FDA Executive Summary

Prepared for the May 31, 2019 Meeting of the General and Plastic Surgery Devices Panel

Reclassification of Absorbable Collagen-Based Hemostatic Devices

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1. Introduction

The Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Advisory Panel (the Panel) to discuss and make recommendations regarding the regulatory classification of absorbable collagen-based hemostatic devices, currently under the classification regulation 21 CFR 878.4490, which FDA has grouped under product code LMF. The Panel will also be asked to discuss whether this device type fits the statutory definition of a Class II device.

The scope of this panel meeting excludes absorbable collagen-based hemostatic devices containing added biologics and non-collagen-based absorbable hemostatic agents currently designated under product codes PMX and LMG.

FDA is holding this panel meeting to obtain input on the benefits and risks of absorbable collagen-based hemostatic devices. The Panel will also be asked to discuss and make recommendations to FDA whether such devices should remain classified as Class III (subject to Premarket Approval) or reclassified to Class II (subject to General and Special Controls), or Class I (subject only to general controls). FDA is proposing to reclassify absorbable collagen-based hemostatic devices into Class II (Special Controls). FDA is also identifying the proposed special controls that the Agency believes will provide a reasonable assurance of safety and effectiveness of the device and mitigate the risks to health. If the panel believes that classification into Class II is appropriate for these devices, the Panel will be asked to discuss whether the proposed special controls are adequate to provide a reasonable assurance of safety and effectiveness and to mitigate the risks to health.

1.1 Background on the Classification Process

FDA regulates medical devices and categorizes them into one of three classes: I, II, or III.

1.1.1 Class I

Class I devices are subject to the least regulatory controls. They usually present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Class I devices are subject only to general controls, which include but are not limited to establishment registration and listing; prohibitions against adulteration and misbranding; records and reports; and good manufacturing practices (GMPs). Examples of Class I devices include elastic bandages, examination gloves and hand-held manual surgical instruments. Most Class I devices are exempt from premarket review requirements and can be marketed without a premarket submission.

1.1.2 Class II

Class II devices are those devices for which general controls alone are insufficient to provide reasonable assurance of safety and effectiveness, and for which there is sufficient information to establish special controls to provide such assurance. Examples of special controls are performance standards, postmarket surveillance, patient registries, and special labeling requirements. Special controls may also include specific types of performance testing (e.g.,

biocompatibility, sterility, electromagnetic compatibility, pre-clinical testing), which FDA may outline in the regulation. Hence, in addition to complying with general controls, Class II devices are also subject to special controls. Most Class II devices must obtain marketing clearance through premarket notification [510(k)] submissions. Examples of Class II devices include intravascular administration sets (e.g., syringes), medical lasers, endoscopes, stereotactic navigation systems, and radiofrequency ablation systems.

1.1.3 Class III

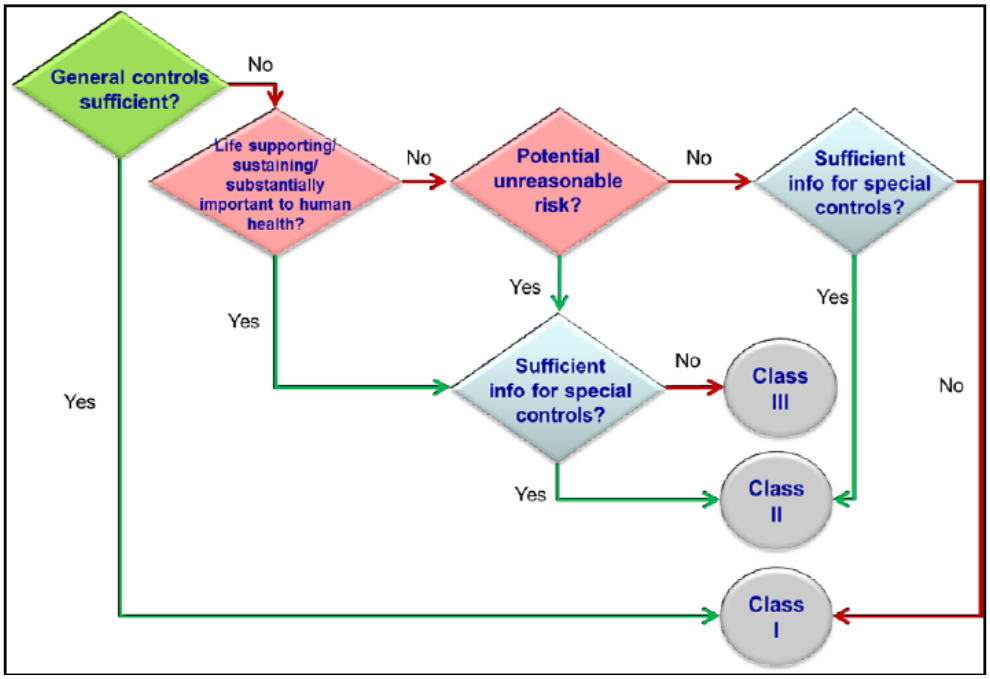
Class III is the most stringent regulatory category for devices. Class III devices are typically high-risk devices and include devices for which insufficient information exists to provide reasonable assurance of safety and effectiveness solely through general or special controls. All devices that are not substantially equivalent to any existing devices in Class I or II are automatically classified in Class III. Examples of Class III devices include breast implants, dermal fillers, and endodontic dry heat sterilizers. Class III devices typically require marketing approval through a premarket approval (PMA) application.

In accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act), a device should be classified in Class III if:

- insufficient information exists to determine that general controls and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

Figure 1: Reclassification Process



2. Device Description and Current Classification

As currently defined in 21 CFR 878.4490 Absorbable Hemostatic Agent and Dressing

(a) *Identification.* An absorbable hemostatic agent or dressing is a device intended to produce hemostasis by accelerating the clotting process of blood. It is absorbable.

(b) *Classification.* Class III.

(c) *Date PMA or notice of completion of a PDP is required.* As of May 28, 1976, an approval under section 515 of the act is required before this device may be commercially distributed. See § 878.3.

Absorbable hemostatic devices are primarily applied during surgical procedures to control bleeding that is not readily controlled via conventional means, such as cautery or ligation. At other times, an absorbable hemostatic device may be applied due to the inaccessibility of a site to conventional hemostatic methods.

A variety of accessories are currently approved for use with absorbable hemostatic devices. Since manual compression is the primary method of application, these accessories facilitate device delivery into confined spaces that would prohibit manual compression after application of the absorbable hemostatic devices. These accessories are typically syringe-like devices with short or long applicator tips to aid device delivery in open, endoscopic, or laparoscopic surgical procedures.

Currently, absorbable hemostatic devices regulated under 21 CFR 878.4490 are grouped under three product codes:

- LMF – Agent, Absorbable Hemostatic, Collagen Based
- PMX – Absorbable Collagen Hemostatic Agent with Thrombin
- LMG – Agent, Absorbable Hemostatic, Non-Collagen Based

The devices within these three product codes are discussed in greater detail below:

Absorbable Collagen-based Hemostatic Agents (Product Code: LMF)

Absorbable collagen-based hemostatic agents are manufactured from the following materials:

Gelatin Sponge: The gelatin sponge is an absorbable material created from porcine gelatin through which nitrogen has been bubbled to produce a porous device. This method was first introduced by Correll and Wise in 1945.[1] The sponge has no intrinsic hemostatic action but induces hemostasis through its intensely porous structure, which enables it to absorb 45 times its weight in blood. As it fills with blood the platelets come into close contact and begin to collide initiating the clotting cascade. The United States Pharmacopeia (USP) includes a monograph for this device, USP29-NF24.

Microfibrillar Collagen: Microfibrillar collagen is a water-insoluble, partial hydrochloric acid amino salt of natural collagen in the form of fibers containing microcrystals prepared from purified bovine dermal collagen. Microfibrillar collagen acts primarily by reaction with platelets. Platelets attach to specific sites on collagen and degranulate initiating the hemostatic cascade leading to a fibrin clot.

Absorbable collagen-based hemostatic agents provide hemostasis through contact activation and the promotion of platelet aggregation, which occur as a direct result of contact between blood and the collagen. Gelatin-based products, a form of denatured collagen, also initiate clotting via contact activation. When held in place at the site of bleeding, gelatin will conform to the wound and swell. The swollen gelatin particles restrict blood flow and provide a stable matrix around which a clot can form. These devices do not promote clotting in a biologically active manner or work in combination with thrombin.

Absorbable Non-collagen-based Hemostatic Agents (Product Code: LMG)

Currently approved absorbable non-collagen based hemostatic agents are composed of plant-derived materials: oxidized cellulose, regenerated oxidized cellulose, and polysaccharides. These devices have been characterized to promote hemostasis via a passive, physical activation of clotting cascade. The biologic component is typically composed of purified thrombin to promote hemostasis through a direct biochemical activation of the factor(s) in the clotting cascade.

Absorbable Collagen-based Hemostatic Agents Containing Biologics (Product Code: PMX)

The devices in this category are regulated as combination products because they have a

biologic component in addition to the device component. The device component is predominantly composed of gelatin or collagen-based materials, as described above, to promote hemostasis via a passive, physical activation of clotting cascade. The biologic component is typically composed of purified thrombin to promote hemostasis through a direct biochemical activation of the factor(s) in the clotting cascade.

3. Indications for Use

The Indications for Use (IFU) statement describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended. Generally, 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. This device type is predominantly composed of collagen-based materials derived from animal sources and is absorbable. The range of indications for use statements approved through PMA submissions varies; see representative examples below.

> *Microfibrillar Collagen*: 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.
>
> *Gelatin Sponge*: 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 but are provided to illustrate the relatively narrow range of approved statements. FDA recognizes that science and clinical practice have evolved over time, and indications for use that have been approved historically may not represent current clinical practice.

4. Clinical Background

4.1 Methods to Obtain Hemostasis

The method ultimately chosen by the surgeon is based on surgical judgment, the operative approach, and the severity of bleeding at the target bleeding site. Traditional methods of attaining hemostasis include compression, suture ligation, clipping, and stapling of blood vessels. These methods of hemostasis may be supplemented with use of bipolar and monopolar cautery, thermal energy tissue coagulation devices, energy devices which focus ultrasonic energy, high frequency harmonic vibratory energy devices which can cauterize and seal vessels, or laser energy devices.

When conventional methods of hemostasis fail, or are ineffective or impractical for minimal, mild and moderate bleeding, then topical hemostatic devices may be used. The absorbable collagen-based hemostatic device has been shown to prevent extended bleeding, reduce surgical morbidity due to blood loss, and reduce the need for transfusions.[2, 3] These hemostatic devices

are typically absorbable and may be left in situ to maintain hemostasis after completion of the procedure. Conversely, the intraoperative application of an absorbable collagen-based hemostat may obscure the anatomy making it more difficult to proceed with the surgical procedure.

The use of an absorbable collagen-based hemostat may be preferred in some surgical approaches, e.g. minimally invasive surgery, that can present unique challenges in achieving hemostasis. In minimally invasive surgery, the bleeding site can be restricted by the anatomy, position of the trocars, patients body habitus, visibility, and lack of haptic feedback. Additionally, the pneumo-peritoneum required to create an operative space for laparoscopy can exert pressure on venous bleeding sites, giving a false impression of hemostasis.

5. Classification and Regulatory History

5.1 Submission Approvals

In the *Federal Register* of December 16, 1977 (42 FR 63472), FDA identified the absorbable hemostatic agent and dressing as a transitional device that FDA previously regulated as a drug that is statutorily classified in class III under section 520(*l*)(1) of the FD&C Act and for which premarket approval was immediately required. Since enactment of the 1976 Amendments, FDA has approved numerous PMA and PMA supplements authorizing the commercial distribution of new absorbable hemostatic agents and dressings in the United States.

Between 1990 and 2013, FDA approved two original PMAs for absorbable collagen-based hemostatic devices which are eligible for consideration as part of the 6-year rule. On August 15, 1995, FDA approved P930030 from Coletica, S.A. for the Hemostagene Absorbable Collagen Hemostatic Sponge ("Hemostagene Sponge") (60 FR 65347). On September 30, 1999, FDA approved P990004 from Ferrosan A/S for the Surgifoam Absorbable Gelatin Sponge ("Surgifoam Sponge") (60 FR 16921). FDA is relying on information in these PMAs, including information from clinical and preclinical tests or studies that demonstrate the safety and effectiveness of a device, but excluding descriptions of methods of manufacture and product composition and other trade secrets to reclassify absorbable collagen-based hemostatic devices.

Table 1: Absorbable Collagen-based Hemostatic Devices (LMF) Approved Through PMA or NDA

Product	**Present Application Holder**	**Application Number***	**Characteristics**	**Approval Date**
Gelfoam	Pharmacia and Upjohn	N18286	Porcine Gelatin sponge	Available 1945 July 8, 1983
Avitene	Davol	N17600 and P800002	Bovine Collagen	August 26, 1976 October 24, 1980
Collastat	Integra LifeSciences	P810006	Bovine Collagen	December 10, 1981
Superstat**	Superstat	P810040	Bovine Collagen	January 29, 1982
Instat	Ethicon	P830079	Bovine Collagen	October 10, 1985
Helistat **Helitene**	Integra LifeSciences	P850010	Bovine Collagen	November 8, 1985

Hemopad Novacol	Datascope	P850023	Bovine Collagen	May 27, 1986
Actifoam**	Coletica	P930030	Bovine Collagen	August 15, 1995
Surgifoam Spongistan	Ethicon	P990004	Porcine Gelatin sponge	September 30, 1999

*Application Numbers starting with "N" indicate devices submitted to the Center for Drugs (CDER) and Numbers starting with "P" are devices submitted to the Center for Devices (CDRH). Some of the applications with numbers starting with N were approved in CDRH even though they were submitted to CDER.
** Not sold in the U.S. at this time.

5.2 Classification History

2002 Panel Overview

At a July 8, 2002, public meeting of FDA's General and Plastic Surgery Devices Panel (the 2002 Panel), the 2002 Panel requested that the Agency provide information on the potential content of a class II special controls guidance document for the absorbable hemostatic device. The 2002 Panel requested this information to enable them to make an appropriate recommendation on possible reclassification of the device. This proposal for reclassification considered all absorbable hemostatic agents under 21 CFR 878.4490, and did not differentiate between collagen-based hemostatic agents, non-collagen-based hemostatic agents, and collagen-based hemostatic agents with added biologics.

2003 Panel Overview

At a July 24, 2003, public meeting of the FDA's General and Plastic Surgery Devices Panel (the 2003 Panel), the Agency presented the possible content of a class II special controls guidance for the absorbable hemostatic device. The 2003 Panel unanimously recommended that absorbable hemostatic devices be reclassified from class III into class II and recommended that a class II special controls guidance document serve as the special controls for the device. The 2003 Panel based the recommendations on the information provided by FDA, the presentations to the panel by manufacturers and FDA, the 2003 Panel's deliberations at the meeting, and their personal experience with the device. The information provided by FDA included informational sections of such a guidance document relating to device materials, device performance, animal testing, clinical testing, device sterilization, biocompatibility, and labeling that would address potential risks to health. The Panel's discussion and recommendation did not differentiate between collagen-based and non-collagen based hemostatic devices agents or those containing thrombin.

2006 Proposed Rule

On October 31, 2006, FDA issued a proposed rule to reclassify absorbable hemostatic devices from Class III (premarket approval) into Class II (special controls) (71 FR 63728). Concurrently, FDA announced the availability of a draft special controls guidance document that detailed what the special controls for the absorbable hemostatic devices would be if FDA were to reclassify the device (71 FR 63774). FDA later withdrew the draft guidance document for the absorbable hemostatic devices on April 27, 2015.

2006 to Current Panel Meeting

As part of CDRH's 2014 – 2015 strategic priority entitled, "Strike the Right Balance Between Premarket and Postmarket Data Collection," a retrospective review of Class III devices subject to PMA was completed to determine whether, based on our current understanding of the technology, reclassification may be appropriate. On April 29, 2015, FDA published a notice in the Federal Register entitled, "Retrospective Review of Premarket Approval Application Devices; Striking the Balance Between Premarket and Postmarket Data Collection" (80 FR 23798). As part of the retrospective review, FDA announced plans to consider reclassifying absorbable hemostatic devices under product code LMF (Agent, Absorbable Hemostatic, Collagen Based) from Class III to Class II, but also noted that absorbable hemostatic devices under product code LMG (Agent, Absorbable Hemostatic, Non-Collagen Based) would likely remain as Class III.

Following this notice, FDA received 12 comments, 3 of which were related to absorbable hemostatic devices under product code LMF. Of these 3 comments, 2 were duplicate comments recommending that the Agency hold another reclassification panel to address the medical and scientific issues regarding the reclassification of absorbable collagen-based hemostatic devices and the proposed special controls. One commenter stated it did not support reclassification of absorbable collagen-based hemostatic devices because manufacturing controls, extensive clinical and animal studies, ongoing lifecycle review, and post market surveillance are integral to safety and efficacy of these devices; this comment also stated that absorbable collagen-based hemostatic devices that are indicated for use with a biologic and absorbable non-collagen-based hemostatic devices should remain Class III. FDA considered all comments in proceeding with the current panel meeting to reclassify absorbable hemostatic, collagen-based devices from class III to class II.

6. Overview of Proposed Reclassification

To properly delineate absorbable hemostatic devices and their intended uses, FDA is proposing to revise the existing device identification in the classification regulation to "absorbable hemostatic device," and create two subcategories to distinguish between (a) absorbable collagen-based hemostatic devices and (b) 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 (a) "absorbable collagen-based hemostatic devices," while devices under product codes PMX and LMG would fall within subcategory (b) "absorbable-collagen based hemostatic devices containing added biologics and absorbable non-collagen-based hemostatic devices."

The Agency is proposing to reclassify absorbable collagen-based hemostatic agents, a class III transitional device (regulated under product code LMF), into class II (special controls), subject to premarket notification (510(k)). FDA is also identifying proposed special controls that the Agency believes are necessary to provide a reasonable assurance of safety and effectiveness of the device.

Absorbable hemostatic collagen-based devices containing added biologics, and absorbable hemostatic non-collagen-based devices, are outside the scope of this proposed reclassification. These devices, which are for a use that is of substantial importance in preventing impairment of human health, will remain class III devices pursuant to section 520(*l*)(1), as FDA has neither received nor identified sufficient evidence from nonclinical or clinical studies to establish special controls to provide a reasonable assurance of their safety and effectiveness.

The panel will be asked to discuss whether special controls can provide reasonable assurance of device safety and effectiveness for absorbable collagen-based hemostatic agents.

7. Summary of Data to Support Reclassification

7.1 Literature Review on Absorbable Collagen-Based Hemostatic Devices

7.1.1 Methods

FDA conducted a systematic literature review to assess the potential risks to health associated with the use of absorbable collagen-based hemostatic devices. The search was limited to any relevant references published from January 1, 2003, and through December 14, 2018. We searched electronic databases MEDLINE and Embase using search terms limited to currently approved absorbable collagen-based hemostatic devices and outcomes identified as potential risks to health; see Appendix 12.2 for detailed methods. The searches were limited to studies conducted in humans and in English. After results from each set of search terms were combined and duplicate references were removed, this search yielded a total of 919 results (Figure 3 in Appendix 12.2). Following a review of the titles and abstracts, 626 articles were excluded based on the criteria identified in Figure 3 (e.g., if they were not original U.S. clinical research relevant to absorbable collagen-based hemostatic devices (without added biologics) or did not present results on their safety). FDA reviewed the remaining 293 articles in greater detail. An additional 280 articles were further excluded for similar reasons (see Figure 3 for exclusion criteria). The summary of the assessment of the four studies[4-7] that evaluated the use of absorbable collagen-based hemostatic devices within the scope of the approved indication for use is presented below. There were nine studies[8-16] evaluating the off-label use of these devices that are not relevant to the proposed reclassification.

7.1.2 Overview of the Published Literature

Four articles were identified that assessed absorbable collagen-based hemostatic devices (without added biologics) in accordance with their labeled indication for use.[4-7] These articles included a randomized control trial (RCT)[4], a retrospective cohort study[7] and two case series.[17, 18]

Verhoef et al. studied surgical hemostasis in a RCT in the United States.[4] The study evaluated an approved absorbable collagen-based hemostatic device and a hemostatic device that is not currently approved. The study included 23 subjects treated with an absorbable collagen-based hemostatic device alone, our population of interest, during their spinal (n=13) or vascular (n=10) procedure. About 22% (5/23) of these subjects reported re-bleeding at the target bleeding site during the 10-minute assessment period. While none (0/13) of these subjects undergoing a spinal

procedure required blood transfusion, 60% (6/10) of subjects undergoing a vascular procedure were transfused. In a retrospective cohort study conducted by Guzzo et al., 1 out of the 21 patients (4.8%) treated with an absorbable collagen-based hemostatic device alone needed a transfusion after undergoing laparoscopic partial nephrectomy.[5]

The literature review also identified two case series for which the residual absorbable collagen-based hemostatic device mimicked tumors after removal of primary cancer.[6, 7] Tublin et al. reported six patients with thyroid carcinoma in whom sonographic appearance of residual absorbable collagen-based hemostatic devices looked like recurrent or residual tumors on early postoperative sonography after thyroidectomy.[6] In the other case series, Ribalta et al. reported that three patients with intracranial carcinoma had foreign body reactions resulting in masses mimicking a recurrent tumor after neurosurgery, which may or may not be clinically symptomatic.[7] Masses, resulting from the foreign body response to collagen topical absorbable hemostatic devices, have also been misdiagnosed as abscesses, recurrent or persistent tumor, infarction, radiation necrosis, even recurrent disc herniation after spinal surgery at the surgical sites.[7, 17-19] These types of adverse events can result in errant diagnosis, additional diagnostic studies, and invasive procedures.

7.1.3 Literature Summary

This review of the literature was conducted to evaluate the potential risks to health associated with the use of absorbable collagen-based hemostatic devices without added biologics. The safety outcomes reported varied across the studies included in the assessment. This may be a reflection of the use of absorbable collagen-based hemostatic devices in a variety of procedures treating different health conditions. The adverse events reported by these studies (e.g., bleeding and foreign body reactions) are known to be related to the use of absorbable collagen-based hemostatic devices. Some of the percentages for re-bleeding could be associated with the type of patients and procedures in the studies.

7.2 Medical Device Reports (MDRs)

7.2.1 Overview of the MDR System

The FDA receives medical device reports (MDRs) of suspected device-associated deaths, serious injuries, and certain malfunctions. MDRs are submitted by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters, such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a “real world” setting/environment

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information

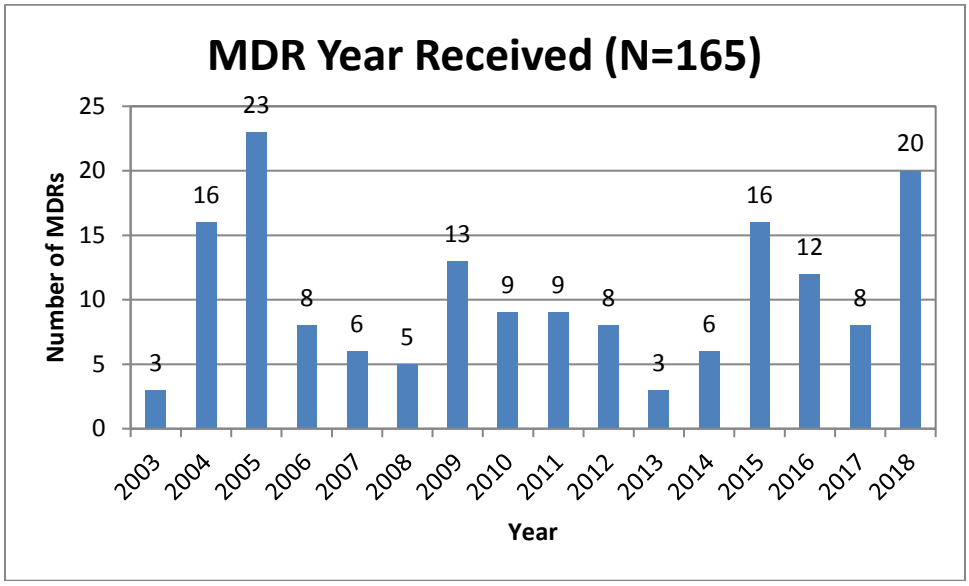
about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

7.2.2 MDR Data

FDA conducted a query of the MDR database for all reports posted between July 24, 2003 (i.e., the date of the 2003 Panel Meeting) and December 31, 2018 referring to absorbable collagen-based hemostatic devices not containing thrombin.

The search resulted in 165 MDRs. The Manufacturer/Distributor reported 138 MDRs, voluntary sources reported 23 MDRs, and User Facilities reported 4 MDRs. The reports included 8 deaths, 117 injuries, and 40 malfunctions. The number of reports received by FDA each year is shown in Figure 2. In comparison to the number of adverse event reports, absorbable hemostatic devices are used in millions of surgeries every year. For example, in 2012 alone, absorbable hemostatic devices were used in 6.9 million surgical procedures.[20]

Figure 2: Number of Reports Received by Year



The reported deaths include three instances of off-label use: two events report transcatheter arterial embolization with one event resulting in hepatic infarction and one event resulting in pulmonary embolism. There was one event reported in which the absorbable hemostat was used to achieve hemostasis on a bleeding liver surface and was embolized into an arteriovenous shunt resulting in shunt occlusion, hepatorenal syndrome and death. The remaining five death reports included two reports describing one event of stroke due to right vertebral artery occlusion by the applied collagen hemostat, one report of pulmonary infarction, one report of cardiac arrest after unintended intravascular injection, and one report of a patient who had a liver biopsy with 5 cc

Avitene injected into the tract which also embolized and resulted in the patient's death.

Infection was the most commonly reported patient problems (n=15). Also common were: allergic reaction (n=11) including 6 anaphylactic reactions; foreign body reaction (n=10); and paralysis (n=9) including 3 instances of facial paralysis. Hematoma (n=6); acute renal failure (n=5); hydrocephalus (n=5); numbness/tingling (n=5); nerve compression (n=4); seizure (n=4); and loss of bowel or bladder control (n=4) were also reported. In addition, reports included a few instances of compression of brain and/or spinal cord, hematoma, necrosis, or stroke.

The most commonly reported device problems involved off-label use (n=33); these included 31 reports of arterial embolization and two reports of use in sclerotherapy. Packaging issues were reported 20 times. There were eight reports of embolization not involving off-label use, including three instances of embolization to the heart, two reports of embolization to the basilar artery, one report of embolization in the rectal artery, and one instance of embolization to the lungs. Device problems were also reported involving failure to be absorbed (n=5); poor adhesion (n=3); and poor absorbency (n=2). In one instance, the product appeared on imaging months later, and in one instance the product caused potential artifacts on imaging.

7.3 Data from PMA Submissions

In accordance with the 6-year rule, FDA considered data contained in two original PMAs approved for absorbable collagen-based hemostatic devices six or more years before the date of this panel to support our proposed classification recommendation. On August 15, 1995, FDA approved P930030 from Coletica, S.A. for the Hemostagene Sponge, a hemostatic sponge consisting of cross-linked, purified bovine collagen (60 FR 65347). The Hemostagene Sponge is indicated in surgical procedures (other than in neurosurgical, ophthalmic, and urological) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical. To evaluate the safety and effectiveness of the Hemostagene Sponge, a multi-center, 300-patient clinical study was conducted evaluating use of the device in general, gynecologic, cardiothoracic, and vascular surgery. Safety was assessed by the nature and incidence of complications, and effectiveness was defined as the ability to achieve hemostasis within ten minutes of sponge application when compared to a control sponge. Results show that successful hemostasis was achieved in 89% of the patients treated with the Hemostagene Sponge, and that the performance of the Hemostagene Sponge was not statistically different from the control sponge. No complications or adverse effects related to use of the Hemostagene Sponge were reported in the clinical study. Nonclinical tests evaluating the collagen content and purity, shelf life, and biocompatibility of the Hemostagene Sponge were also conducted to support the safety and effectiveness of the device.

On September 30, 1999, FDA approved P990004 from Ferrosan A/S for the Surgifoam Sponge, a porcine gelatin absorbable sponge intended for hemostatic use (65 FR 16921). The Surgifoam Sponge is indicated for use in surgical procedures (other than neurological, urological, and ophthalmological surgery) as an adjunct to hemostasis when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures is ineffective or impractical. Toxicological and biocompatibility evaluations were performed with successful outcomes, and the hemostatic properties of the Surgifoam Sponge were evaluated in swine

spleen bleeding models. A multi-center, 281-patient clinical study evaluated the ability of the Surgifoam Sponge to achieve hemostasis within 10 minutes of application in cardiovascular, orthopedic, and general surgical procedures when compared to a control gelatin sponge. Results showed that successful hemostasis was achieved in 95% of the patients receiving the Surgifoam Sponge, and that the performance of the Surgifoam Sponge was not statistically different from the control sponge. The most common adverse events in the study were fever, tachycardia, and asthenia, although none of the adverse events were considered related to the device.

Although few adverse events were observed in the clinical studies for the Hemostagene and Surgifoam Sponges, both manufacturers noted several potential adverse events associated with use of absorbable collagen-based hemostatic devices, including but not limited to, hematoma, infection/abscess formation, potentiation of bacterial growth, wound dehiscence, inflammation and edema, foreign body reaction.

7.4 Conclusions

FDA reviewed the available literature, adverse event information, and information from PMA reviews. Although adverse events associated with absorbable collagen-based hemostatic devices may result in loss of life and significant loss of function, the incidence of adverse events for absorbable collagen-based hemostatic devices is low compared to the large number of surgeries performed with these devices.

In the analyses of the literature and MDR data, it was determined that a predominance of the adverse events was seen with for absorbable collagen-based hemostatic devices containing thrombin, which are being excluded from the reclassification recommendation, or for uses outside the labeled indications of these devices (e.g., arterial embolization) that are not relevant to the proposed reclassification. FDA believes general and special controls are adequate to mitigate the risks of absorbable collagen-based hemostatic devices included in the scope of this reclassification.

8. Risks to Health

After considering available information for the classification of absorbable collagen-based hemostatic devices, including reports in the Medical Device Reporting database, information available to FDA under section 520(h)(4) of the FD&C Act (21 U.S.C. 360j(h)(4)), the published literature, and the recommendations of the 2002 and 2003 Panels, FDA has identified the following risks to health associated with the use of absorbable collagen-based hemostatic devices:

- *Uncontrolled Bleeding* – The absorbable collagen-based hemostatic device is intended for use during surgical procedures as an adjunct to hemostasis when conventional means fail to produce hemostasis or are impractical. Patients receiving antiplatelet or anticoagulation therapy have increased blood clotting times. This increase in blood clotting time occurs even when an absorbable collagen-based hemostatic device is used during the surgical procedure to control bleeding. Failure to completely control bleeding can lead to death or severe injury.

- *Hematoma* – If small amounts of bleeding persist following the application of an absorbable collagen-based hemostatic device, the accumulation of blood behind the device will form a hematoma. The hematoma may press on soft tissue and cause soft tissue or nerve damage. A hematoma may also result in infection.
- *Infection* – An absorbable collagen-based hemostatic device may serve as a nidus for infection and abscess formation. Absorbable collagen-based hemostatic devices are manufactured from materials derived from animal sources such as collagen and gelatin; bacteria can grow on these device materials. For example, the use of absorbable collagen-based hemostatic devices in nasal surgery has been associated with toxic shock syndrome.
- *Wound Dehiscence* – The use of an absorbable collagen-based hemostatic device near sites of incision closures has interfered with the healing of the incision. This interference is due to mechanical interposition of the device and is not due to intrinsic interference with the wound healing process.
- *Foreign Body Reactions* – The absorbable collagen-based hemostatic device has been associated with foreign body reactions involving fluid accumulation due to encapsulation of the device. Such encapsulated devices have resulted in granuloma formation, inflammation, and edema, which may require surgical removal. Encapsulated devices can also present as an image artifact mimicking residual or recurrent tumor or abscess resulting in additional diagnostic studies and surgical procedures.
- *Immunological Reactions* – Absorbable collagen-based hemostatic devices are made of collagen-based materials derived from animal-based sources such as porcine and bovine gelatin or collagen. Some patients are allergic to these animal-derived materials.
- *Adhesion Formation* – An absorbable collagen-based hemostatic device, in the presence of coagulated blood and tissue fluid, often leads to scarring and adhesion formation in the weeks and months following the surgical procedure. The surgical procedure itself may result in additional scarring and adhesion formation.
- *Failure to be Absorbed* – Absorbable collagen-based hemostatic devices are readily degraded by enzymatic and hydrolytic action. Occasionally, an absorbable collagen-based hemostatic device may be implanted in an area with low enzymatic and hydrolytic activity. In such instances, it may not be efficiently absorbed. Subsequently, it may become encapsulated and exert pressure or create a chronic granulomatous inflammatory reaction on surrounding soft tissue to cause necrosis or injury, requiring surgical intervention.
- *Interference with Methylmethacrylate Adhesives* – Some types of absorbable collagen-based hemostatic devices have been reported to reduce the strength of methylmethacrylate adhesives used to fixate orthopedic prosthetic devices to bone.
- *Aspiration into Blood Salvage System Filters* – Fragments of an absorbable collagen-based hemostatic device may pass through blood salvage system filters and occlude the systems or the patient's vasculature.
- *Embolization* – Absorbable collagen-based hemostatic devices used near moderate to large blood vessels may result in embolization of the blood vessel. Such embolization

has been associated with severe adverse effects, including fever, duodenal and pancreatic infarct, embolization of lower extremity vessels, pulmonary embolization, splenic abscess, necrosis, asterixis, and death.

- *Paralysis/Nerve Damage/Tissue Necrosis* – Absorbable collagen-based hemostatic devices absorb fluids and swell to varying degrees, up to 40 times their weight in volume. This device swelling can encroach on surrounding nervous tissue to cause paralysis or tissue necrosis.
- *Disease Transmission* – Absorbable collagen-based hemostatic devices are composed of animal-derived collagen-based materials. Animal-derived materials may carry a risk of transmitting infectious disease when improperly collected, stored or manufactured.
- *Adverse tissue reaction* – Absorbable collagen-based hemostatic devices may result in local or systemic adverse tissue reaction due to material composition or interaction of the material with the body.
- *Toxicity* - Absorbable collagen-based hemostatic devices may contain materials or ingredients that result in local or systemic toxicity.

The panel will specifically be requested to comment on the risks to health identified by FDA and whether these risks are appropriate, and/or whether there are additional risks to health that should be considered for these devices.

9. Mitigation of Risks to Health/Proposed Special Controls

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified in Section 8 above, and provide reasonable assurance of the safety and effectiveness of absorbable collagen-based hemostatic devices.

When evaluating the adequacy of the special controls, it is important to understand that the FDA correlates the ability of each special control identified to mitigate an identified risk to health. Hence, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness

Table 2. below shows how FDA believes the risks to health can be mitigated by special controls.

Table 2: Risks to Health and Mitigation Methods for Absorbable Collagen-based Hemostatic Devices

Identified Risks to Health	**Mitigation Method**
Uncontrolled bleeding	Material Characterization Non-Clinical Performance Testing In Vivo Evaluation Labeling Shelf-Life
Hematoma	Non-Clinical Performance Testing In Vivo Evaluation Labeling
Infection	Material Characterization In Vivo Evaluation Sterility Shelf-Life Labeling
Wound dehiscence	Labeling
Foreign body reactions	Material Characterization In Vivo Evaluation Biocompatibility Evaluation Labeling
Immunological reactions	Material Characterization In Vivo Evaluation Biocompatibility Evaluation Shelf-Life Labeling
Adhesion formation	In Vivo Evaluation
Failure to be absorbed	Material Characterization Non-Clinical Performance Testing In Vivo Evaluation Biocompatibility Evaluation Shelf-Life
Interference with methylmethacrylate adhesives	Material Characterization Non-Clinical Performance Testing In Vivo Evaluation Labeling
Aspiration into blood salvage system filters	Materials Characterization Non-Clinical Performance Testing Labeling
Embolization	Materials Characterization Non-Clinical Performance Testing In Vivo Evaluation Labeling

Identified Risks to Health	Mitigation Method
Paralysis/nerve damage/tissue necrosis	Material Characterization Non-Clinical Performance Testing In Vivo Evaluation Labeling Shelf-Life
Disease transmission	Material Characterization Sterility
Adverse tissue reaction	Biocompatibility Materials Characterization In Vivo Evaluation
Toxicity	Biocompatibility Materials Characterization In Vivo Evaluation

The following special controls are proposed for absorbable collagen based hemostatic devices:

- Materials characterization of the device must include the following:
    - Material source information must be sufficient to demonstrate that the likelihood of the risk that the device is transmitting infectious diseases is minimized.
    - Material processing information must detail all reagents used in the manufacture of the device, and residual amounts must be quantified.
    - For crosslinked devices, the density of crosslinks must be provided.
    - Device-related particulates must be characterized.
    - Collagen characterization information, including elemental analysis and de-cellularization efficiency determination, must demonstrate the identity, purity, and quality of the collagen.

- Biocompatibility evaluation of the device must include the following:
    - Patient-contacting components of the device must be demonstrated to be biocompatible.
    - Residual reagents in the final product must be demonstrated to be safe for human exposure.
- Performance data must demonstrate the sterility of patient-contacting components and acceptable levels of endotoxins and material-mediated pyrogens.

- 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.

- Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, and must characterize:

    - Amount of swelling, e.g., change in volume or change in weight, of the device;
    - In vitro clotting time;
    - Reliability of the delivery system mechanism and compatibility of the delivery system with the hemostatic device;
    - Absorption of the device under physiologically relevant conditions; and
    - Fragmentation of the device.

- For devices intended for use on bone surfaces, non-clinical performance testing must demonstrate that the device does not interfere with the bonding strength of methylmethacrylate adhesives.

- For devices intended to be used in applications that involve blood transfusion systems, non-clinical performance testing must demonstrate that the device does not impair the 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 type of bleeding and targeted tissue(s) of bleeding.
        - A validated bleeding scale tool for bleeding severity must be used for selection and evaluation of bleeding sites to support the intended use.

    - The following characteristics must be evaluated:

        - Reliability of deployment mechanism and anticipated compatibility issues of deployment, e.g. passage of device through trocars;
        - Effectiveness of hemostasis at 10 minutes or less, and characterization of the following: re-bleeding potential, blood loss, and thromboembolic risk;
        - Immunogenicity of non-mammalian collagens;
        - Inflammatory cell response/potential histotoxicities;
        - Time to complete absorption
        - Macroscopic and microscopic histology at implant site and sites distant from implant site; and
        - Hematological and clinical chemistry parameters.

- Labeling must include:

    - Specific instructions for deployment by users;
    - Warnings, precautions, and limitations needed for safe use of the device. Unless available information indicates that the following do not apply, the labeling must provide appropriate warnings, precautions or limitations regarding how to avoid known hazards associated with device use including:

        - Interference with healing of wound edges;
        - Interference with methyl methacrylate adhesives; and
        - Use with autotransfusion systems.

- 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 use of the device;

- For devices intended for general surgical use, a hemostatic effectiveness table comparing device performance in multiple specialties of surgical procedures; and

- An expiration date/shelf life.

The panel will be asked whether the proposed special controls can adequately mitigate the risks to health for absorbable collagen-based hemostatic devices and provide a reasonable assurance of safety and effectiveness in light of the available scientific evidence.

10. Summary

Absorbable collagen-based hemostatic devices are currently classified in Class III. In light of the information available, the Panel will be asked to comment on whether absorbable collagen-based hemostatic devices meet the statutory definition associated with a Class III device designation. FDA believes these devices may be more appropriately regulated as:

- Class II, meaning general and special controls are sufficient to provide reasonable assurance of safety and effectiveness

as opposed to:

- Class III, meaning

    - insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

For the purposes of classification (refer to the Regulatory Reference Sheet for additional information), FDA considers the following items, among other relevant factors, as outlined in 21 CFR §860.7(b):

1. The persons for whose use the device is represented or intended;
2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use
3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. The reliability of the device.

Part (g)(1) of this regulation further states that it "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is **reasonable assurance of the safety and effectiveness** of the device, if regulated by general controls alone, or by general controls and special controls, may support a determination that the device be classified into Class III."

10.1 Indications for Use

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. This device type is predominantly composed of collagen-based materials derived from animal sources and is absorbable.

10.2 Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), "there is 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 any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

In plain language, the definition states that a reasonable assurance of safety exists if, when using the device properly:

- The probable benefits to health outweigh the probable risks, and
- There is an absence of unreasonable risk of illness or injury.

FDA has identified potential risks to health associated with absorbable collagen-based hemostatic devices, based on the public and non-public information (published literature, MDRs, annual reports, and Summary of Safety and Effectiveness Data documents) available to FDA. The risks to health are discussed in Section 8 of this document.

FDA will ask the Panel whether the evidence demonstrates a reasonable assurance of safety for the indications for use described above.

10.3 Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), "there is 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."

In plain language, the definition states that if using the device properly provides clinically significant results in a significant portion of the target population, there is a reasonable assurance of effectiveness.

FDA will ask the Panel whether there is a reasonable assurance of effectiveness absorbable collagen-based hemostatic devices for the indications for use described above.

10.4 Special Controls

If the Panel were to recommend a Class II determination, FDA believes that the special controls proposed in Section 9, above, should be included as part of the full list of special controls.

The panel will be asked whether the proposed special controls can adequately mitigate the risks to health for absorbable collagen-based hemostatic devices and provide a reasonable assurance of safety and effectiveness in light of the available scientific evidence.

10.5 Reclassification

As previously noted, FDA considers a device Class II when general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness.

In order to change the classification of absorbable collagen-based hemostatic devices from Class III to Class II, FDA must have sufficient information to establish special controls that can provide reasonable assurance of the safety and effectiveness that, when using the device properly:

1. The probable benefits to health from using the device will outweigh the probable risks (per the definition of a reasonable assurance of safety, 21 CFR 860.7(d)(1))

2. There is an absence of unreasonable risk of illness or injury (per the definition of a reasonable assurance of safety)

3. The device will provide clinically significant results in a significant portion of the target population (per the definition of a reasonable assurance of effectiveness, 21 CFR 860.7(e)(1))

Special controls include "the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents (including guidance on the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the FD&C Act), recommendations, and other appropriate actions as the Commissioner deems necessary to provide such assurance."

FDA believes that the available evidence supports a reasonable assurance of safety and effectiveness; the proposed special controls, in addition to general controls, would be sufficient to provide such assurance; and there is not an unreasonable risk of illness or injury for absorbable collagen-based hemostatic devices. Consequently, FDA recommends that absorbable collagen-based hemostatic devices under regulation 21 CFR 878.4490 be reclassified to Class II (Special Controls).

Based on the available scientific evidence and proposed special controls, the panel will be asked whether a Class III or Class II designation is appropriate absorbable collagen-based hemostatic devices for the indications listed above.

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12. Appendices

12.1 Current Approvals for Absorbable Collagen-based Hemostatic Devices

Table 3: Current Approvals for Absorbable Collagen-based Hemostatic Devices

PMA Number*	Approval Date	Trade Name	Sponsor	Device Description	Indications for Use
N17600*/ P800002	08/26/1976 10/24/1980	Avitene Microfibrillar Collagen Hemostat	Davol, Inc.	Several dry forms of microfibrillar bovine-derived collagen.	AVITENE (MCH) is used in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
P810006	12/10/1981	Collastat Absorbable Collagen Hemostatic Sponge and Hemostatic Agent-Microfibrillar Form	Integra Lifesciences Corp.	Soft, white, pliable, microfibrillar bovine-derived collagen.	Collastat Absorbable Collagen Hemostatic Agents are indicated in surgical procedures (other than ophthalmological and urological surgery) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
P850010	11/08/1985	Helistat, Helitene Absorbable Collagen Hemostat	Integra Lifesciences Corp.	Soft, white, pliable, microfibrillar bovine-derived collagen.	Helistat Absorbable Collagen Hemostatic Agents are indicated in surgical procedures (other than ophthalmological and urological surgery) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
P810040	01/29/1982	Superstat	Superstat Corp.	Dry, white, bovine-derived collagen.	Superstat is indicated for use when hemostasis is desired along suture lines in diffusely bleeding sites, incisions, dissections, and around arterial or venous anastomoses. It is not intended to replace surgical ligature. Superstat is indicated in oozing bleeding, either capillary or venous, in practically all incisions or wounds and as an adjunct to conventional closure techniques.
N18286*	07/08/1983	Gelfoam Sterile Sponge/Powder	Pfizer, Inc.	Dry, malleable, porcine-derived gelatin sponge or powder mixed with sterile saline.	GELFOAM Sterile Sponge, used dry or saturated with sterile sodium chloride solution, is indicated in surgical procedures as a hemostatic device, when control of capillary, venous, and arteriolar bleeding by pressure, ligature, and other conventional procedures is either ineffective or impractical.

P830079 **	10/10/1985	Instat Collagen Absorbable Hemostat	Ethicon, Inc.	Cross-linked bovine collagen in the shape of a sponge-like pad.	INSTAT MCH is indicated for use in surgical procedures (other than Urological and Ophthalmological surgery) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
P850023 **	05/27/1986	Hemopad Novacol	Datascope Corp.	A soft, white pad of long non-woven fibers of bovine-derived collagen.	Novocol is indicated in surgical procedures (other than in neurological, urological and ophthalmological surgery) for use as an adjunct to hemostasis when control of bleeding by ligature or conventional method is ineffective or impractical.
P930030 **	08/15/1995	Actifoam	Coletica S.A. BASF Corp.	Absorbable bovine collagen sponge.	The Hemostagene Absorbable Collagen Hemostatic Sponge is indicated in surgical procedures (other than in neurosurgical, ophthalmic, and urological) as an adjunct to hemostasis when control by ligature or conventional procedures is ineffective or impractical.
P990004	09/30/1999	Surgifoam Absorbable Gelatin Sponge, U.S.P.; Surgifoam Powder; SurgiFlo	Ethicon, Inc.	White, malleable, porcine gelatin sponge.	SURGIFOAM Sponge, used dry or saturated with sterile sodium chloride, is indicated for surgical procedures (except ophthalmic) for hemostasis, when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures is ineffective or impractical. Although not necessary, SURGIFOAM Sponge can be used with thrombin to achieve hemostasis.

*Applications starting with “N” indicate products approved in CDER

**No longer being manufactured or marketed in the U.S.

12.2 Literature Review Methods

FDA conducted a literature search to identify any relevant references published up to and including December 14, 2018. We searched two electronic databases (MEDLINE and Embase). The search terms were limited to currently approved absorbable collagen-based hemostatic devices and outcomes identified as potential risks to health. The search terms also filtered studies conducted in humans and published in English since 2003. The following search terms were used:

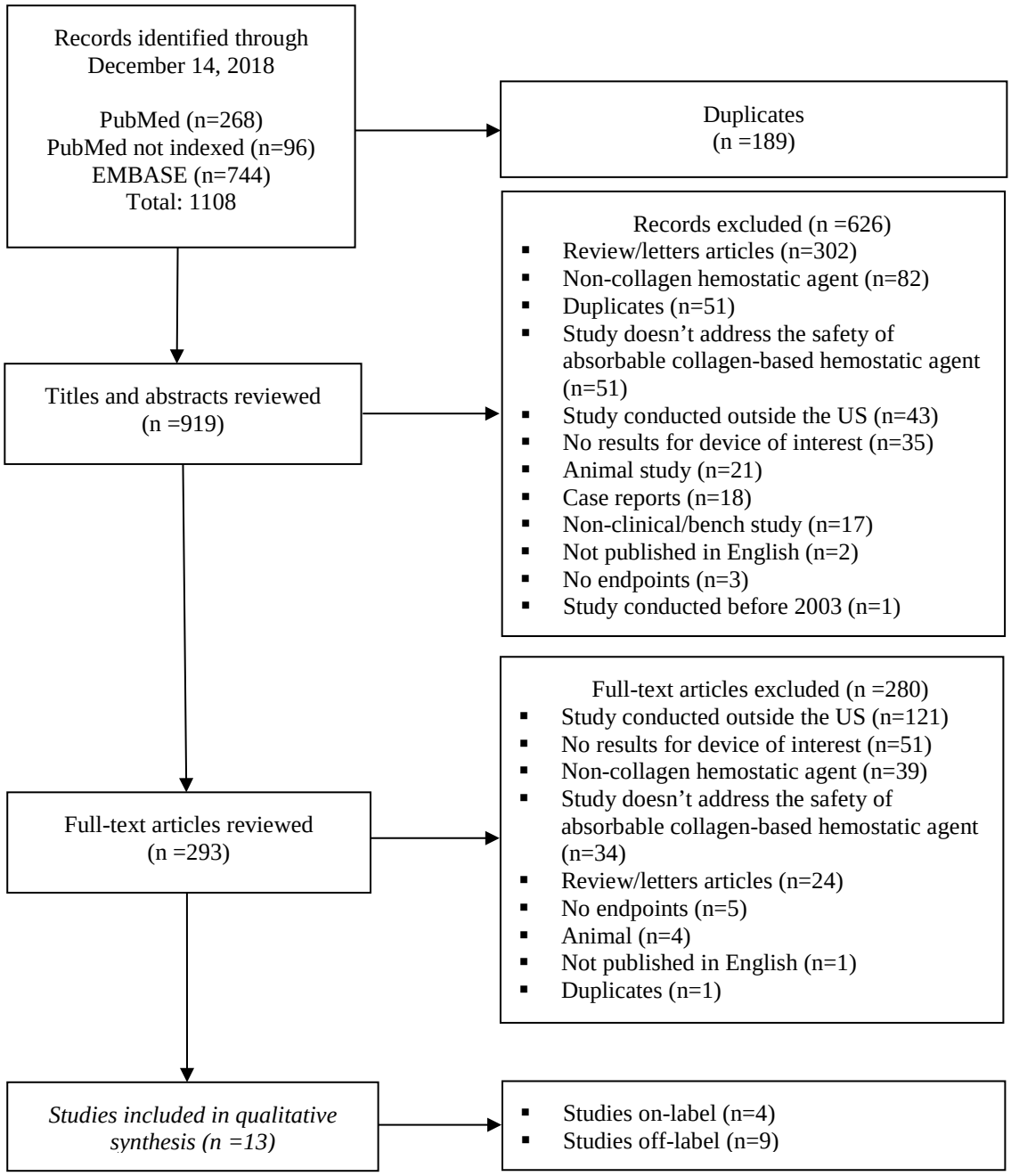
(1) PubMed: ((bleed* OR hematoma OR infection OR dehiscence OR immun* OR allerg* OR adhes* OR foreign body OR methylmethacrylate OR methacrylate OR (blood AND salvage) OR emboli* OR paralys* OR (nerve AND damage) OR necros* OR heal*) AND (Gelfoam [TW] OR Avitene[TW] OR Collastat[TW] OR Superstat[TW] OR Instat[TW] OR Helistat[TW] OR Helitene[TW] OR Hemopad[TW] OR Novacol[TW] OR Actifoam[TW] OR Surgifoam[TW] OR Spongistan[TW]))

(2) PubMed search terms for references not indexed at the time of the search: ((bleed* OR hematoma OR infection OR dehiscence OR immun* OR allerg* OR adhes* OR foreign body OR methylmethacrylate OR methacrylate OR (blood AND salvage) OR emboli* OR paralys* OR (nerve AND damage) OR necros* OR heal*) AND (Gelfoam [TW] OR Avitene[TW] OR Collastat[TW] OR Superstat[TW] OR Instat[TW] OR Helistat[TW] OR Helitene[TW] OR Hemopad[TW] OR Novacol[TW] OR Actifoam[TW] OR Surgifoam[TW] OR Spongistan[TW]) NOT Medline[SB])

(3) EMBASE: ('bleeding'/exp OR bleeding OR 'hematoma'/exp OR hematoma OR 'infection'/exp OR infection OR dehiscence OR 'immune'/exp OR immune OR 'allergy'/exp OR allergy OR 'adhesion'/exp OR adhesion OR 'foreign body'/exp OR 'foreign body' OR (foreign AND ('body'/exp OR body)) OR 'methylmethacrylate'/exp OR methylmethacrylate OR 'methacrylate'/exp OR methacrylate OR salvage OR 'embolism'/exp OR embolism OR 'paralysis'/exp OR paralysis OR (('nerve'/exp OR nerve) AND damage) OR 'necrosis'/exp OR necrosis OR 'healing'/exp OR healing) AND ('gelfoam':dn OR 'gelfoam'/dn OR 'gelfoam':ti OR 'gelfoam':ab OR 'avitene':dn OR 'avitene'/dn OR 'avitene':ti OR 'avitene':ab OR 'collastat':dn OR 'collastat'/dn OR 'collastat':ti OR 'collastat':ab OR 'superstat':dn OR 'superstat'/dn OR 'superstat':ti OR 'superstat':ab OR 'instat':dn OR 'instat'/dn OR 'instat':ti OR 'instat':ab OR 'helistat':dn OR 'helistat'/dn OR 'helistat':ti OR 'helistat':ab OR 'helitene':dn OR 'helitene'/dn OR 'helitene':ti OR 'helitene':ab OR 'hemopad':dn OR 'hemopad'/dn OR 'hemopad':ti OR 'hemopad':ab OR 'novacol':dn OR 'novacol'/dn OR 'novacol':ti OR 'novacol':ab OR 'actifoam':dn OR 'actifoam'/dn OR 'actifoam':ti OR 'actifoam':ab OR 'surgifoam':dn OR 'surgifoam'/dn OR 'surgifoam':ti OR 'surgifoam':ab OR 'spongistan':dn OR 'spongistan'/dn OR 'spongistan':ti OR 'spongistan':ab) AND [2003-2018]/py AND [humans]/lim AND [english]/lim

In addition to excluding the references using the search filters, articles were excluded if they were non-systematic reviews (review, letter to the editor, non-clinical methods, editorial, etc.), case reports, or the studies were conducted outside the United States.

Figure 3: Flow diagram of article retrieval and selection



Off-label use of absorbable collagen-based hemostatic devices (n=9)

After reviewing the full-text articles for eligibility, we identified nine (9) studies evaluating off-label use of absorbable collagen-based hemostatic devices for full-text data extraction.[8-16] These studies were published between 2005 and 2018. The majority (n=6 studies) were retrospective cohorts, and none of them were randomized. The

remaining three studies were a prospective cohort study, a prospective and retrospective cohort study, and a case series. The number of patients in these studies ranged from 3 to 100 cases and majority of the studies (7 studies) had a relatively small sample size (including ≤35 patients using one of devices of interests).

Of the nine (9) studies evaluating off-label use, five (5) studies reported use of absorbable collagen-based hemostatic devices as an embolic agent[8-12] to: (1) occlude a bleeding vessel from trauma injuries (e.g. embolization of lumbar artery injuries[12]) or conditions (e.g. trans-splenic portal intervention to treat congenital arterio-portal malformation[11]); (2) decrease or occlude the blood flow for treatment purpose (e.g. splenic artery embolization[9]; uterine artery embolization[8]); or (3) occlude a blood vessel to protect the organ from non-target radioembolization (e.g. cystic artery embolization before radioembolization[10]). One (1) study used absorbable collagen-based hemostatic devices as an antibiotic-delivery agent.[13] One (1) of the off-label studies reported use of absorbable collagen-based hemostatic devices to seal an operative site (burr hole).[14] One (1) study used AHD as a hemostatic agent after removal of the opercular block of tissue in hemispherectomy procedure[15], and one (1) study used AHD as both a hemostatic agent and an adjunct in tissue repair.[16]

The safety outcomes collected and reported varies across studies. This could be due to that these studies applied absorbable collagen-based hemostatic devices in a variety of procedures treating different health conditions. Therefore, the relevant outcomes captured would depend on the types and purpose of the treatment procedures.

Safety data related to use of absorbable collagen-based hemostatic devices as an embolic agent (n=5).

Among the five (5) studies where absorbable collagen-based hemostatic devices were used as an embolic agent, one (1) study, by McLucas B et al., reported purulent necrosis in patients who underwent uterine artery embolization using an absorbable collagen-based hemostatic device.[8] The proportion of patients with necrosis of leiomyomata side effect was 36.4% in the absorbable collagen-based hemostatic device-embolized group, which was higher than the 2.3% reported in patients embolized with traditional particles. However, it is unclear what “traditional particles” are. The interpretation of these results is limited given that they were not adjusted for potential confounders (i.e. the absorbable collagen-based hemostatic device group was statistically significantly younger and had less children than the particle group).

Pimpalwar et al.[11] reported high proportions of procedures with intraperitoneal bleeding (27% or 12/44) and blood transfusions (20.5% or 9/44) after using two brands of absorbable collagen-based hemostatic devices to embolize the access tract during trans-splenic portal interventions in children. Intraperitoneal bleeding was reported in 33% (7/21) of the procedures when one brand was used and 23.5% (4/17) when the second brand was used. Sofocleous et al. used an absorbable collagen-based hemostatic device as embolic agent to stop bleeding for treating lumbar artery injuries.[12] The study reported data from 11 patients, where the absorbable collagen-based hemostatic device was used in 5 of the patients. Formation of retroperitoneal abscess was reported in one of these patients and re-bleeding four days later due to late pseudoaneurysm formation in another patient. None of the results reported in these three (3) studies were adjusted

for potential confounding factors. The remaining two of the studies[9, 10] did not report safety events that were of concerns.

Safety data related to other off-label uses of absorbable collagen-based hemostatic devices (n=4)

Starkweather et al. used absorbable collagen-based hemostatic device packing soaked with Ciprodex during tympanoplasty procedure.[13] It appears that the absorbable collagen-based hemostatic device was used as an antibiotic-delivery method, rather than as a hemostatic agent. Several postoperative complications were reported including incision-site discharge/redness/infection, allergic reaction, and bleeding. However, it is not clear whether the absorbable collagen-based hemostatic device use was associated with these events. The goal of the study was not to evaluate the safety of the absorbable collagen-based hemostatic device, but to evaluate the effect of Ciprodex during tympanoplasty.

One study reported two cases when an absorbable collagen-based hemostatic device was used to seal an operative site after neuroendoscopy.[14] An absorbable collagen-based hemostatic device combined with bone fragments and dust created by the burr whole was used to cover the endoscopy tract. In both cases, the absorbable collagen-based hemostatic device and bone fragments were found migrating/displacing into the endoscopy tract. Both patients reported high-grade fever, headaches, and vomiting.

Lew et al. reported data from 50 patients who underwent hemispherectomy surgery.[15] The use of an absorbable collagen-based hemostatic device during procedure (as a hemostatic agent after removal of the opercular block of tissue) was significantly associated with a higher incidence of postoperative hydrocephalus compared to patients who didn't use the absorbable collagen-based hemostatic device (absorbable collagen-based hemostatic device:56% vs. no absorbable collagen-based hemostatic device: 18%; odds ratio=5.8 (95% CI: 1.2-28.4, p=0.03). When restricting the analyses in a sub-cohort using modified lateral hemispherectomy procedure, hydrocephalus event was still higher in cases with the absorbable collagen-based hemostatic device (71%) than cases without the absorbable collagen-based hemostatic device (13%). This study has a few limitations, including lacking detailed information, such as demographic characteristics between the absorbable collagen-based hemostatic device cases vs. non-absorbable collagen-based hemostatic device cases, was not adjusted for cofounders, and had limited sample size.

Another study used an absorbable collagen-based hemostatic device to aid in hemostasis and as an adjunct for tissue repair in Modified-Furlow Palatoplasty.[16] This study included 100 cases that underwent the procedure; all were performed by the same surgeon between 2010 and 2015. The study showed minimal blood loss for all subjects and none received intraoperative or postoperative transfusions, suggesting the absorbable collagen-based hemostatic device interposition minimizes risk of postoperative bleeding in this procedure. However, this study doesn't have a comparison group without an absorbable collagen-based hemostatic device incorporated in the procedure.

Limitations in the interpretation of the results of the studies evaluating off-label use of

absorbable collagen-based hemostatic devices include the retrospective data collection, lack of adjustment of potential confounders, small sample size, and generalizability. Most of the studies evaluating off-label use of absorbable collagen-based hemostatic devices were retrospective cohort studies and conducted in one institution. There were only two (2) studies with prospective data collection with a comparison group evaluating off-label use of absorbable collagen-based hemostatic devices. One of them reported a much higher proportion of purulent necrosis in the absorbable collagen-based hemostatic device group than the comparison group. However, interpretation of the results in both of these studies is limited given that the results were not adjusted for potential confounders.