's not going to disperse, but if it's something you're going to sprinkle on as they do at a prize fight, you want to know what the dispersion of the powder is in order to be effective.

DR. LEWIS: Okay.

Yes, Dr. Miller.

DR. MILLER: I'll defer to your judgment on these things, but it seems like there's a different manufacturing process involved with the sheet form versus the powdered form, and if there's important points of, you know, manufacturing that are different between the two, perhaps that would justify some different special control because of that different manufacturing process. But I don't know enough about the manufacturing to say, but I just speculate.

DR. PIERCE: Yeah. So, I would also remember this in the context of the materials that we're focusing on that have been around since the '30s and '40s. The manufacturing process, you know, we understand technology does change, but it's a -- we see a lot of similarities across manufacturers, you know, you may have a proprietary grinding process, or you know, anything cross-linking, you know. But if you see in terms of the safety and effectiveness of that manufacturing that should be evaluated by biocompatibility, material source information, and then in the end is it going to be effective with this different

manufacturing.

So, if it's safe from a manufacturing standpoint you're introducing, say, harmful impurities, we recognize that these materials are routinely processed with hazardous reagents such as methanol, glutaraldehyde, etc. But then if they're effective with those manufacturing changes, then that's controlled in the special control. Did I answer your question? Or speculation?

DR. MILLER: Yeah, I think so. Yes.

DR. PIERCE: Okay.

DR. LEWIS: Questions 2 and 3, it seems to me those are highly technical issues about the methods of assessing bleeding ability, the bleeding scale. Seems like objectively that would be a fairly hard thing to arrive at, and effectiveness of hemostasis in the time periods, those are really technical issues related to the performance. I'm not sure this Panel has the expertise to comment on that knowledgeably.

DR. KRAUSE: So, for Number 2, it can simply be yes or no, I mean, do you think that FDA should assess effectiveness, use -- you know, using a validated bleeding scale should be part of our assessment, and that can be yes or no. You don't have to talk about the scale, you don't have to do anything else, just -- you know, whether you think it's -- should be one of the special controls that when somebody does either a human clinical trial or when they do an animal study, that there should be an assessment of how much bleeding there is and whether or not we should use a scale to determine how much bleeding there is and then, you know, determine whether or not the device is safe and effective for that amount of bleeding. So, you don't have to say, you know, the scale should be this or the scale should be that; it should just be simply yes or no, you think we should or shouldn't use a bleeding scale.

DR. LEWIS: I guess the issue that rises in my mind, Dr. Krause, is -- I mean, I think

we'd all answer that if you have it available, yes, it would obviously add a level of objectivity to the whole thing, but at the same time, you've had these things in a Class III designation now for 42 years, and if that were something that were worthwhile and easy, I would assume you would've already done it.

DR. KRAUSE: It's interesting because up until recently we didn't use a bleeding scale, and in the last, say 5-6 years we've been working with manufacturers to get validated bleeding scales, and to their credit, many of the manufacturers have done an excellent job of coming up with good bleeding scales that are -- I believe they're now published, and some companies have said, well, we don't think we need a bleeding scale, but others have been fine. So, I think for our benefit -- and it would nice to get into the record whether or not the Panel members think using a bleeding scale is a good idea or not.

DR. LEWIS: Are there opinions?

Dr. Meurer.

DR. MEURER: I guess I'll ask a question, and then I guess I have an opinion, too. Are these bleeding scales used in human clinical studies, animal studies, or both, Dr. Krause?

DR. PIERCE: Both. So, I think our goal here is to look at a standardized approach when people present their new device into the future and how to take a standardized approach to evaluating them compared to a currently approved -- or a currently marketed device. And this is a potentially useful tool, if you've guessed.

DR. LEWIS: Dr. Miller.

DR. MILLER: Yeah, Mike Miller.

I think you should certainly have a standardized measure because the whole -- the most important feature of whether this is going to work or not is the rate of bleeding. So, if you don't have an objective way to assess the rate of bleeding, you're really not objecting probably the most important factor about whether this is going to work or not, so I think

that you should have a scale.

DR. MEURER: But I think if the Panel -- this is Will Meurer.

If the Panel is worried that there might not be a scale and we're subjecting undue burden on -- as noted by Dr. Krause, in the March 2017 *Journal of Surgery*, Volume 161, Issue 3, pages 771 to 781, they have a paper that was an industry-academic partnership, Kevin M. Lewis, Doctor of Veterinary Medicine is the first author, "Development and validation of an intraoperative bleeding severity scale for use in clinical studies of hemostatic agents." One of the conclusions was the scale fulfills requirements of the Food and Drug Administration for a clinician-reported scale and can be used to generate clinically meaningful labeling claims. So, if there's anybody who was worried there isn't a good scale, it sounds like there's a pretty good scale.

DR. GIBEILY: Yeah. There are at least three validated bleeding scales. Just to say, the bleeding scale allows us to compare one hemostat against another objectively, and like I mentioned in my talk, that these scales have been validated gravimetrically as well as getting raters to recruit patients and/or bleeding sites in animals that have been trained on video, on video examples of the different severities of bleeding, looking at inter- and intra-rater reliability. So, I think it's as good you get to getting an objective idea as to how one hemostat compares to another, and I think it's worthwhile. Personally, I think it is useful for us to see that.

The other issue is what is hemostasis? Believe it or not, different surgeons have different impressions of hemostasis, and I think that might be a question coming up, so it will be interesting seeing what you all have to say.

DR. MEURER: Believe it or not, yeah.

DR. LEWIS: It sounds like the consensus of the Panel is if such scales are actually available, that the answer to the question would be, yes, that it's a good point to use it. As

far as the effectiveness being evaluated at 10 minutes or less or a different time point, I really don't think the Panel can answer that question. Basically, the people who are setting it up need to establish whatever the objective endpoints are that are meaningful, and I think that's highly technical and not something that we really have the expertise to comment on.

DR. PIERCE: So that performance was based on currently marketed devices and what was in the PMA submission.

DR. LEWIS: No, I understand that.

DR. PIERCE: Okay.

DR. LEWIS: But, again, I don't think we know whether 5 minutes, 10 minutes, or 15 minutes is the right time. That's a scientific question that would need to be evaluated in the study.

Four, are clinical data necessary to demonstrate device safety and effectiveness for all absorbable collagen-based hemostatic devices? How is that different from what you're doing now?

DR. PIERCE: Clinical data is typically received as part of an original PMA submission.

DR. LEWIS: So, under the 510(k) process, are you asking if that should also be included?

DR. PIERCE: I think it would depend on what changes that they're making. So, we've talked about some of these changes, changes in technology or a change in indications for use to include anticoagulated patients. So those considerations may go through the 510(k) process.

DR. KRAUSE: So, let me clarify. So, you can answer that in a couple of ways. One is if you think every time we get a submission for a new collagen hemostat, should we have -- are clinical data necessary to establish safety and effectiveness? That's part of the

question.

The other part of the question is if we get a new absorbable hemostat made of collagen, do you think that we can use the 510(k) pathway to establish that it is safe and effective without clinical data?

So, the question is asking do you think it's necessary for every one of these, no matter what the formulation, no matter how it's made, and no matter how similar it is to all the ones that are out there, do we need clinical data? If not, I mean, you can answer the question, no, you don't if it's similar and you can use the 510(k) pathway.

So I think that's the question: Do we automatically need to have a clinical study, or can we use substantial equivalence pathway by comparing the characteristics of the device, benchtop testing, purity, you know, running gels to show that it's the same type of collagen, those kinds of scientific evidence to establish that the devices are similar enough with, you know, animal data as -- you know. So, I think that's the question.

Dr. Pierce's point was let's say the company changes their indications for use or the technology is very different; that doesn't preclude us from using clinical data, but the question is asking do we need it every time?

DR. LEWIS: Well, it would seem that if you know that the structure of the -- I mean, collagen obviously comes in a lot of different forms and different cross-linking, but as long as you know the collagen in a device is similar to something that's already been proven, it would not seem to be necessary to repeat testing that's the same. If it's structurally different in a substantial way, then you anticipate different effectiveness, and it probably would be. Do the Panel members have any comments about this?

Dr. Miller.

DR. MILLER: I think that if the device is different because the company's come up with a way to do it in a way that costs less but it's identical, are -- and no discernible

difference between existing devices that clinical data are not necessary. But if it's significantly different in terms of its formulation or anything about it which may suggest that its performance in vitro would be different in vivo, then I think a clinical study is necessary. It's difficult just to have a blanket position on this, but I think that, you know, it depends on how identical it is to existing products, I think.

DR. LEWIS: Dr. Pawelski.

MS. PAWELSKI: One of the special controls says that they'll be devices intended for general surgical use, a hemostatic effectiveness table comparing device performance in multiple specialties, so I guess the challenge would be how do you ensure that your in vitro testing or whatever is validating that. That was probably put together based on clinical data, and somehow, you're going to have to bridge to a product that doesn't have it but yet gets to use the same table, so that just may be a challenge.

DR. LEWIS: Is the Panel in agreement with the position stated by Dr. Miller? Is there any disagreement with that?

DR. POSNER: I just have one question, maybe to simplify it. Instead of saying clinical data, say human data, because clinical data has the implication of a full clinical trial and looking at everything that was in that statement. But testing it in humans, I think, might make it a little bit simpler and more straightforward.

DR. LEWIS: Dr. Meurer.

DR. MEURER: It might, but it also might make it more complicated. They could test it in human blood, which wouldn't be the same as a clinical trial. Like it depends, you know, like I think clinical data implies, you know, real-life surgical situation, and if we need to specify that that's not necessary, that is, I think, perhaps good. I think if the Agency felt that they wanted to see clotting tests in human blood, I would hate for this to be sort of saying don't do -- you don't need to do anything in humans. So, I don't know. I would defer

to the Agency on their best phrasing. I think what we're meaning is clinical trials and real-life surgery aren't necessary. I think that's -- I think we have consensus on that.

DR. LEWIS: Number 5, are additional special controls --

DR. KRAUSE: Could you summarize Number 4 before you go on?

DR. LEWIS: I think the summary is what was stated by Dr. Miller.

DR. KRAUSE: Sorry, Number 3.

DR. LEWIS: Number 3 we've already answered.

DR. KRAUSE: Sorry, I'm looking at three-three. Number 3, Roman numeral IV, yes, I mean I just want -- summarize the Panel's -- what the Panel said.

DR. LEWIS: Dr. Miller, do you want to summarize your statement again?

DR. MILLER: Certainly. I think that whether or not clinical data is necessary depends on how equivalent a new product is to existing products in terms of its composition primarily, and if it's really identical, then clinicalness is not necessary. If it's significantly different in terms of its collagen composition, whether it's Type 1 or Type 4 or different collagen types, something like that, and there's any possibility they may perform differently in patients than it does in vitro, then a clinical, you know, study or clinical use needs to be done, and I would just defer to your judgment on that and speculating as to how important a change may be in a new product.

DR. KRAUSE: So, in summary, what you're saying then is -- and I'm just -- I want this, you know, to be down in the record. It says, "Are clinical data necessary to demonstrate device safety and effectiveness for all absorbable collagen-based hemostatic devices," and you're saying not always.

DR. MILLER: I would say no --

DR. KRAUSE: Okay.

DR. MILLER: -- to that question.

DR. KRAUSE: All right.

DR. MILLER: But, you know, a qualified no. I mean -- yeah.

DR. KRAUSE: Right, that's fine. I just wanted to make sure that, you know, you're not saying that we need it every time; we can use our judgment when we need it and when we don't.

DR. MILLER: Yes, I agree with that.

DR. PORIES: Could we put the wordage in it that it is -- that you have the judgment to decide this question?

DR. KRAUSE: Yeah, that's implied.

DR. LEWIS: Number 5, are additional special controls that could be implemented to mitigate risks associated with inappropriate device use unnecessary, i.e., postmarket surveillance?

Dr. Bloom.

DR. BLOOM: Not nearly as big as postmarket surveillance, but with respect to special controls and labeling, I'd like to make a pitch that the -- back to my earlier point, that the postoperative radiographic appearance of these devices can mimic other conditions, and I know of many patients that have been put on a course of antibiotics and gotten drains because radiologists and clinicians have been fooled. If you put that on the label and someone somewhere reads it somewhere and we save one thing, I think it's worth the ink.

DR. LEWIS: The list of special controls you've already included is pretty exhaustive, and so I think there are relatively few things additionally that we would add that would be necessary unless your MDRs indicate some hazard that's unanticipated.

Dr. Gibeily.

DR. GIBEILY: Yeah, George Gibeily.

I was involved in this question a little bit as well. One of the things we lose by going to a Class II device is that postmarket routine, a review of literature, for example, where we'll get reports, summarized abstracts, three or four pages, and I'll go through all the abstracts, this is an interesting thing to look at, let me dig deeper. We won't get that kind of routine annual feedback or annual reports that -- so the question is should we make that a special control that we, at some -- you know, periodically get literature reviews. We're doing that now to some extent, but this would be a more rigorous way of doing it.

DR. LEWIS: Dr. Miller.

DR. MILLER: Yeah, I mean, I'm not sure that's necessary based on the amount of adverse events that occur with this. I think if there were a significant risk, but clinicians would see that, and they would start to talk about it and start to report it, and I think that it is not necessarily something that we need to depend on FDA to do for this particular topic.

DR. LEWIS: So, I think the answer to the question is, no, unless you become aware of special hazards from the MDR process or some other mechanism.

Dr. Krause, any further comments?

DR. KRAUSE: No, I think that's adequate. Thank you.

DR. LEWIS: Let's move on to Question 4.

DR. PIERCE: So, you guys are aware of general and special controls in Class I, II, and III, so I'm going to save you reading Section 513 of the FD&C Act. Is that okay?

(No audible response.)

DR. PIERCE: All right. So please comment on whether the general controls, required for all medical devices, are insufficient to provide a reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices. That's essentially Class I. Consensus.

DR. LEWIS: So, I think the answer to that is yes. Based on prior discussion.

DR. PIERCE: Thank you.

Please comment on whether you agree or disagree with FDA's view that the application of general controls and special controls are sufficient to provide reasonable assurance of safety and effectiveness for absorbable collagen-based hemostatic devices when intended to be placed in the body during surgery to produce hemostasis by accelerating the clotting process of blood.

DR. LEWIS: The answer to that question, I believe, based on our prior discussion is probably yes. Does anyone disagree with that?

Ms. Pawelski.

MS. PAWELSKI: The one comment I would make is that the list of special controls by FDA's own admission is equal to the PMA requirements currently.

DR. PIERCE: No. In some respects. So, we draw on the lessons from it.

So, essentially, the person who is reviewing a PMA is going to review a 510(k), but the clinical data is not routinely received for a 510(k), and I mentioned the shortened premarket process, and I mentioned the annual reporting. And manufacturing controls.

DR. LEWIS: Any further comment?

(No response.)

DR. LEWIS: Okay. So, the answer to (b) would be yes; (c)?

DR. PIERCE: FDA does not believe that absorbable collagen-based hemostatic devices are life-supporting or life-sustaining. Do you agree with this assessment? If not, please explain why. Please comment on whether you believe that absorbable collagen-based hemostatic devices are for a use which is of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury when intended to be placed in the body during surgery to produce hemostasis by accelerating the clotting process of blood.

DR. LEWIS: As I understand it, if the answer to this was yes, it would require a Class III designation; is that correct?

DR. PIERCE: That's correct.

DR. LEWIS: So, again, based on prior discussion, it would appear the answer to that is no. Does anyone disagree with that on the Panel?

(No response.)

DR. PIERCE: Also, please comment on whether you believe that these devices are of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury. I'm assuming the same answer for all of it.

DR. LEWIS: Same answer.

DR. PIERCE: Okay, okay.

DR. LEWIS: So, let's go to 5.

DR. PIERCE: So, our last question. Based upon the available scientific evidence and special controls proposed in Question 3, do you recommend Class II or Class III for absorbable collagen-based hemostatic devices when intended to be placed in the body during surgery to produce hemostasis by accelerating the clotting process of blood? Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence and your responses to Question 4 above.

DR. LEWIS: Again, I believe we've already answered that question. Let's have a -- just for further confirmation, a vote here. How many Panel members support Class II designation?

(Show of hands.)

DR. LEWIS: How many support Class III designation?

(Show of hands.)

DR. LEWIS: Note that one person votes for Class III. Two?

MS. PAWELSKI: I just wanted to make a comment.

DR. LEWIS: Just a second.

Dr. Posner, did you --

DR. POSNER: I was just abstaining.

DR. LEWIS: Oh, okay.

DR. POSNER: I'm deferring to the experts.

DR. LEWIS: So, there's one abstention, one no, and the remainder yes to that question.

MS. PAWELSKI: Can I --

DR. LEWIS: And I don't know that -- we've discussed fairly exhaustively rationales. I'm not sure we need to recapitulate all that.

Ms. Pawelski, do you want to comment?

MS. PAWELSKI: Yeah. So, my only comment is that the sponsor here today was clearly opposed to the reclassification. I've been in contact with two other companies that aren't currently in this classification, and one company also opposes it, one supports it, and I've encouraged them to submit their comments formerly to FDA, so I just wanted to be clear as to why -- have that recommendation.

DR. LEWIS: Great, thank you.

MS. PAWELSKI: Okay.

DR. LEWIS: So, do we need anything further?

DR. PIERCE: This is it. Thank you, everybody, for your efforts.

DR. LEWIS: Thank you.

Dr. Krause, do you have any closing comments?

DR. KRAUSE: Well, I'd like to thank everybody on the Panel for their hard work, the rousing discussions, and appreciate all of your efforts, and travel safely on your way home.

And thank you.

DR. LEWIS: Commander Garcia, would you like to make any closing comments?

CDR GARCIA: I just want to personally thank each and every single Panel member for attending today's meeting, and safe travels home. Thank you.

DR. LEWIS: Thanks to all the panelists for excellent efforts and expedited process. We're getting out a little early. Hopefully, you won't have too much trouble getting to the airport or your other travel destinations. Thank you all for your excellent work. Appreciate everything you've done. We stand adjourned. Thank you.

(Whereupon, at 11:23 a.m., the meeting was adjourned.)

# C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

May 31, 2019

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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