

Dear Panel Member:

We seek your recommendation on the appropriate device classification of the following devices:

Bone Wax
Medical Maggots
Medicinal Leeches
Tissue Expanders &
Wound Dressings with Drugs

To assist in your preparation for the Panel discussion, the following information is enclosed regarding this topic:

- TAB 1 Information describing the classification process for unclassified devices and slides pertinent to the classification of each of the above referenced devices
- TAB 2 The Bone Wax Device
- TAB 3 Medical Maggots
- TAB 4 Medicinal Leeches
- TAB 5 Tissue Expanders
- TAB 6 Wound Dressings with Drugs
- TAB 7 Literature Articles pertaining to each device
- TAB 8 Classification Topics
- TAB 9 Panel Questionnaire
- TAB 10 *“Class II Special Controls Guidance Document: Surgical sutures; Draft Guidance of Industry and FDA”*
- TAB 11 *“The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final guidance for FDA and Industry”*

If you need additional information or clarification regarding the information provided in this package, please contact me at 301-594-3090 X132.

LT Ayanna Hill, Project Manager
FDA/CDRH/ODE/DGRND/PRSB

Date

TAB 1

MEMORANDUM

Date: July 27, 2005

To: General and Plastic Surgery Devices Panel

From: Division of General, Restorative, and Neurological Devices (DGRND)
Scientific Reviewers

Subject: Classification of the following devices:
Bone Wax
Medical Maggots
Medicinal Leeches
Tissue Expanders &
Topical Wound Dressing that Contain Drugs and/or Biologics

Summary of Device Regulation and Unclassified Devices:

Inadvertently a few medical devices were not classified at the time of the Medical Device Amendments of 1976 (the 1976 Amendments) to the Food, Drug and Cosmetic Act (the Act) (21 USC 360C). These medical devices are currently regulated as unclassified devices via pre-market notification [510(k)].

The 1976 Amendments to the Act as amended by the Safe Medical Device Act (SMDA) of 1990, the FDA Modernization Act (FDAMA) of 1997, and the Medical Device User Fee Modernization Act (MDUFMA) of 2002 provide regulations for the classification and regulation of medical devices intended for human use. FDA is required to classify all medical devices, including the remaining unclassified medical devices into the lowest regulatory class that can reasonably assure their safety and effectiveness for their intended use.

The Act established three categories (classes) of medical devices depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three classes are Class I (general controls), Class II (special controls), and Class III (pre-market approval). General controls are sufficient to provide reasonable assurance of the safety and effectiveness of Class I devices. General controls include the following: prohibition against adulterated or misbranded devices, pre-market notification (510(k)), banned devices, the quality system regulation that includes design controls and good manufacturing processes (GMPs), registration of manufacturing facilities, listing of device types, record keeping, etc. Class II devices are those that cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of such devices. These devices are regulated using special controls and general controls. Special controls include guidelines (guidance documents), performance standards, post-market surveillance, clinical data, labeling, tracking requirements, and other appropriate actions the Secretary of the Department of Health and Human Services deems necessary to provide such assurance. Class III devices are those for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness. These devices are life sustaining, life supporting,

or substantially important in preventing impairment of human health, or they present unreasonable risk of illness or injury. Class III devices are regulated by using “valid scientific evidence” to establish the safety and effectiveness of the device. Valid scientific evidence includes well-controlled investigations, partially-controlled studies, uncontrolled studies, well-documented case histories, and reports of significant human experience.

When most device types were classified in the late 1970s and early 1980s, most Class I and Class II devices were cleared for marketing via the 510(k) process. Some Class I devices were also exempted from 510(k) clearance. Now most Class I devices and a few Class II devices are exempt from 510(k) clearance because their safety and effectiveness can be reasonably assured by other general controls, particularly by the quality system regulation general control. Examples of class I exempt products include surgical apparel, nonabsorbable gauze for internal use; hydrogel wound dressings and manual surgical instruments such as clip applicators and forceps. Examples of non-exempt Class II devices include implantable surgical meshes, sutures, implantable clips and staples, dura mater substitute devices, and chin prosthesis. Examples of Class III devices include interactive wound dressings, adhesion barriers, silicone gel-filled breast prostheses and injectable fillers for facial aesthetic correction.

Draft Special Controls Guidance Document:

If the Office of Device Evaluation (ODE) considers classifying a medical device that was previously unclassified into regulatory Class II, such classifications are accompanied by what the Agency refers to as a draft “Special Controls” guidance document that is released for public comment. In the vast majority of cases, the special control has been in the form of a guidance document. The guidance document: “*Class II Special Controls Guidance Document: Surgical sutures; Draft Guidance of Industry and FDA*”, issued on June 3, 2003, is provided in **TAB 10** as an example of a Class II special controls guidance document for a transitional device that was reclassified from Class III to Class II. The content of a Class II special controls guidance document for any of the above referenced devices should be very similar to the sample guidance document provided with the exception that specific device information would be different.

While the agency has not developed nor provided you with a copy of a proposed draft special controls guidance document for the above referenced devices, we are providing memos which includes sections for guidance documents for your review. At present, a special controls guidance document may be comprised of up to 12 sections.

The Least Burdensome Provisions of FDAMA:

A central purpose of the Food and Drug Administration Modernization Act of 1997 (FDAMA) is “to ensure the timely availability of safe and effective new devices that will benefit the public and to ensure that our Nation continue to lead the world in new device innovation and development. Congress’ goal was to streamline the regulatory process (i.e., reduce burden) to improve patient access to drugs and devices that could benefit the public.

One of the concepts central to this “least burdensome” approach to the regulation of medical devices is to review devices at the Class level (Class I, Class II, Class III) where they will receive an appropriate level of oversight in accordance with what is known about the safety and effectiveness of the device type. Since bone waxes have been in use for approximately 100 years, the Agency believes that they

can be appropriately regulated at the Class II, Special Controls, regulatory level because the assessment of their effectiveness and the known complications are well understood due to the many years of experience in their use. More than just risk is taken into account when devices are classified. An understanding of the methods to assess safety and effectiveness is a central factor in the classification of medical devices. Other Class II devices that are considered to have high risks associated with their use are dura replacements, surgical meshes and sutures.

The Guidance Document: *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final guidance for FDA and Industry*, is provided as a reference for your convenience, located in **TAB 11**.

As described in the Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry (www.fda.gov/cdrh/ode/guidance/1332.pdf), the purpose of a 510(k) submission is to determine whether the device is “substantially equivalent.” to a predicate device. Section 513(i) of the act establishes the criteria for determining whether “substantially equivalent.” This section of the act states that FDA may issue an order of substantial equivalence only if it determines that the device has the same intended use as a predicate device and is as safe and effective as a legally marketed device.

FDA and industry should focus on those issues that can affect the substantial equivalence determination, that is, whether the device has the same intended use as the predicate device and is as safe and effective as a legally marketed device. Information unrelated to the substantial equivalence decision should not be submitted to nor requested by, the agency. This would normally include information related to cost effectiveness, consumer preference testing and comparative testing. Information that is scientifically interesting but not necessary for the purpose of determining substantial equivalence should not be part of the submission.

TAB 2

Bone Wax

Brief History and Regulation of Bone Wax:

In general, bone waxes are medical devices that contain white beeswax as the major component. Most medical texts assign the invention of bone wax to two individuals: Rushton Parker, who, in 1892, reported that a mixture of white beeswax, olive oil and phenol had significant hemostatic properties when applied to broken bones and Sir Victor Horsley, who, later that same year, employed the same bone wax recipe to control bleeding in orthopedic surgical procedures. Most of the bone waxes in use today are based on the bone wax described and employed by Parker and Horsley in 1892 and are, for the most part, formulated as approximately 70% white beeswax and approximately 30% of some type of softening agent or agents. The hemostatic character of these products is dependent on the beeswax because it gives the material the ability to cling to the bone and physically block bleeding. The softening agent is added to make the beeswax soft and kneadable so that the surgeon may place it and remove what is not needed in order to maintain a tamponade effect. The softening agents are most often oils, paraffin waxes, palmitates and petrolatum.

Bone waxes have been regulated as unclassified medical devices through the clearance of a pre-market notification [510(k)] since the first one (Lukens Bone Wax) was cleared in 1979. The Lukens Bone Wax had been marketed since 1904, but they submitted a 510(k) for a sterilization change. Following the 1979 clearance of the Lukens Bone Wax (manufactured by Lukens, Inc., cleared via K791495 and formulated from beeswax, almond oil and salicylic acid), CDRH has cleared five additional bone waxes: Auto Suture Bone Wax (US Surgical, cleared via K971680 and formulated from glycolide, caprolactone, mannitol and β -tricalcium phosphate), Aesculap Bone Wax (Aesculap, Inc., cleared via K000021 and formulated from beeswax and petroleum jelly), CP Medical Bone Wax (CP Medical, Inc., cleared via K024372 and formulated from beeswax, paraffin and isopropyl palmitate), AOC Bone Wax (Ceremed, Inc., cleared via K041363 and formulated from a mixture of alkylene oxide copolymers) and Sharpoint Lukens Bone Wax (Surgical Specialties Corp., cleared via K050292 and formulated from beeswax, paraffin and isopropyl palmitate). There appears to be one additional pre-amendment bone wax that is still on the market, the Ethicon Bone Wax (Ethicon, Inc. formulated from beeswax, paraffin and isopropyl palmitate), for which there is evidence that it has been sold in the US since at least 1942.

Up until recently, bone waxes were understood to be non-absorbable implant materials that remained inside the body for an extended period of time and were considered by FDA to be a long-term implant as opposed to absorbable hemostatic agents, which were absorbed within a few months following implantation. While bone waxes most probably are eventually absorbed, the process may take many years. However, with the clearance of the absorbable US Surgical Bone Wax, the Agency removed that distinction as the US Surgical Bone Wax is a mixture of absorbable polymers: glycolide, caprolactone, mannitol and β -tricalcium phosphate, and is absorbed in a relatively short period of time (months rather than years). Table 1 identifies the bone waxes that have been cleared to date or that have pre-market status, gives a brief description of each and identifies the pre-market notification number and clearance date.

Table 1**Pre-Amendment Bone Waxes and Those Cleared Through Pre-market Notification [510(k)]**

Product	Present Application Holder	Notification Number	Characteristics	Clearance Date
Horsley's Wax	None	Pre-amendment	Beeswax, olive oil, phenol	Invented in 1892
Bone Wax	Ethicon, Inc.	Pre-amendment	Beeswax, paraffin, isopropyl palmitate	Available before 1976
Bone Wax	Lukens, Inc.	Pre-amendment and K791495	Beeswax, almond oil, salicylic acid	Available since 1904, 510(k) for sterilization change, September 24, 1979
Auto Suture Bone Wax	US Surgical Corp.	K971680	Glycolide, caprolactone, mannitol, tricalcium phosphate	October 24, 1997
Bone Wax	Aesculap, Inc.	K000021	Beeswax, petroleum jelly	March 27, 2000
Bone Wax	CP Medical, Inc.	K024372	Beeswax, paraffin, isopropyl palmitate	June 19, 2003
AOC Bone Wax	Ceremed, Inc.	K041363	Alkylene oxide copolymers	July 27, 2004
Sharpoint Lukens Bone Wax	Surgical Specialties Corp.	K050292	Beeswax, paraffin and isopropyl palmitate	March 9, 2005

Risks to Health

In order to summarize the potential risks associated with the use of bone waxes, we reviewed the adverse event reports submitted to the agency via the Medical Device Reporting (MDR) System, which was voluntary from 1992 until 1996 when it became mandatory for manufacturers to report any device failures they were aware of. The MDRs (up until June 13, 2005) for bone wax received by the Agency are summarized in Table 2.

Table 2: Adverse Events Reported

Adverse Event	Number of Reports
Granuloma	1
Infection	2
Paralysis	1
Total	4

The following literature articles are indicative of the published literature on bone waxes. These articles discuss bone waxes and also describe some potential risks of using these devices. Copies of the following articles are provided in **TAB 7**:

1. Tan, Tze-Ching and Peter McL. Black. Sir Victor Horsley (1857-1916): Pioneer of neurological surgery. *Neurosurgery* 50(3): 607-12 (2002).
2. Schonauer, Claudio, Enrico Tessitore, Giuseppe Barbagallo, Vincenzo Albanese and Aldo Moraci. The use of local agents: bone wax, gelatin, collagen, oxidized cellulose. *European Spine Journal* 13(Suppl. 1): S89-S96 (2004).
3. Finn, Maxwell D., Sterling R. Schow, and Emet D. Schneiderman. Osseous regeneration in the presence of four common hemostatic agents. *Journal of Oral and Maxillofacial Surgery* 50: 608-12 (1992).

These articles, as well as others, and bone wax labels were reviewed in order to compile the risks identified in Table 3. Table 3 also identifies the methods that will be proposed to ameliorate these risks.

Table 3: Table of Potential Risks and Controls

Potential Risk	Control
Uncontrolled bleeding due to device failure	Animal Studies, Clinical Data
Infections due to improper sterilization and enhanced bacterial growth	Animal Studies, Device Labeling, QSR, Bench Testing
Inflammation and/or edema due to foreign body reaction	Device Labeling, Biocompatibility Testing
Granuloma formation	Animal Studies, Device Labeling
Failure to be absorbed	Bench Testing, Animal Studies
Reduced strength of methylmethacrylate adhesion when used to attach prosthetic devices to bone surfaces	Device Labeling
Use of antiplatelet drug therapy and systemic heparinization may increase risk for device failure	Device Labeling

Interference with bone regeneration	Bench Testing, Animal Studies and Labeling
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FDA believes that the risks to health identified in Table 3 may be controlled by use of special controls, i.e., a guidance document that outlines the testing and studies that should be performed in order to ameliorate these risks.

Proposed Identification for Bone Wax for the Code of Federal Regulations:

Identification. A bone wax is a bone adherent material used to control bleeding from bone via the physical mechanism of tamponade.

Rationale for Proposed Class II Regulatory Status for Bone Wax:

The Agency’s rationale for suggesting that this device be classified into Class II is summarized as follows:

- We have years of experience regulating these devices (since 1979)
- We understand the device specifications and performance characteristics (bench testing, animal testing and clinical data) needed to evaluate and control their safe and effective use.
- Classification to Class II meets the FDA mandate to apply the “least burdensome” approach to regulating medical devices.

The Agency’s rationale for identifying a Class II designation as appropriate is based on the long history of safe and effective use of these devices over the past 100 years and the scarcity of adverse event reports in the medical literature and the FDA’s Medical Device Reporting System. The Agency proposes that all of the potential risks to health can be ameliorated via a special controls guidance document that includes recommendations and advice on device materials, device performance, animal testing, clinical testing, device sterilization, biocompatibility and device labeling.

The recent MDUFMA amendment to the FD&C Act directed the Agency to regulate medical devices in the “least burdensome” manner possible based on the available safety and effectiveness information. Please keep this in mind as you consider classification of these devices. A copy of the least burdensome guidance document is included in **TAB 11**.

FDA proposes that the bone waxes can be regulated with special controls. Following are the relevant draft sections of a proposed bone wax guidance document for your consideration as you discuss the appropriate classification for this device.

For a proposed absorbable surgical hemostatic agent devices special control document, sections 1 through 4 and 9 through 11 should be mostly boilerplate language except for references to the device type and regulation numbers. For your information and review we are providing some suggestions for the content being considered for inclusion in Sections 5 through 8 of a proposed special controls guidance document for bone waxes. Please note that the information presented in this memorandum is suggested content and, therefore, the exact format and information contained in any draft special controls guidance document is subject to change.

Suggested Content for Sections 5 through 8

Section 5-Risks to Health

This section would include information quite similar to the table above, which discusses the risks to health associated with the use of bone waxes. The information to be placed in that chapter is proposed as follows:

In the table below, FDA has identified the risks to health generally associated with the use of bone waxes. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, prior to submitting your 510(k), to identify any other risks specific to your device. The 510(k) should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Uncontrolled bleeding due to device failure	Guidance document sections on: Material and Performance Characteristics, Animal Testing, Clinical Data and Labeling
Infection due improper sterilization and enhanced bacterial growth	Guidance Document Sections on: Animal Testing, Sterility, and Labeling
Inflammation and Edema due to foreign body reactions	Guidance Document Sections on: Animal Testing, Biocompatibility and Labeling
Granuloma formation	Guidance Document Sections on: Animal Testing and Labeling
Failure to be absorbed	Guidance Document Sections: Material and Performance Characteristics, Animal Testing and Biocompatibility
Reduced strength of methylmethacrylate adhesion when used to attach prosthetic devices to bone surfaces	Guidance Document Section on: Device Labeling
Antiplatelet drug therapy and heparinization may increase risk for device failure	Guidance Document Section on: Device Labeling
Interference with bone regeneration	Guidance Document Sections on: Bench Testing, Animal Studies and Labeling

Section 6-Material and Performance Characterization:

This section would include the types of bench top testing, material characterization and manufacturing information that the Agency would be looking for. The proposed chapter would read as follows:

We recommend that you provide the information below to establish the material and performance characteristics of the device.

Material Specification

We recommend that you provide all material components of the device. Such information should identify the source and purity of each component. Such information may also be supplied by reference to a Master Access File(s), if the appropriate letter of cross reference is included. Submission of a Certificate(s) of Analysis (CoA) and/or a Materials Safety Data Sheet(s) (MSDS) can also greatly simplify FDA's review of components/materials.

Product Characterization

We recommend that the product manufacturing process be briefly described and compared to that of the legally marketed predicate device.

We recommend that you provide the following product characterization information regarding your bone wax:

- a complete description of all components and amounts of components,
- the time to complete device resorption determined in animal studies, and
- a profile of the ability of the device to adhere to bone and form a tamponade.

Final Product Specification

We recommend that you provide information about the relevant in-process and final product tests, including identification of the test method and time of testing during manufacture and the final product release specifications.

Examples of final product release specifications include:

- specific melting temperature
- residual levels of manufacturing reagents
- residual levels of heavy metals
- pyrogen levels
- sterility

We also recommend that you provide the rate of product absorption. Such studies should be performed *in vivo* or in a manner expected to accurately predict product decomposition (e.g., in comparable cellular and proteolytic environments at 37°C). Please see Section 7 (**Animal Testing**) below for more details regarding this recommendation.

Shelf Life

We recommend that you provide both stability testing of the device and packaging testing to establish the shelf life (i.e., expiration date) for the labeling of your bone wax. Accelerated testing should be supported/validated by real-time shelf life testing. With regard to mechanical testing, we recommend that you provide the data from the applicable test(s) described in Section C above on representative aged samples. With regard to packaging testing, we recommend that you provide data for the final finished package for initial integrity and maintenance of integrity after selecting the appropriate materials and qualifying the package configuration. We recommend that you use test methods that are either validated or standardized.

Section 7-Animal Testing

This chapter discusses the animal testing the Agency would recommend. The information proposed for inclusion into this chapter is as follows:

FDA recommends that you provide animal testing that models each surgical application for which your device is to be indicated. For example, for control of bleeding from bone, we recommend that the animal testing include specific bone bleeding models that assess the ability of the bone wax to adhere to the bone and that assess the time to complete hemostasis.

FDA recommends that your animal study evaluate the time to hemostasis, time to resorption of the bone wax, the ability of the bone wax to adhere to bone, and any complications. We recommend that you monitor complications, such as infection, hematoma, coagulopathies, increased wound healing time, etc.

FDA also recommends that your animal study include testing of a legally marketed predicate device of similar components and manufacture so that observations can be made as to the substantial equivalence of the two devices in reference to the evaluations outlined in the paragraph above.

The extent of animal testing needed will be dependent upon the differences between the proposed device and a legally marketed predicate device.

Section 8-Clinical Testing:

This chapter of the special controls guidance document discusses clinical data. The information proposed for this chapter is as follows:

In accordance with the Least Burdensome provisions of the FDA Modernization Act of 1997, FDA will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies will not be needed for most bone waxes, FDA may recommend that you collect clinical data for a bone wax with:

- new technology (i.e., technology different from that used in a legally marketed bone wax); or
- new indications for use for a bone wax of the same type.

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. Please contact the Plastic and Reconstructive Surgery Devices Branch (PRSB) to discuss any clinical testing before initiating studies.

If a clinical study is needed to demonstrate substantial equivalence (i.e., conducted prior to obtaining 510(k) clearance of the device), the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR 812.

After FDA determines that the device is substantially equivalent, clinical studies conducted in accordance with the indications reviewed in the 510(k), including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the investigational device exemptions (IDE) requirements. However, such studies must be performed in conformance with 21 CFR 56 and 21 CFR 50.

Some additional clinical study information specific to bone wax is provided below. If you have questions about protocol design not addressed in this guidance document, you are encouraged to contact the Plastic and Reconstructive Surgery Devices Branch.

Bone waxes are primarily applied during orthopedic surgical procedures or bone trauma treatment procedures in order to control bleeding from bones. Accordingly, a clinical study should address the following:

- The study should be a controlled, prospective, randomized clinical investigation where the subject bone wax is compared to a legally marketed predicate device. In most cases, such comparisons should be made between bone waxes manufactured from similar materials and with similar indications for use.
- The study should be conducted at an adequate number of institutions to assure that the product performance will be acceptable with potential technical and procedural differences encountered when the product is marketed.
- Patients should be followed for the amount of time required for complete healing of the bone injured or surgically repaired or for two months, whichever is longer. Relevant blood work should be performed before and after application of the device. In some cases, when a combination of more than one hemostatic product (i.e., absorbable hemostatic agent, bone wax and thrombin) is employed, antibody formation may need to be assessed at the time when antibody production would reach its maximum level (approximately 4 to 6 weeks after exposure to the combination of hemostatic devices).
- Patients with both traumatic orthopedic surgical repairs and planned orthopedic procedures should be enrolled.

- For any specialized use of bone wax, beyond the standard bleeding from bone indication, we recommend that you collect additional safety and effectiveness data.
- The primary effectiveness endpoint for the clinical study should be either (1) time to complete hemostasis or (2) hemostasis within a specified time limit – yes/no.
- The primary safety endpoints should be a full evaluation of all adverse events observed during the administration of the device and recovery period from surgery until the patient exits the study.
- Additionally, data on the ability of the bone wax to adhere to the bone should be collected.

David Krause, PhD, Expert Biologist
Plastic & Reconstructive Surgery Devices Branch
Division of General, Restorative & Neurological Devices

Date

TAB 3

Medical Maggots

Device Definition

FDA is proposing the following identification for Medical Maggots:

Medical Maggots are blow fly (i.e., *Phaenicia Sericata*) larvae intended for debriding non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers and non-healing traumatic or post-surgical wounds

Device Summary and Intended Use/Indications:

Extract from the History of Maggot Therapy
(http://www.larve.com/maggot_manual/docs/history.html)

“Maggot therapy in ancient times”

The primitive, carrion-breeding habit of blowflies has been known and recorded for centuries. A very early reference can be found in the *Hortus Sanitatus*, one of the earliest European medical texts, published at Mainz in 1491.

In contrast, there are some indications that some primitive societies have recognized that the larvae of certain flies can have beneficial effects upon the healing of infected wounds. In the early part of this century, the Ngemba tribe of New South Wales, Australia, commonly used maggots to cleanse suppurating or gangrenous wounds and it is said that the aborigines traced this practice back to their remote ancestors^{1,2}. The Hill Peoples of Northern Burma were observed during World War II placing maggots on a wound then covering them with mud and wet grass: the Mayans of Central America ceremoniously exposed dressings of beef blood to the sun before applying them to certain superficial tumors; after a few days the dressings were expected to pulsate with maggots^{2,3}.

Maggots in military conflicts

The opportunistic infestation of wounds, particularly those sustained in battle, has similarly been observed throughout the centuries. Ambroise Paré (1509-1590), Chief Surgeon to Charles IX and Henri III, recorded that in the battle of St. Quentin (1557) maggots frequently infested suppurating wounds⁴.

Napoleon's Surgeon in Chief, Baron Dominic Larrey, quoted by Goldstein⁴ reported that when maggots developed in battle injuries, they prevented the development of infection and accelerated healing. *‘These insects, so far from being injurious to their wounds, promoted rather their cicatrization by cutting short the process of nature and causing the separation of cellular eschars which they devoured. These larvae are indeed greedy only after putrefying substances and never touched the parts endowed with life’*. There is no evidence, however, that Larrey deliberately introduced maggots into his patients' wounds.

During the American Civil War, a Confederate medical officer Joseph Jones, quoted by Chernin⁵ noted the beneficial effects of wound myiasis as follows; *'I have frequently seen neglected wounds filled with maggots, as far as my experience extends, these worms only destroy dead tissues, and do not injure specifically the well parts. I have heard surgeons affirm that a gangrenous wound which has been thoroughly cleansed by maggots heals more rapidly than if it had been left to itself.'*

According to Baer⁶ and McLellan⁷ the Confederate surgeon J. Zacharias, may have been the first western physician to intentionally introduce maggots into wounds for the purpose of cleaning or debriding the wound. Baer quotes Zacharias as stating: *'During my service in the hospital in Danville, Virginia, I first used maggots to remove the decayed tissue in hospital gangrene and with eminent satisfaction. In a single day would clean a wound much better than any agents we had at our command.... I am sure I saved many lives by their use, escaped septicaemia, and had rapid recoveries'*
A fascinating review of the early history of maggots in wound care was published in 1932 by Goldstein⁸.

Maggot therapy in the early 20th century

The founder of modern maggot therapy is William Baer (1872-1931), Clinical Professor of Orthopaedic Surgery at the Johns Hopkins School of Medicine in Maryland⁶. He described how, during the First World War, he had treated two wounded soldiers who had remained overlooked on the battlefield for seven days having sustained compound fractures of the femur and large flesh wounds of the abdomen and scrotum. On arrival at the hospital they showed no sign of fever or septicaemia despite the very serious nature of their injuries and their prolonged exposure to the elements without food or water. On removal of their clothing Baer found *'thousands and thousands of maggots that filled the entire wounded area.'* To Baer's surprise, when these were removed *'there was practically no bare bone to be seen and the internal structure of the wounded bone as well as the surrounding parts was entirely covered with most beautiful pink granulation tissue that one could imagine'*. This at a time when the mortality rate for compound fractures of the femur was about 75-80%. Support for Baer's observations was provided by Crile & Martin⁹ who also reported that soldiers whose wounds were infested with maggots did far better than their wounded comrades who wounds were not similarly afflicted.

Following these wartime experiences, Baer treated four children with intractable bone infections (osteomyelitis) at the Children's Hospital in Baltimore in 1928⁶. His initial use of unsterilized maggots was very successful and the wounds healed within six weeks. Encouraged by these results, Baer began to use the technique more widely, but unfortunately several of his patients developed tetanus and he concluded that it would be necessary to use sterile maggots for future work.

The importance of sterility

Having once accepted the importance of using larvae that were free from microorganisms, Baer devoted some considerable efforts to developing a suitable sterilization process⁶. He initially attempted to sterilize maggots themselves by first exposing them to full strength hydrogen peroxide for two hours, and then immersing them in mercuric chloride solution 1 in 1000. Although he was able to demonstrate that this process effectively sterilized the outer surface of the larvae, viable bacteria persisted within their gut. He then decided to sterilize the eggs, believing correctly that the contents were sterile. He tried many different solutions including mercuric chloride, phenol, alcohol, Mercurochrome, gentian violet,

hexylresorcinol and silver nitrate. These efforts were more successful at achieving sterility, but most also proved lethal to the eggs. Eventually a technique was developed which involved the use a solution containing mercuric chloride 1 in 1000, 25% alcohol and 0.5% hydrochloric acid.

Because of the popularity of maggot therapy in the 1930s, numerous papers were published describing techniques for breeding flies^{10,11} and producing sterile maggots.

Although Livingston¹¹ and Weil's group³ claimed some success with the sterilization of hatched larvae, the latter with a solution of iodine, most centers adopted Baer approach and concentrated on developing methods for sterilizing the eggs^{3,6,10,12,13}. A commonly used method began with pretreatment in Dakin's solution (dilute sodium hypochlorite, or bleach) followed by immersion in mercuric chloride or formaldehyde. Simmons¹⁴ reported satisfactory sterilization using 5% formalin, 1% sodium hydroxide; yet, even his method did not kill all spore forming bacteria such as *Cl. perfringens* or *Cl. tetanii*.

First commercial production of maggots

In the absence of any equally effective alternative for the treatment of osteomyelitis or infected soft tissue injuries, the use of maggots spread quickly during the 1930's. In the USA, *Lucilia sericata* larvae were produced by Lederle Corporation¹⁵ and sold for \$5 per 1000 (now equivalent to about \$100).

In the mid-1930s, Robinson surveyed 947 North American surgeons known to have employed maggot therapy¹⁶. Of the 605 responding surgeons who had treated 5750 patients, 91.2 % expressed a favorable opinion; only 4.4% expressed an unfavorable view. The most common complaints raised by surveyed practitioners were the cost of the maggots, the time and effort required to construct the maggot dressings, and the degree of discomfort suffered by patients. Robinson's paper also included a list of 54 papers on maggot therapy that had been published by that time.

Other than Baer's cases of tetanus and one case of erysipelas, thought to be associated with the use of non-sterile larvae³ no other serious adverse reactions were reported.

During the 1930s, attempts to isolate the 'maggot active principle' led to the use of a topical application of maggot extract to promote wound debridement and disinfection. Livingston¹⁷ described the treatment of 567 patients using maggot therapy alone or in combination with 'maggot active principle' derived from *Lucilia sericata*. He also used a polyvalent vaccine of pyogenic organisms suspended in the maggot principle as a vehicle administered intra-muscularly. Using this technique they claimed a success rate of 88%, 38% higher than control cases treated by other methods. Perhaps not surprisingly, this was associated with significant systemic reactions, and eventually abandoned.

The demise of maggot therapy

These years also marked the beginning of the antibiotic era. By 1940, sulfonamides already were available, and Chain *et al.*¹⁸ had discovered the methods for mass-producing Flemming's penicillin. As a result, by the mid-1940s, maggot therapy had virtually ceased, except as a treatment of last resort^{19,20} due largely to the ready availability of the new wonder drug and general improvements in surgical and wound management techniques.

Early evidence for the effectiveness of maggot therapy

The early maggot therapy literature contains many references to the successful treatment of chronic or acutely infected soft tissue injuries, including those infected with *Clostridium welchii* (*Cl. perfringens*) the 'gas bacillus'. Wounds treated with maggots included abscesses³ carbuncles²¹ leg ulcers²² pressure ulcers, mastoiditis¹⁹ and compound fractures²¹.

Maggots were primarily used, however, in the treatment of osteomyelitis,^{3,6,7,11-13,21-24} and although unable to digest or liquefy dead bone (sequestra) they were said to facilitate its separation at the interface with normal bone, leaving behind clean healthy granulation tissue³. Very many dramatic accounts of its use appear in the literature summarized by Pomerantz²⁵ who stated that following maggot therapy *'the end product approximates more closely to normal bone structure than any of the hitherto accepted methods of treatment'*

It was also claimed repeatedly that in addition to removing devitalized tissue, the application of maggots had a positive effect upon the speed of wound healing. This was first noted by Larrey in 1829 who reported that when maggots developed in wounds sustained in battle, they prevented the development of infection and accelerated healing²⁶. This view was also shared by Baer⁶ and Fine²¹ who stated that *'Maggots produce rapid and thorough debridement and stimulate granulation tissue production'* He was so convinced of their ability in this area that he stated that *'when debridement is complete, fewer maggots are used and their function at this time is to complete to keep the wound clean and promote healing'*.

Weil et al.³ the first to coin the term 'Larval Therapy' also asserted that; *'Coincident with the removal of necrotic and devitalized soft structures, is the development of highly vascular granulation tissue which excretes abundant serum and which may be looked upon as a very beneficial factor in wound defense in this form of therapy. ... The apposition of wound margins following larval therapy brings about a rapid development of granulation tissue, which can often be noted within a few hours'*.

Maggots appear to have another interesting and potentially very valuable ability. They are able to destroy unhealthy or abnormal tissue leaving healthy tissue in its place. Weil et al.³ observed, *'when the larvae come into contact with exuberant and edematous granulations, they attack it vigorously, and remove it as any other abnormal structure, after which the change to healthy granulation tissue soon occurs. We have observed that the larvae will attack almost any type of abnormal viable structure, including malignant tissue as well as devitalized soft or bony tissues'*.

This they illustrated by reference to two cases of inoperable breast cancer and two sarcomas of the thigh. *'On admission, each breast ulcer measured the approximate size of half a dollar with the malignant tissue presenting itself upon a level with the surrounding skin. There was extensive invasion of almost the entire breast substance. Following four implantation of larvae in one case there was observed an excavation of the underlying malignant tissues for a depth of 3.5-4 cm but with only slight variation in the size of the original skin opening. As the larvae cleared away the malignant tissue, clean healthy granulation tissue appeared, the odor disappeared and the wound attempted to close'*. The remaining

cases showed a similar response and the authors concluded that malignant tissue has a very weak defense against the activity of larvae.

Subsequently, Bunkis et al.²⁷ and Reames et al.²⁸ described the benefits of debridement and odor control resulting from accidental myiasis of head and neck tumors, and Seaquist and colleagues²⁹ also reported benefits from naturally occurring *Phormia regina* myiasis in a malignant lesion. This infestation, however, was accompanied by pain.

Methods of application

Over the years, numerous techniques and dressing systems have been described for ensuring that maggots are contained within the area of the wound but many were difficult to construct and almost certainly very uncomfortable to wear. They typically consisted of layers of crinoline or gauze²¹ but Child et al., used a piece of 80 mesh brass net set in a foam frame secured to the skin¹². Others including Weil³ and Mckeever³⁰ adopted a similar approach using copper mesh or milk strainer wire held in place with adhesive tape or, sometimes, Unna's Paste - a mixture of zinc oxide, gelatin, glycerin, and water³¹. Self retaining metal³, or glass³⁰, devices were developed to hold wounds open during therapy and these allow drainage of the wound and providing access to the maggots. Ochsenhirt and Komara³², described a complex technique for intraoral treatment, involving dentures with tubes through which the larvae were introduced.

As part of the application process, Livingston¹¹. recommended exposing the maggots, once applied, to a bright light in order to drive them deep into the wound, but this was considered unnecessary by Robinson³³, who also emphasized the need to control the number of larvae applied, proposing that as few as 6 might be sufficient for a finger tip injury although 500-600 may be required for more extensive wounds

Large quantities of larval enzymes can cause significant excoriation if they are allowed to run onto unprotected skin around the margin of a wound. In severe cases this resembles a superficial burn, but like such an injury, this will rapidly resolve over a few days³⁴. Robinson³³, who had also encountered this problem, suggested that the surrounding skin should be covered to protect it from larval secretions and to eliminate the tickling sensation caused by the maggots' movements. He considered that the collodion proposed by Weil et al.³ and adhesive plaster advocated by Child¹² were not suitable as they tended to separate from the skin once wet. He suggested that a liquid adhesive system described by Buchman and Blair¹³ or the Unna's paste described by Jewett³¹ would both be far more satisfactory for this purpose.

Early problems with maggot therapy

Although no serious side effects were noted following the use of maggots, a transient pyrexia was of 2-4°F was noted on a number of occasions by Fine²¹ Weil,³ McLellan⁷ and Buchman¹³ who suggested that this was due to '*the opening of chronically infected lymphatics*' This invariably subsided upon removal of the maggots.

A more inconvenient problem, then as now, was the unexplained failure of some applications of maggots to survive on the wound. McKeever³⁰ suggested that this could be due to the maggots drowning due to poor drainage but an alternative explanation is that the pH of the wound is not suitable for the young larvae. Hobson³⁵ showed that secretions of *Lucilia* larvae contain proteolytic enzymes which

function optimally at pH 8.5. As conditions become progressively more acidic the enzyme activity is reduced. It is possible, therefore, that in a wound with a relatively low pH, the enzymes will be unable to breakdown the necrotic tissue and the maggots will therefore starve to death. Some support for this theory was provided by Wilson et al.²³ who showed that larvae do not survive well in an acid environment.

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Risk to Healths

FDA currently regulates Medical Maggots as an unclassified medical device. FDA cleared one pre-market notification (510(k)) application for Medical Maggots devices. We searched medical device reports for device-related adverse events and found no adverse events reported.

The following literature articles are indicative of the published literature on Medical Maggots. These articles also describe some potential risks of using these devices. They are provided in this package under **TAB 7**.

- RA Sherman, MJR Hall, S Thomas, “Medicinal Maggots: An Ancient Remedy for Some Contemporary Afflictions,” *Ann. Rev. of Entomol.*, 2000, **45**, 55 – 81

- G. N. Jukema, A. G. Menon, A. T. Bernards, P. Steenvoorde, A. Taheri Rastegar, and J. T. van Dissel, “Amputation-Sparing Treatment by Nature: "Surgical" Maggots Revisited”, *Clinical Infectious Diseases*, volume 35 (2002), pages 1566–1571
- K.Y. Mumcuoglu, “Clinical Applications for Maggots in Wound Care” *American Journal of Clinical Dermatology*, 1 April 2001, **vol. 2**, no. 4, pp. 219-227(9)

In the table below, the risks to health generally associated with the use of the Medical Maggots are identified. The measures recommended to mitigate these identified risks are also shown in the table below.

Identified Risk	Recommended Mitigation Measures
Adverse tissue reactions	Biocompatibility Device Manufacture Clinical Data Labeling
Infection	Sterility and Disinfection Device Manufacture Animal Derived Components Clinical Data Labeling

As stated earlier, this unclassified device will be classified into Class II which will be subject to special controls.

Special Controls Guidance Document:

For a proposed Medical Maggots document, sections 1 through 4 should be mostly boilerplate language except for references to the device type and regulation numbers. For your information and review we are providing some suggestions for the content being considered for inclusion in Sections 5 through 12 of a proposed special controls guidance document for Medical Maggots. Please note that the information presented in this memorandum is suggested content and, therefore, the exact format and information contained in any draft special controls guidance document is subject to change.

Suggested Content for Sections 5-12

Section 5-Device Description

We recommend that you provide the following device description information:

We recommend that you identify your device, by the regulation and product code described in section 4. **Scope** and we recommend that you provide the following device description information:

- A description of the genus and species of the proposed product.

- The methods for packaging and transport of the Medical Maggots to insure viability.
- Identification of any other patient contact material such as wound dressings or pouches used to retain the Medical Maggots at the site of application.
- A description of the storage conditions and time (between shipping and device use) that are known to result in safe and effective product use.

Section 6-Risks to Health

This section should include information quite similar to the table above, which discusses the risks to health associated with the use of Medical Maggots. The information to be placed in that chapter is proposed as follows:

In the table below, FDA has identified the risks to health generally associated with the use of the Medical Maggots addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, before submitting your 510(k), to identify any other risks specific to your device. The 510(k) should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risk	Recommended Mitigation Measures
<p align="center">Adverse tissue reactions</p>	<p align="center">Section 7: Biocompatibility Section 9: Device Manufacture Section 11: Clinical Data Section 12: Labeling</p>
<p align="center">Infection</p>	<p align="center">Section 8: Sterility and Disinfection Section 9: Device Manufacture Section10: Animal Derived Components Section 11: Clinical Data Section 12: Labeling</p>

Section 7-Biocompatibility

This section discusses the biocompatibility testing FDA would recommend. The information proposed for inclusion into this chapter is as follows:

Depending on the methods of product manufacture and other patient-contacting materials in the final product (residual antibiotics, wound dressing accessories), FDA recommends that you consider conducting biocompatibility testing recommended in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing**. We recommend that testing be conducted on extracts of the final product(s) ready for patient administration. Because Medical Maggots will be in contact with breached skin for less than 30 days, we recommend that the following tests be evaluated:

- cytotoxicity
- sensitization
- irritation or intracutaneous reactivity

Section 8-Sterility and Disinfection

This section discusses the information concerning sterilization and disinfection that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

As a living organism, Medical Maggots cannot be sterilized. However, if other device components (e.g., wound dressings or shipping containers) undergo sterilization, the following information should be provided:

1. The method of sterilization;
2. The validation method for the sterilization cycle;
3. The sterility assurance level (SAL) to be achieved; and
4. The method for monitoring the sterility of each production lot.

For addition guidance, review of **510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, (<http://www.fda.gov/cdrh/ode/guidance/361.html>) is recommended.

Methods used to remove or kill microorganisms on the surface of fly eggs should be described. Such information should identify the effectiveness of the disinfection procedure (i.e., via aerobic and anaerobic cultures of disinfected eggs) as well as the resulting viability of eggs after treatment. The results of testing assessing the level of residual disinfectant(s) present in the final product should also be presented.

Section 9-Device Manufacture

This section discusses the information concerning device manufacture that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

The application should contain information about all reagents and processing steps used in device manufacture. Information about the source and purity of reagents (e.g., CoA and/or MSDS) can be very helpful in evaluating the substantial equivalence of proposed and legally marketed devices.

Information should also be provided for the methods of manufacturing any ancillary wound dressings or pouches used to maintain the devices at their initial site of patient application.

Section 10-Animal Derived Material

This section discusses the information and testing related to animal-derived material that FDA would recommend be included in the application. The information proposed for inclusion into this section is as follows:

Because growth and maintenance of Medical Maggots may require feeding with animal tissue, information for each animal reagent used should be fully described in a 510(k) application or by reference to other regulatory submissions (e.g., Master File, PMA, 510(k)), when a letter of cross reference is provided. For each animal tissue, regulatory applications and facility records should describe the following test methods and results:

Control of Animal Tissue Collection

- Animal species
- Specific tissue(s) used
- Animal country of origin and residence (more specific geographic location when appropriate)
- Methods for monitoring the health of herd and the health of the specific animals from which tissue are collected (including herd vaccinations such as live modified viruses that can co-purify in the desired tissue)
- USDA status of the abattoir
- Methods and conditions for transporting animal tissue
- Procedures for maintaining records on the above cited issues should be presented in regulatory submissions
- Records of the corresponding test results for each lot of material should be maintained at the manufacturing facility or submitted in regulatory documents when appropriate

Manufacturing Controls for Animal Tissue Components

- Test methods and release criteria permitting animal tissues to be further processed and/or combined with other animal tissue or device components for device manufacture
- Quarantine procedures for tissues that have not met the release criteria
- Test methods and acceptance criteria for assessing in-process and final product bioburden/sterility
- Methods for facility decontamination/sterilization so that cross-contamination is avoided
- Procedures for maintaining records of the above cited issues should be provided in regulatory submissions

- Records of the corresponding test results for each lot of material should be maintained at the manufacturing facility or submitted in regulatory documents when appropriate

Eliminating Viral Contaminates

The 510(k) should document all appropriate methods for eliminating human infectious agents from the animal tissue used in device production. This may include when appropriate, evaluating the ability of processing methods and disinfection techniques to inactivate and remove viruses.

Such data may be obtained by determining the amount of virus in the unprocessed source material and the viral inactivation properties of scaled down versions of the specific production and sterilization methods (e.g., acid extraction of collagen or dry heat sterilization) using appropriate model viruses. The results of these studies should demonstrate that the sum of the log clearance of virus from the selected processing steps and sterilization processes are at least six logs greater than the concentration of virus anticipated in the unprocessed source material.

In addition, if bovine material derived from a country in which Bovine Spongiform Encephalopathy (BSE) has been observed or a country which presents a significant risk of BSE (See 9 CFR § 94.18), the application should include a certification that the herd is not infected with (BSE). This certification may require information such as a herd history, descriptions of the methods use to isolate the herd, including the sources of breeding stock, the control of feeds, the disposition of animals with central nervous system signs, and testing for the BSE agent. Certification that the material was not processed using equipment contaminated by animal materials from other herds may also be requested.

Section 11-Clinical Data

This chapter discusses the related to clinical experience that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

The application should provide a summary of any clinical experience obtained with the device. Reference to the appropriate 510(k), PMA or IDE number (or cited as overseas experience) may greatly simplify the review process when appropriate letters of cross-reference are included in the application.

Section 12-Labeling

This chapter discusses the information and testing related to product labeling that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

The pre-market notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.

Directions for use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR 807.87(e), we recommend submitting clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

Instructions:

The instructions should describe the methods for applying Medical Maggots to a wound and the methods for insuring that the insects do not migrate from the initial site of application to unprotected skin around the margin of a wound.

Because, Medical Maggots may be a biohazard after use, product labeling should also provide adequate instructions for destroying and disposing of the product after use.

The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR § 807.87(e).

For prescription use, under 21 CFR § 801.109, Medical Maggots are exempt from having adequate directions for lay use. Nevertheless, under 21 § CFR 807.87(e), we expect to see clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients.

Intended Use/Indications for Use

With regard to indications for use, we recommend that you describe the type of surgical cases for which Medical Maggots will be used (e.g., pressure ulcers, venous stasis ulcers, neuropathic foot ulcers and non-healing traumatic or post-surgical wounds).

Charles N. Durfor, Ph.D. Date
FDA/CDRH/ODE/DGRND/PRSB

TAB 4

Medicinal Leeches

Device Definition

FDA is proposing the following identification for Medicinal Leeches:

Medicinal Leeches (*Hirudo medicinalis*) are freshwater Annelida worms intended for use as an adjunct to the graft tissue healing (when problems of venous congestion may delay healing) or to overcome the problem of venous congestion by creating prolonged localized bleeding.

FDA currently regulates Medicinal Leeches intended for use as adjuncts to graft tissue healing (when problems of venous congestion may delay healing) or to overcome the problem of venous congestion by creating prolonged localized bleeding as unclassified pre-amendment medical devices. One product has been cleared for marketing.

FDA's rationale for recommending that this device be a Class II medical device can be summarized as follows:

- There are many years of experience documenting the clinical use of this device category
- The device specifications and performance characteristics (bench testing, animal testing and clinical data) needed to evaluate and control the safe and effective use of these devices are known.
- Control of these products as Class II medical devices meets the FDA mandate to apply the "least burdensome" approach to regulating medical devices

Device Summary and Intended Use/Indications:

*An extract from "A Sanguine Attachment 2000 Years of Leeches in Medicine" by Roy T Sawyer
Managing Director, Biopharm. Encyclopedia Britannica INC found at From - <http://www.biopharm-leeches.com/>*

"The pioneering use of leeches in modern plastic and reconstructive surgery can be attributed to two Slovenian surgeons, M. Derganc and F. Zdravic from Ljubljana who published a paper in the British Journal of Plastic Surgery in 1960 describing leech-assisted tissue flap surgery (in which a flap of skin is freed or rotated from an adjacent body area to cover a defect or injury). These surgeons credit their own use of leeches to a Parisian surgeon, one Philippe-Frédéric, who reported in 1836 that he had used leeches to restore circulation following reconstruction of a nose.

The rationale behind the use of leeches in surgical procedures is fairly straightforward; nonetheless, it is subject to misunderstanding, even by clinicians. The key to success is the exploitation of a unique property of the leech bite, namely, the creation of a puncture wound that bleeds literally for hours. The leech's saliva contains substances that anaesthetize the wound area, dilate the blood vessels to increase blood flow, and prevent the blood from clotting.

Microsurgeons today are adept at reattaching severed body parts, such as fingers. They usually have little trouble attaching the two ends of the arteries, because arteries are thick-walled and relatively easy to suture. The veins, however, are thin-walled and especially difficult to suture, particularly if the tissue is badly damaged. All too often the surgeon can get blood to flow in the reattached arteries but not veins. With the venous circulation severely compromised, the blood going to the reattached finger becomes congested, or stagnant; the reattached portion turns blue and lifeless and is at serious risk of being lost. It is precisely in such cases that leeches are summoned.”

Risk to Health

FDA currently regulates Medicinal Leeches as an unclassified medical device. FDA cleared one pre-market notification (510(k)) application for Medicinal Leeches devices. We searched medical device reports for device-related adverse events and found no adverse events reported.

The following literature articles are indicative of the published literature on Medicinal Leeches. These articles also describe some potential risks of using these devices. They are provided in this package under **TAB 7**.

- Conforti, Michael L. D.V.M., M.S.; Connor, Nadine P. Ph.D.; Heisey, Dennis M. Ph.D.; Hartig, Gregory K. M.D., “Evaluation of Performance Characteristics of the Medicinal Leech (*Hirudo medicinalis*) for the Treatment of Venous Congestion. “ *Plastic & Reconstructive Surgery*, **109(1)**:228-235, January 2002.
- Valauri FA., “The use of medicinal leeches in microsurgery”, *Blood Coagul Fibrinolysis*. 1991 Feb; **2(1)**:185-7.
- Dabb RW, Malone JM, Leverett LC., “The use of medicinal leeches in the salvage of flaps with venous congestion.” *Ann Plast Surg*. 1992 Sep; **29(3)**:250-6.
- Mackay DR, Manders EK, Sagggers GC, Banducci DR, Prinsloo J, Klugman K. “Aeromonas species isolated from medicinal leeches”, *Ann Plast Surg*. 1999 Mar; **42(3)**:275-9.

In the table below, the risks to health generally associated with the use of the Medicinal Leeches are identified. The measures recommended to mitigate these identified risks are also shown in the table below.

Identified Risk	Recommended Mitigation Measures
Adverse tissue reactions	Biocompatibility Device Manufacture Clinical Data Labeling
Infection	Sterility and Disinfection Device Manufacture Animal Derived Components Clinical Data Labeling

As stated earlier, this unclassified device will be classified into Class II which will be subject to special controls.

Special Controls Guidance Document:

For a proposed Medicinal Leeches document, sections 1 through 4 should be mostly boilerplate language except for references to the device type and regulation numbers. For your information and review we are providing some suggestions for the content being considered for inclusion in Sections 5 through 12 of a draft special controls guidance document for Medicinal Leeches. Please note that the information presented in this memorandum is suggested content and, therefore, the exact format and information contained in any draft special controls guidance document is subject to change.

Suggested Content for Sections 5-12

Section 5-Device Description

We recommend that you provide the following device description information:

- A description of the genus and species of the proposed product.
- The methods for packaging and transport of the Medicinal Leeches to insure viability.
- Identification of any other patient contact material such as wound dressings or pouches used to retain the Medicinal Leeches at the site of application.
- A description of the storage conditions and time (between shipping and device use) that are known to result in safe and effective product use.
- Because Medicinal Leeches are an endangered species, the 510(k) application should provide documentation that all appropriate importation and exportation requirements have been addressed by the manufacturer.

Section 6-Risks to Health

This section would include information quite similar to the table above, which discusses the risks to health associated with the use of Medicinal Leeches. The information to be placed in that chapter is proposed as follows:

In the table below, FDA has identified the risks to health generally associated with the use of the Medicinal Leeches addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, before submitting your 510(k), to identify any other risks specific to your device. The 510(k) should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified

risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risk	Recommended Mitigation Measures
<p style="text-align: center;">Adverse tissue reactions</p>	<p style="text-align: center;">Section 7: Biocompatibility Section 9: Device Manufacture Section 11: Clinical Data Section 12: Labeling</p>
<p style="text-align: center;">Infection</p>	<p style="text-align: center;">Section 8: Sterility and Disinfection Section 9: Device Manufacture Section 10: Animal Derived Components Section 11: Clinical Data Section 12: Labeling</p>

Section 7-Biocompatibility”

This chapter discusses the biocompatibility testing FDA would recommend. The information proposed for inclusion into this chapter is as follows:

Depending on the methods of product manufacturing and other patient-contacting materials in the shipping medium, FDA recommends that you consider conducting biocompatibility testing recommended in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing**. We recommend that testing be conducted on extracts of the final Medicinal Leech product ready for shipping. Because the final product will be in contact with breached skin for less than 30 days, we recommend that the following tests be evaluated:

- cytotoxicity
- sensitization
- irritation or intracutaneous reactivity

Section 8-Sterility and Disinfection

This chapter discusses the information concerning sterilization and disinfection that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

As a living organism, Medicinal Leeches cannot be sterilized. However, if the shipping container or other device components undergo sterilization, the following information should be provided:

1. The method of sterilization;
2. The validation method for the sterilization cycle;
3. The sterility assurance level (SAL) to be achieved; and
4. The method for monitoring the sterility of each production lot.

For addition guidance, review of **510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, (<http://www.fda.gov/cdrh/ode/guidance/361.html>) is recommended.

In addition, any procedures used (e.g., antibiotic solutions) to reduce the presence of *A. hydrophila* or other pathogenic bacteria on the surface or in the gut of the leeches, should be fully described. Such information would not only include information about the FDA-approved source of the antibiotic(s) used, but also the residual levels of antibiotic(s) remaining in the final product.

Section 9-Device Manufacture

This chapter discusses the information concerning device manufacture that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

The application should contain information about all reagents and processing steps used in device manufacture. Information about the source and purity of reagents (e.g., CoA and/or MSDS) can be very helpful in evaluating the substantial equivalence of proposed and legally marketed devices.

Information should also be provided about the methods of manufacturing any ancillary wound dressings or pouches used to maintain the devices at their initial site of patient application.

Section 10-Animal Derived Material

This chapter discusses the information and testing related to animal-derived material that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

Because growth and maintenance of Medicinal Leeches may require feeding with animal tissue (e.g., blood), information for each animal reagent used should be fully described in a 510(k) application or by reference to other regulatory submissions (e.g., Master File, PMA, 510(k)), when a letter of cross reference is provided. For each animal tissue, regulatory applications and facility records should describe the following test methods and results:

Control of Animal Tissue Collection

- Animal species
- Specific tissue(s) used

- Animal country of origin and residence (more specific geographic location when appropriate)
- Methods for monitoring the health of herd and the health of the specific animals from which tissue are collected (including herd vaccinations such as live modified viruses that can co-purify in the desired tissue)
- USDA status of the abattoir
- Methods and conditions for transporting animal tissue
- Procedures for maintaining records on the above cited issues should be presented in regulatory submissions
- Records of the corresponding test results for each lot of material should be maintained at the manufacturing facility or submitted in regulatory documents when appropriate

Manufacturing Controls for Animal Tissue Components

- Test methods and release criteria permitting animal tissues to be further processed and/or combined with other animal tissue or device components for device manufacture
- Quarantine procedures for tissues that have not met the release criteria
- Test methods and acceptance criteria for assessing in-process and final product bioburden/sterility
- Methods for facility decontamination/sterilization so that cross-contamination is avoided
- Procedures for maintaining records of the above cited issues should be provided in regulatory submissions
- Records of the corresponding test results for each lot of material should be maintained at the manufacturing facility or submitted in regulatory documents when appropriate

Eliminating Viral Contaminates

The 510(k) should document all appropriate methods for eliminating human infectious agents from the animal tissue used in device production. This may include when appropriate, evaluating the ability of processing methods and disinfection techniques to inactivate and remove viruses.

Such data may be obtained by determining the amount of virus in the unprocessed source material and the viral inactivation properties of scaled down versions of the specific production and sterilization methods (e.g., acid extraction of collagen or dry heat sterilization) using appropriate model viruses. The results of these studies should demonstrate that the sum of the log clearance of virus from the selected processing steps and sterilization processes are at least six logs greater than the concentration of virus anticipated in the unprocessed source material.

In addition, if bovine material derived from a country in which Bovine Spongiform Encephalopathy (BSE) has been observed or a country which presents a significant risk of BSE (See 9 CFR § 94.18), the application should include a certification that the herd is not infected with (BSE). This certification may require information such as a herd history, descriptions of the methods use to isolate the herd, including the sources of breeding stock, the control of feeds, the disposition of animals with central nervous system signs, and testing

for the BSE agent. Certification that the material was not processed using equipment contaminated by animal materials from other herds may also be requested.

Section 11-Clinical Data

This section discusses the related to clinical experience that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

The application should provide a summary of any clinical experience obtained with the device. Reference to the appropriate 510(k), PMA or IDE number (or cited as overseas experience) may greatly simplify the review process when appropriate letters of cross-reference are included in the application.

Section 12-Labeling

This section should discuss the information and testing related to product labeling that FDA would recommend be included in the application. The information proposed for inclusion into this chapter is as follows:

The pre-market notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.¹

The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR § 807.87(e). For prescription use, under 21 CFR § 801.109, Medicinal Leeches are exempt from having adequate directions for lay use. Nevertheless, under 21 § CFR 807.87(e), we expect to see clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients.

Directions for use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR 807.87(e), we recommend submitting clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

Instructions:

¹ Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of Part 801.

The instructions should describe the methods for applying Medicinal Leeches to the patient and the methods for insuring that the insects do not migrate from the initial site of application.

Because, Medicinal Leeches may be a biohazard after use, product labeling should also provide adequate instructions for destroying and disposing of the product after use.

Intended Use/Indications for Use

With regard to indications for use, we recommend that you describe the type of surgical cases for which Medicinal Leeches will be used (e.g., graft tissue healing).

Charles N. Durfor, Ph.D.

Date

FDA/CDRH/ODE/DGRND/PRSB

TAB 5

Tissue Expanders

To date FDA has regulated tissue expanders as unclassified pre-amendment medical devices.

Proposed Classification of a Tissue Expander Device

“A tissue expander is an inflatable silicone elastomer shell filled with Normal Physiological Saline (injection grade) intended for temporary implantation to develop surgical flaps and additional tissue coverage in a variety of applications, such as breast reconstruction following mastectomy, treatment of underdeveloped breasts, scar revision, and treatment of soft tissue deformities or injuries. The tissue expander is intended for temporary subcutaneous or submuscular implantation and is not intended for use beyond 6 months.”

Tissue expanders are available in many different shapes (e.g., round, rectangular). Tissue expansion is a procedure that enables the body to "grow" extra skin for use in reconstructing almost any part of the body. The tissue expander is inserted under the skin near the area to be expanded and then gradually filled with Normal Physiological Saline (injection grade, with a concentration of 0.15M and a pH of 7.2-7.4) over time, causing the skin to stretch and grow.

The tissue expander is intended for temporary implantation to develop surgical flaps and additional tissue coverage in a variety of applications, such as breast reconstruction following mastectomy, treatment of underdeveloped breasts, scar revision, and treatment of soft tissue deformities or injuries. The tissue expander is intended for temporary subcutaneous or submuscular implantation and is not intended for use beyond 6 months.

To date the Tissue Expanders FDA has cleared have been composed of silicone. FDA has classified several silicone devices as class III, class II, class I and unclassified devices. For example, breast implants, which have a silicone elastomer shell with a saline or silicone gel filler, is regulated through the pre-market approval (PMA) process as class III medical device. FDA wants to stress that tissue expander devices are considered a different device type than breast implants, despite some similarities in design. Breast implants are permanent devices held to a much higher standard of review than tissue expanders, which are temporary devices with a different intended use (i.e., stretch the skin). On the other hand, silicone chin, facial, etc. implants are regulated as class II medical devices. Several other medical devices made of silicone are class I devices and are exempt from 510(k) requirements (e.g., drainage tubes). Tissue expanders are currently regulated as an unclassified medical device and are considered an implanted device, as they are within the body for >30 days (but for a maximum of 6 months).

Proposed Identification for the Tissue Expander Device

FDA is proposing the following identification for the tissue expander device:

“A tissue expander is an inflatable silicone elastomer shell filled with Normal Physiological Saline (injection grade) intended for temporary implantation to develop surgical flaps and additional tissue coverage in a variety of applications, such as breast reconstruction following mastectomy, treatment of underdeveloped breasts, scar revision, and treatment of soft tissue

deformities or injuries. The tissue expander is intended for temporary subcutaneous or submuscular implantation and is not intended for use beyond 6 months.”

Tissue Expanders Cleared through the 510(k) Process

FDA has received 45 510(k)s in the time period of 1978 to 2004. In general, round tissue expander devices have been cleared for breast reconstruction after mastectomy, correction of an underdeveloped breast, scar revision, and tissue defect procedures. Rectangular tissue expanders have been cleared for preparation for closure of defects after resection of large tumors (e.g., nevi, basilloma, etc.), scar correction, if primary direct closure is not possible, and preloading of local flaps (e.g., at forehead). Table 1 below contains a list of some of the most recently cleared 510(k)s for tissue expanders.

Table 1: Tissue Expanders recently cleared through (510(k) process.

Product	Sponsor	510(k) Number	Common Name	Indication
Mentor Contour Profile Tissue Expander	Mentor Corp.	K011500	Tissue Expander	The Contour Profile Tissue Expander can be utilized for breast reconstruction after mastectomy, correction of an underdeveloped breast, scar revision, and tissue defect procedures. The device is intended for temporary subcutaneous or submuscular implantation and is not intended for use beyond six months.
Bircoll Balloon Dissector	Wells Johnson Co.	K984448	Surgical Balloon Dissector/Expander	Breast reconstruction, limb reconstruction, correction of congenital deformities, cosmetic defects, scar revision.
Seare Biomedical Silicone Tissue Expander	Seare Biomedical Corp.	K983792	Expander, Skin Inflator	Seare Biomedical Silicone Tissue Expanders are intended for temporary subcutaneous implantation to develop surgical flaps and additional tissue coverage required in a wide variety of applications, particularly to aid in reconstruction following mastectomy, to aid in the treatment of underdeveloped breasts, and to aid in the treatment of soft tissue deformities.
Hutchinson Inflatable Silicone Tissue Expander	Hutchison Intl. Inc	K983385	Tissue Expander	The Hutchinson Inflatable Silicone Tissue Expanders are designed for temporary use in: <ul style="list-style-type: none"> ▪ Scar/defect revision ▪ Reconstruction of the breast following subcutaneous mastectomy and other suitable procedure or trauma ▪ Breast underdevelopment and other combined breast and chest wall

Product	Sponsor	510(k) Number	Common Name	Indication
				abnormalities
Magnetic Port Silicone Tissue Expander	Speciality Surgical Products	K982067	Silicone Tissue Expander	Silicone Tissue Expanders are intended for temporary subcutaneous implantation to develop surgical flaps and additional tissue coverage required in a wide variety of applications, particularly to aid in reconstruction following mastectomy, to aid in the treatment of underdeveloped breasts, and to aid in the treatment of soft tissue deformities.
Silimed Tissue Expander	Silimed LLC	K981852	Tissue Expander	Silimed tissue expanders are intended for temporary subcutaneous implantation to develop surgical flaps and additional tissue coverage required in a wide variety of applications, particularly to aid in reconstruction following mastectomy, to aid in the treatment of underdeveloped breasts, and to aid in the treatment of soft tissue deformities.

Medical Device Reporting (MDR) System Summary

In order to assess the potential risks associated with the use of tissue expanders, we reviewed the adverse event reports submitted to the FDA via the MDR System. This system involves voluntary reporting from 1992 until 1996, after which it became mandatory for manufacturers to report any device failures they were aware of. The MDRs for tissue expanders received by FDA are summarized in Tables 2 and 3 below, stratified by device and patient problems, respectively, for the time period 1976 through June 2005. As a note, the majority of the device and patient problems were reported in the early years 1993 to 1994.

Table 2: Adverse Events Reported; Top Device Problems

Rank	Adverse Events	Total
1	Explanted	179
2	Deflation, cause unknown	72
3	Leaks(s)	64
4	Replace	49
5	Implant Removal	43
6	Invalid Data	33
7	Rupture, cause unknown	25
8	Device Failure	16
9	Tears, rips, holes in device, device material	15
10	Fluid leak(s)	14

Of a total of 694 device problems reported, the top device problems were explantation (25.79%), deflation (cause unknown) (10.37%), and leaks (9.22%).

Table 3: Adverse Events Reported; Top Patient Problems

Rank	Adverse Events	Total
1	Surgical Procedure	153
2	Surgical procedure, repeated	67
3	Infection	49
4	Pain	39
5	Invalid Data	48
6	Capsular contracture	37
7	Implant failure	33
8	Unknown (patient's condition not known)	31
9	Hospitalization required	30
10	Fatigue	18

Of a total of 857 patient problems reported, the top patient problems were surgical procedure (17.85%), surgical procedure - repeated (7.82%), and infection (5.72%).

Literature Summary

In order to further assess the potential risks associated with the use of tissue expanders, we reviewed the published literature. The following literature articles are considered representative of what is available in the published literature for tissue expanders. These articles discuss tissue expanders and also describe some potential risks of using these devices. Copies of these articles are provided in **TAB 7**.

- A history of tissue expansion. Concepts, controversies, and complications.
Bennett RG, Hirt M, J Dermatol Surg Oncol. 1993 Dec; 19(12): 1066-73
- Evolution of the concept of tissue expansion.
Austad ED, Facial Plast Surg. 1988 Jul; 5(4): 277-9.
- The expansion of an area of skin by progressive distention of a subcutaneous balloon; use of the method for securing skin for subtotal reconstruction of the ear.
Neumann CG, Plast Reconstr Surg. 1957 Feb; 19(2): 124-30
- Tissue Expansion
Author: Don R Revis, Jr; Co-author: Michael B Seagel,
<http://www.emedicine.com/ent/topic708.htm>

Risks to Health

The risks to health for tissue expanders were assessed by the review of MDRs, the published literature, and the 510(k)s of cleared tissue expanders. Accordingly, FDA believes that the risks to health for tissue expanders can be grouped into the following risk categories:

- device failure (rupture, injection site/valve failure)
- skin trauma (necrosis, thinning, sloughing)

- infection
- adverse tissue reaction.

Additional information regarding the risks to health and controls to mitigate them are included in Table 4 below, as well as control that we are proposing to address the risk.

Special Controls Guidance Document

For a proposed Tissue Expander document, sections 1-3 should consist of primarily boilerplate language except for references to the device type and regulation numbers. Section 4 would be the Scope section, which would identify the limitations in terms of device description and intended use/indications. It will include the identification information similar to that in part 3 of this review memo, as well as the CFR identification number and procode information.

For your information and review we are providing some suggestions for the content being considered for inclusion in Sections 5 through 10 of a proposed draft special controls guidance document for Tissue Expanders. Please note that the information presented in this memorandum is suggested content and therefore, the exact format and information contained in any draft special control document is subject to change.

Suggested Content for Sections 5 through 10

Section 5 – Device Description

Although this is not a control that will be used to mitigate the identified risks to health, FDA believes that this section will provide much of the information that FDA needs to complete the review of a tissue expander device.

The proposed information for this section is as follows:

This section provides the type of device description information that we recommend that you include in your submission. However, depending on the particular design of your tissue expander, additional information may be recommended.

We recommend that you provide the following device description information:

- a written description of each component that comprises the tissue expander (e.g., shell, patch, injection port/valve)
- magnified sketches of each component
- a table that provides the specific material and supplier for each component of the tissue expander
- a description of the mechanism for filling the implant (e.g., magnetic port, injection dome), including magnified sketches of the implants, depicting the placement/use of the connector systems, fill tubes, and injection domes
- a description of the sealing mechanism of an injection site

- the following summary table of all tissue expanders under review (example of information included):

Style	Shell Surface	Shape / Profile	Volume (cc)	Width (cm)	Height (cm)	Projection (cm)	Range Shell Thickness
XXXX	Smooth	Round, High	125-650	9-16	8.4-15	3.1-5.7	0.015”-0.043”

Section 6 – Risks to Health

This section would include the risks to health and the controls that we believe would mitigate the risks. The proposed information for this section is as follows:

In the table below, FDA has identified the risks to health generally associated with the use of the tissue expander device addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you conduct a risk analysis to identify any other risks specific to your device and submit the results of this analysis. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risk	Recommended Mitigation Measures
Skin trauma (e.g., necrosis, thinning, sloughing)	Section 10: Labeling
Device failure (e.g., rupture, injection site/valve failure)	Section 7: Preclinical testing Section 10: Labeling
Infection	Section 8: Sterility
Adverse tissue reaction	Section 9: Biocompatibility

Section 7 – Preclinical Testing

This section would include preclinical testing for a tissue expander. The proposed information for this section is as follows:

This section provides the type of preclinical testing that we recommend that you include in your submission. However, depending on the particular design of your tissue expander, additional information may be recommended.

Material Property Testing of the Shell

Please provide complete reports of material property testing (e.g., tensile strength, % elongation, tensile set, joint testing) of your subject device compared to a predicate device. All testing should be performed on components from the final, sterilized product. As part of the test report, please provide a description of the test set-up and methods, and state which tissue expanders were tested (e.g., model, size).

Injection Site Testing

We recommend that you provide appropriate preclinical testing to show that your tissue expander can be accessed accurately through the skin. For example, if your device has a magnetic port to locate the injection site, please provide data that show you can accurately access that site through the skin.

In addition, please provide appropriate preclinical testing to show how many punctures the injection site of your tissue expander can handle before compromising the material integrity of the site.

Valve Competency Testing

If your tissue expander includes a valve for postoperative filling, we recommend that you provide valve competency testing to demonstrate that valve integrity is maintained at *in vivo* loads. Although ASTM 2051 is intended for saline-filled breast implants, FDA believes that this test methodology would be applicable for a tissue expander with a valve. ASTM F2051 states that there shall be no leakage observable after a normally closed valve is subjected to a retrograde pressure equivalent to 30cm H₂O for 5 minutes and then to a retrograde pressure equivalent to 3cm H₂O for 5 minutes. FDA does not believe that the load levels described in the ASTM F2051 methodology are clinically relevant; however, this methodology may provide useful information in terms of the valve handling shifts in pressure. Therefore, you should provide a complete report of valve competency testing as per ASTM F2051. You should provide the pass/fail results for leakage.

In addition to the testing above, you should perform destructive testing to address *in vivo* loading conditions. Gradually load the samples until valve failure occurs to define a maximum pressure for the device. Please provide the burst pressures, the failure modes (including whether the failed test valves reseal upon removal of the excess failure-inducing pressures), and the clinical rationale for the resulting burst pressures.

Self-Sealing Patch Testing

If your tissue expander has a self-sealing patch, we recommend that you provide a complete report of preclinical testing that shows that a punctured patch can self-seal and maintain that self-seal for the entire duration of the use of the tissue expander.

Section 8 – Sterility

This wording in this section is essentially consistent across guidance documents for medical devices. The proposed information for this section is as follows:

FDA recommends that you provide sterilization information in accordance with the **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, <http://www.fda.gov/cdrh/ode/guidance/361.html>. The device should be sterile with a sterility assurance level (SAL) of 1×10^{-6} .

Section 9 – Biocompatibility

This wording in this section is also essentially consistent across guidance documents for medical devices. The proposed information for this section is as follows:

FDA recommends that you conduct biocompatibility testing as described in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing**, <http://www.fda.gov/cdrh/g951.html>, for blood-contacting, long-term implanted devices. We recommend that you select biocompatibility tests (Parts 5 and 10 of ISO-10993) appropriate for the duration and level of contact with your device. If *identical* materials are used in a predicate device with the same type and duration of patient contact, you may identify the predicate device in lieu of providing biocompatibility testing.

Section 10 – Labeling

This last section of the guidance document provides recommendations for the labeling specific to the tissue expander device. The proposed information for this section is as follows:

The 510(k) should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.²

² Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of Part 801.

Directions for use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR 807.87(e), we recommend submitting clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

In addition, we recommend that the labeling include:

- device name, style, etc.
 - name and address of manufacturer, packer, or distributor
 - “Sterile,” “Do not re-sterilize,” and “Single use only” notations (or similar wording)
 - expiration date
 - brief device description with material information
 - indications for use
 - any relevant contraindications (including patient groups in which the implant is contraindicated, surgical procedures which are contraindicated due to interference with implant integrity and/or performance), warnings (e.g., if device has a magnetic port, it should therefore not be used in patients who have implanted devices that could be affected by a magnetic field), and precautions
 - list of potential complications
 - procedures such as descriptions how to prepare the patient (e.g., prophylactic antibiotics), operating room (e.g., what supplies should be on hand), and troubleshooting procedures
 - instructions for implantation, including surgical approach and device specific information (depends on type of tissue expander)
 - instructions for proper filling of the expander, intraoperatively and postoperatively, including the specific fill volume instructions
-

- intraoperative test procedures to ensure implant integrity and proper placement (if necessary)
- instructions for follow-up, including whether patient antibiotic prophylaxis is recommended during the post-implant period and during any subsequent surgical procedures, postoperative patient care, etc.

Nada O. Hanafi, MSc

Date

Biomedical Engineer/Expert Reviewer

Plastic and Reconstructive Surgery Devices Branch

Division of General, Restorative, and Neurological Device

TAB 6

Wound Dressings with Drugs

Until 1999 all the wound dressings (Non-absorbable Gauze, Hydrogels, Occlusive Wound Dressings, and Hydrophilic Wound Dressings) with and without drugs were regulated as unclassified devices. The wound dressings that do not contain drugs were classified as Class I, exempt devices. The wound dressings that contain drugs are still regulated as unclassified devices.

Your panel package includes information on the classification of medical devices. Please note that some slides of the presentation in TAB 1 on Device Classification/ Reclassification Procedures have an asterisk (*). The asterisked slides pertain to the classification of unclassified pre-amendment devices and are relevant to the classification of the wound dressing devices containing drug components. TAB 8 lists our panel discussion topics for the classification of these devices. TAB 7 contains a bibliography of some articles on the use of wound dressings with drugs. The product labels for some of the pre-amendment wound dressing devices with drugs are provided at the end of this memo.

Proposed identification of the devices:

FDA is proposing the following identification for the wound dressings containing drugs:

Wound Dressing Containing a Drug:

A wound dressing containing a drug is a sterile or non-sterile device product in which the primary mode of action is provided by the device component. It is intended to cover a wound, to absorb exudate, to provide or support a moist wound environment, and to control bleeding or fluid loss. It consists of nonresorbable materials and contains added drugs such as antimicrobials.

Wound dressings that include drug are considered by the agency to be combination products. FDA jurisdiction over combination products is determined by the product's primary mode of action.

FDA currently regulates several wound dressing devices as Class III, Class I (exempt) and unclassified devices. For example, interactive wound dressings like Orcel, Dermagraft, and Apligraf which contain live human cells are regulated as Class III medical devices. Wound dressings that do not contain drugs such as, e.g., Biobrane, Bard Occlusive Wound Dressing are regulated as Class I (exempt) devices. The wound dressings that contain drug components such as, e.g., Silverlon Contact Wound Dressing, Hydrofera Bacteriostatic Wound Dressing are currently regulated as unclassified devices.

FDA cleared approximately fifty pre-market notification (510(k)) applications for wound dressing devices containing drug components in the last 5 years (see Table 1 for examples). We searched medical device reports for the device adverse events. Some of the adverse events are reported for these unclassified wound dressings are provided in Table 2.

Table 1 lists some of the recently cleared wound dressings that contain drugs. These dressing devices were found substantially equivalent to pre-amendment dressing devices that were in commercial distribution prior to 1976. These pre-amendment devices include Mercurochrome marketed since 1929 and Borated Band-Aid bandage marketed since 1924 by J & J, the labels of which are included at the end of this memo.

Table 1: Wound Dressings with Drugs

Product, Sponsor, 510(k) #	Characteristics	Drug	Indication
Contreet Foam Cavity Dressing with Silver, Coloplast Corp., K033869	Sodium hydrogen silver zirconium phosphate on polyurethane film	Silver	For deep wounds with moderate to high amounts of exudate such as stage II, III, & IV pressure ulcers, leg ulcers and burns, but not third degree burns
Antimicrobial Alginate Dressing, Advanced Medical Solutions, K024298	Calcium alginate, carboxymethylcellulose nylon and elemental silver	Silver	An effective barrier to bacterial penetration. The barrier functions of the dressing may help reduce infection in heavily exudating partial and full thickness wounds including: pressure ulcers, venous ulcers, donor sites, traumatic and surgical wounds
Hydrofera Bacteriostatic Wound Dressing, Hydrofera LLC, K023138	Poly vinyl alcohol (PVA) with two organic pigments, Methylene Blue and Crystal Violet	Methylene Blue and Crystal Violet	Local management of pressure ulcers, donor sites, venous stasis ulcers, arterial ulcers, diabetic ulcers, abrasions, lacerations, and superficial burns, post-surgical incisions, and other external wounds inflicted by trauma
Suile Wound Dressing, Hedonist Biochemical Technologies Co. Ltd., K022967	Gauze impregnated with Bismuth subgallate, Borneol	Bismuth subgallate	For helping healing burns, partial thickness wounds, donor sites, abrasions, surgical incision sites, colostomies and urological procedures.
Inman Xeroform Petrolatum Dressing, Inman Medical Corp, K921289	Gauze impregnated with petrolatum containing Bismuth-tribromopheneate	Bismuth tribromopheneate (external antiseptic)	To be used as a general external wound dressing
Actisorb Silver 220 Antimicrobial Binding Dressing, J&J Wound Management, K022483	Activated charcoal cloth impregnated with silver	Silver	An effective barrier to bacterial penetration and for absorbing offending odor resulting from wounds – pressure ulcers, venous ulcers, diabetic ulcers, first and second degree burns, donor sites and surgical wounds
Calcium Alginate-Silver Alginate Topical Wound Dressing, ADRI, K011618	Silver alginate foam with or without a backing.	Silver	Medium to heavily exudating wounds including ulcers of the leg, pressure sores, chronic wounds, first and second degree burns, donor sites.
Silverlon Wound	Silver-coated nylon	Silver	Local management of lacerations.

Packing Strips, Argentum Intl. LLC, K984210	wound packing strip		
Biopatch Antimicrobial Dressing, Ethicon, K003229	Polyurethane film impregnated with chlorohexidine gluconate	Chloro- hexidine	To absorb exudate and to cover a wound caused by the use of vascular and non-vascular percutaneous medical devices such as: IV catheters, central venous lines, arterial catheters, peripherally inserted coronary catheters, mid- line catheters, drains, chest tubes, externally placed orthopedic pins, and epidural catheters. It is also intended to reduce local infections, catheter related blood stream infections (CRBSI), and skin colonization of microorganisms commonly related to CRBSI, in patients with central venous or arterial catheters.

MDR reports for adverse events reported under the product codes FRO were reviewed and the following adverse events were noted (see Table 2)

Table 2: Adverse Events Reported

Adverse Event	Total Events
Blistering	9
Injury	8
Severe Burning Pain	1
Irritation/Swelling	2
Allergic Reaction	3
Skin Necrosis	2
Inflammation	8
Infection	3

Exemplary of the type of adverse events observed with these devices, as described in MDR reports are in the following table (Table 3)

Table 3 MDR Reports of a few wound dressing with drugs

Device Name and 510(k) #	Device Components	Adverse Event	Device-related or not
K973507 Kendall Xeroform Petrolatum	Gauze impregnated with petrolatum and 3% Bismuth bromopheneate	1. Allergic reaction/swelling 2. Allergic contact dermatitis	Patient reacted to the dressing. May be device- related

Dressing			
K991463 Silverlon	Silver Dressing	Pain	Unclear
K003229 Biopatch Antimicrobial Dressing	Polyurethan foam with chlorohexidin (200- 300ug/mg)	<ol style="list-style-type: none"> 1. Skin “burned” with full thickness wound 2. Skin injury 3. Blisters 4. Redness 5. Skin breakdown 	Appears to be device-related
K013814 Aquacel-Ag	Carboxymethylcellulose with ionic silver	<ol style="list-style-type: none"> 1. Patient death 2. Patient developed skin necrosis, patient improved after discontinuation of the dressing 	Unclear
K022416 Contreet Foam Dressing	Polyurethane foam containing silver	Blisters observed at the site of application	May be device- related

Rationale for Proposed Class II Regulatory Status for Wound Dressings with Drugs:

The Agency’s rationale for suggesting that this device be classified into Class II is summarized as follows:

- We have years of experience regulating these devices (since 1976)
- We understand the device specifications and performance characteristics (bench testing, animal testing and clinical data) needed to evaluate and control their safe and effective use.
- Classification to Class II meets the FDA mandate to apply the “least burdensome” approach to regulating medical devices.

The Agency’s rationale for identifying a Class II designation as appropriate is based on the long history of safe and effective use of these devices over the past 100 years and the scarcity of adverse event reports in the medical literature and the FDA’s Medical Device Reporting System. The Agency proposes that all of the potential risks to health can be ameliorated via a special controls guidance document that includes recommendations and advice on device materials, device performance, animal testing, clinical testing, device sterilization, biocompatibility and device labeling.

The recent MDUFMA amendment to the FD&C Act directed the Agency to regulate medical devices in the “least burdensome” manner possible based on the available safety and effectiveness information. Please keep this in mind as you consider classification of these devices. A copy of the least burdensome guidance document is included in TAB 11 of the panel pack.

FDA proposes that the wound dressings containing drugs can be regulated with special controls. Following are the relevant draft sections of a proposed Wound Dressings with Drugs Guidance Document for your consideration as you discuss the appropriate classification for this device.

Special Controls Guidance Document:

When the Office of Device Evaluation (ODE) classifies a medical device into regulatory Class II, such classifications are accompanied by what the Agency refers to as “Special Controls”. In the vast majority of cases, the special control has been in the form of a guidance document. A recently published Class II special controls guidance document is included for your reference TAB 10 of the panel pack. The Class II special controls guidance document for Wound Dressings with Drugs would be very similar to the sample guidance document provided with the exception that specific device information would be different.

While the agency has not provided you with a copy of a draft proposed special controls guidance document for Wound Dressings with Drugs, this panel package includes the sections for such a guidance document for your review. At present, a special controls guidance document is comprised of 11 chapters. For a proposed absorbable surgical hemostatic agent devices document, chapters 1 through 4 and 9 through 11 would be mostly boilerplate language except for references to the device type and regulation numbers. For your information and review we are providing the information that is proposed for Chapters 5 through 8 of a special controls guidance document for wound dressings with drugs. Please note that the information presented in this memorandum is in draft form and, therefore, the exact format and information contained in the final guidance document is subject to change.

Wound dressings containing a drug component are combination products for which the primary purpose of the dressing is a device function. For combination products for which the primary purpose is not clearly a device, the sponsor should contact the Office of Combination products at <http://www.fda.gov/oc/combinations/>.

A drug is defined in Section 201(g)(1) of the Federal Food, Drug and Cosmetic Act and may be searched in the Orange Book at <http://www.fda.gov/ob>.

Chapter 5, “Risks to Health”:

This chapter discusses risks to health associated with the use of wound dressings containing drugs. The information to be placed in that chapter is proposed as follows:

In the table (Table 4) below, FDA has identified the risks to health generally associated with the use of wound dressings containing drugs. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. A risk analysis should be conducted prior to submitting your 510(k), to identify any other risks specific to the device. The 510(k) should describe the risk analysis method. If an alternative approach was elected to address a particular risk identified in this document, or there are additional risks identified other than those in this document, sufficient details to support the approach should be provided to address that risk.

Table 4: Table of Potential Risks and Controls

Potential Risk	Control
Skin Trauma Blister Formation Dura-genic Patch Interaction	Animal Testing and/ or Clinical Data
Infection Cellulitis Toxic Shock Syndrome Sepsis	Bench Testing & QSR (Sterility)
Sterility Compromised Bacterial Fungal	Animal Studies and Device Labeling (Sterility)
Physical Product Problems	Bench Testing and Design Controls
Necrosis	Device Labeling, Biocompatibility, Clinical Data
Pain	Clinical Data
Inflammation/ Irritation and Swelling	Biocompatibility, Animal Studies and Device Labeling, Clinical Data
Allergic Reactions	Biocompatibility, Device Labeling
Injury	Animal Studies/ Clinical Studies and Device Labeling

Chapter 6, “Material and Performance Characterization”:

This chapter would include the types of bench top testing, material characterization and manufacturing information that the Agency recommends for. The proposed chapter would read as follows:

We recommend that you provide the information below to establish the material and performance characteristics of the device.

Material Specification

We recommend that you provide all material components of the device. Such information should identify the source and purity of each component. Such information may also be supplied by reference to a Master Access File(s), if the appropriate letter of cross reference is included. Submission of a Certificate(s) of Analysis (CoA) and/or a Materials Safety Data Sheet(s) (MSDS) will facilitate FDA’s review of components/materials.

Product Characterization

We recommend that the product manufacturing process be briefly described and compared to that of the legally marketed predicate device.

We recommend that you provide the following product characterization information regarding your dressing device containing a drug:

- a complete description of all components and a detailed list of the amounts of each components contained in the dressing,
- a profile of the ability of the device to provide a moist wound environment at the site of application, and a description of how it will do so
- the biocompatibility profile of the device (biocompatibility testing should be conducted in accordance with International standard ISO-10993, Biological Evaluation of Medical Devices Part-1, evaluation and Testing and FDA General Memorandum G-95-1),
- complete information regarding the drug component

With regard to the drug(s) used as a component in the dressing, the following information should be provided:

- identification of the drugs' purpose in the dressing
- the claim associated with the drug (if applicable)
- data using the finished sterilized device to support any claim associated with the drug

With regard to labeling, the box label should identify all drugs present in the wound dressing as follows:

- the name and form of the drug being used
- the amount of drug present

Final Product Specification

We recommend that you provide information about the relevant in-process and final product tests, including identification of the test method and time of testing during manufacture and the final product release specifications.

Examples of final product release specifications include:

- specific melting temperature
- residual levels of manufacturing reagents
- residual levels of heavy metals
- pyrogen levels
- sterility (Sterility Review Guidance K90-1; Final Guidance for Industry and FDA, www.fda.gov/cdrh/ode/guidance/361.html)

We also recommend that you provide the rate of product absorption (if the device is made of any biodegradable materials). Such studies should be performed *in vivo* or in a manner expected to accurately predict product decomposition (e.g., in comparable cellular and proteolytic environments at 37⁰C). Please see Section 7 (**Animal Testing**) below for more details regarding this recommendation.

Shelf Life

We recommend that you provide both stability testing of the device and packaging testing to establish the shelf life (i.e., expiration date) for the labeling of your dressing device. Accelerated testing should be supported/validated by real-time shelf life testing. With regard to packaging testing, we recommend that you provide data for the final finished package for initial integrity and maintenance of integrity after selecting the appropriate materials and qualifying the package configuration. We recommend that you use test methods that are either validated or standardized.

Chapter 7, “Animal Testing”:

This chapter discusses the animal testing the Agency would recommend. The information proposed for inclusion into this chapter is as follows:

Animal testing may be needed if the biocompatibility testing has indicated that the dressing may have delaying effect on the wound closure. FDA recommends that your animal study include testing of a legally marketed predicate device of similar components and manufacture so that observations can be made as to the substantial equivalence of the two dressings.

The extent of animal testing needed will be dependent upon the differences between the proposed device and a legally marketed predicate device.

Chapter 8, “Clinical Testing”:

This chapter of the special controls guidance document discusses clinical data. The information proposed for this chapter is as follows:

In accordance with the Least Burdensome provisions of the FDA Modernization Act of 1997, FDA will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies will not be needed for most wound dressings containing drugs, FDA may recommend that you collect clinical data for a dressing with:

- new technology (i.e., technology different from that used in a legally marketed wound dressing); or
- new indications for use for a wound dressing of the same type.
- FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. Please contact the Plastic and Reconstructive Surgery Devices Branch (PRSB) to discuss any clinical testing before initiating studies.

Additional Labeling Considerations:

Labeling claims beyond the indications for use should be supported with data. We recommend that the labeling be accurate as the nature of the supporting data, e.g., bench testing supporting that the

device is a bacterial barrier. The text of the labeling claim should be data-driven and be limited to a summary of the testing methods and results obtained. The labeling should not include hypothetical claims such as “may reduce infections.” Broad, poorly defined claims for which it is difficult to provide supporting data should not be used. “Hypoallergenic and “sensitive skin” are examples of broad, poorly defined claims. For labeling that indicates that the device may act as an antibacterial barrier, it is expected that the claim would be the data demonstrating that the wound dressing has an antibacterial effect *in vitro*, and that the wound dressing is a barrier to the passage of the specific microorganisms tested. Specifically, we recommend that the testing demonstrate that if 1 million bacteria are placed on top of the dressing, none should come through to the agar in 24 hours. The antibacterial effectiveness of the device should be compared with positive and negative controls. In liquid culture, the titer should be reduced by at least 10^4 . Likewise, the claim should state that the supporting data were collected in bench testing.

The Least Burdensome Provisions of FDAMA:

A central purpose of the Food and Drug Administration Modernization Act of 1997 (FDAMA) is “to ensure the timely availability of safe and effective new devices that will benefit the public and to ensure that our Nation continue to lead the world in new device innovation and development. Congress’ goal was to streamline the regulatory process (i.e., reduce burden) to improve patient access to drugs and devices that could benefit the public.

One of the concepts central to this “least burdensome” approach to the regulation of medical devices is to review devices at the Class level (Class I, Class II, Class III) where they will receive an appropriate level of oversight in accordance with what is known about the safety and effectiveness of the device type. Since wound dressings with drugs have been in use for approximately 100 years, the Agency believes that they can be appropriately regulated at the Class II, Special Controls, regulatory level because the assessment of their effectiveness and the known complications are well understood due to the many years of experience in their use. More than just risk is taken into account when devices are classified. An understanding of the methods to assess safety and effectiveness is a central factor in the classification of medical devices. Other Class II devices that are considered to have high risks associated with their use are dura replacements, surgical meshes and sutures.

The Guidance Document: *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final guidance for FDA and Industry*, is provided as a reference for your convenience, located in the appendix (Tab 11).

Your panel package includes information on the classification of medical devices in the appendix (Tab 1). The slides with an asterisk pertain to the classification of unclassified pre-amendment devices and are relevant to the classification of wound dressings with drugs. This Appendix also contains the questionnaire that you will vote on as part of your recommendation on the classification of this device.

TAB 7

Tab 7 of the material sent to the panel members consists of literature articles referred to in each of the six previous memos. These are publicly available.

TAB 8

Classification Topics

1. Please discuss the proposed classification for all of the devices presented in this package to include bone wax, medical maggots, medicinal leeches, tissue expanders, and wound dressing with drugs.
2. Please discuss the possible risks to health that may be associated with each device.
3. Please discuss whether the special controls identified for the FDA Guidance Document are adequate.

TAB 9

Tab 9 is simply a copy of the standard questionnaire each panel member fills out during the recommendation process. This will be displayed as it is filled in during the panel meeting.

TAB 10

Tab 10 is a sample guidance document presented to the panel. It is entitled: “*Class II Special Controls guidance Document: Surgical Sutures; Draft Guidance for Industry and FDA*” This is available on the FDA Web Site at the following web address: <http://www.fda.gov/cdrh/ode/guidance/1387.html>

TAB 11

Tab 11 is a guidance document presented to the panel to explain the “Least Burdensome” concept of the FDA Modernization Act of 1997. It is entitled: “*The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry*” This is available on the FDA Web Site at the following web address:

<http://www.fda.gov/cdrh/ode/guidance/1332.html>