Regulation of Absorbable Hemostatic Agents: Guidance for Encouraging Innovation Without Compromising Patient Safety

ABSTRACT

Objective: The Food and Drug Administration (FDA) is contemplating changing the regulatory status of absorbable hemostatic agents. The Absorbable Hemostat Consensus Conference was called to develop expert recommendations regarding the special controls required to ensure the safety and efficacy of these agents if and when their regulatory status is changed.

Participants: The participants in the Absorbable Hemostat Consensus Conference comprised seven clinicians with extensive and diverse expertise in hemostasis, vascular biology and the use of absorbable hemostats in a variety of highly relevant surgical settings.

Method: The panel identified and discussed the potential ramifications of changing the regulatory status of absorbable hemostats from Class III (pre-market approval) to Class II (special controls or standards). Panel members used a list of specific questions to help guide the development of consensus recommendations.

Results: The panel reached consensus on five recommendations regarding the regulation of absorbable hemostats should they be reclassified by FDA as Class II devices: 1)

Approval of new absorbable hemostats should require demonstration of equivalence to currently approved devices in both animal models and human clinical trials. 2) Approval for an indication of general surgery should exclude neurology, ophthalmology and urology indications. Approval in these specific indications should require relevant preclinical and clinical data demonstrating safety and efficacy in these surgical settings. 3) Novel materials that meet the broad definition of absorbable hemostats but lack established safety and efficacy should continue to be regulated as Class III devices (pre-market approval including clinical studies). 4) The mechanism of action and potential interactions with commonly used medical therapies known to affect hemostasis should be addressed during development of these devices and relevant data should be required on the label and package insert for all absorbable hemostats. 5) Professional medical associations should include hemostasis physiology on board certification exams and should provide educational opportunities for physicians to become qualified in the use of absorbable hemostatic agents.

Conclusions: Changing the FDA approval process to facilitate the introduction of new manufacturers' absorbable hemostats may help to advance medical technology by encouraging the development of new devices in the class, which could be beneficial to both patients and surgeons. However, maintaining patient safety must be the paramount concern of the regulatory process. Adoption of the recommendations of the Absorbable Hemostat Consensus Conference should provide guidance for a regulatory strategy that meets both of these objectives.

INTRODUCTION

Absorbable hemostats are used in a variety of surgical settings to control hemostasis in situations where ligature or conventional procedures are either ineffective or impractical.[1] These devices play an important role in controlling bleeding during surgery and in minimizing re-bleeding and oozing in the post-operative period. Failure of the product may have a significant negative impact on surgical outcomes and post-operative complications. Excessive blood loss can result in significant complications during surgery and may necessitate additional interventions such as transfusion or secondary surgery and extended recovery times. Additionally, because increased operating room time and longer hospital stays increase the cost of medical care, failure of absorbable hemostats may also have significant healthcare economic effects.

Absorbability and biocompatibility are also critical features of these devices. Because these devices remain in the body for a significant period of time, they must demonstrate excellent biocompatibility so as not to trigger immune or inflammatory responses. Failure of a product to function properly or to pose absorption problems can lead to adverse events and poor outcomes for patients. Incomplete absorption of these products in the post-operative period may lead to chronic inflammation, adhesions or infections. In severe situations additional surgery may be required to remove unabsorbed material.

The U.S. Food and Drug Administration identifies an absorbable hemostatic agent or dressing as "a device intended to produce hemostasis by accelerating the clotting process of blood."[2] Since 1976, when the U.S. Congress enacted legislation to regulate medical devices separately from pharmaceuticals, absorbable hemostats have been

regulated as Class III medical devices, requiring "valid scientific evidence" to establish safety and efficacy.[3]

Based on a long history of safety and efficacy of these products, and in keeping with the its mandate to apply the "least burdensome" approach to regulating medical devices, the FDA has said it will formally propose reclassifying absorbable hemostats as Class II devices.[4] Reducing the time and cost associated with the approval of new absorbable hemostats would help to encourage the development of new absorbable hemostatic devices, creating an environment that supports the advance of medical science. Although a panel of the General and Plastic Surgery Devices Advisory Committee recommended in 2003 that the FDA proceed with reclassification,[5] a formal proposal for reclassifying absorbable hemostats as Class II devices was released in October, 2006.

Given the important role that absorbable hemostats play in managing hemostasis in a wide variety surgical settings, a group of physicians with extensive expertise in their use gathered in an Absorbable Hemostat Consensus Conference to discuss how best to balance the desire for increased innovation with the absolute need of assuring patient safety. Johnson and Johnson Inc supported the expenses associated with the assembly of this conference.

Currently Approved Absorbable Hemostat

The class of absorbable hemostats under consideration for reclassification comprises four distinct materials: absorbable gelatin sponge, oxidized cellulose, oxidized

regenerated cellulose and microfibrillar collagen.[6] The properties of these materials have been described previously[7] and are summarized below.

Absorbable gelatin sponge is created from porcine gelatin (denatured collagen) through which nitrogen has been bubbled in during polymerization in order to produce a porous device. The porous structure of the sponge enables it to absorb 45 times it weight in blood. As the sponge fills with blood, platelets come into contact with one another, initiating the clotting cascade.

Oxidized cellulose (OC) is generated through the oxidation of cotton, gauze, or other cellulose fabric. This reaction results primarily in the conversion of hydroxyl groups to carboxylic acid groups, making the material soluble at physiological conditions. Cellulosic acid within the device causes localized denaturation of blood proteins, which results in hemostasis. Other oxidation products (i.e., ketones and alcohols) may also affect biologic properties. Although approved for use by the FDA, oxidized cellulose is not currently available in the United States.

Oxidized regenerated cellulose (ORC) induces hemostasis through the same mechanism as OC. However, in the production of ORC, cellulose is first dissolved and then extruded as a continuous fiber. The fabric made from the fiber is very uniform in chemical composition and exhibits less variation in absorbability than does OC.

Collagen hemostats can be provided as purified, lyophilized collagen or microfibrillar collagen. The latter is a water-insoluble, partial hydrochloric acid amino salt of natural collagen in the form of fibers containing microcrystals. Highly purified collagen may be prepared from dermal or tendon sources. Platelets attach to specific

sites on collagen and degranulate, initiating the hemostatic cascade that results in a fibrin clot.

Regulation of Absorbable Hemostats as Class III Medical Devices

Absorbable hemostats were first introduced into the market in the 1940s. The products now available have a long history of safety and efficacy. Initially, these devices were regulated as drugs and required a New Drug Application (NDA) for marketing approval.[8] Shortly after the passage of the Medical Device Amendments (MDA) of 1976 to the Federal Food, Drug and Cosmetics Act, the regulation of absorbable hemostats was transferred to the FDA's device regulatory organization, now known as the Center for Devices and Radiological Health (CDRH). All devices transitioned to CDRH in this manner were automatically classified as Class III medical devices.[9]

The MDA established three regulatory classes for medical devices, based on the degree of control necessary to assure that various types of devices are safe and effective. The most strictly regulated devices are in Class III. The amendments define a Class III device as one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury. Insufficient information exists on a Class III device so that performance standards or general controls used to regulate Class II or Class I devices, respectively, cannot provide reasonable assurance that the device is safe and effective for its intended use. All devices placed into Class III are subject to a rigorous pre-market approval (PMA) process that requires scientific review, including reports of significant human experience, to ensure their safety and efficacy.[10]

Each of the currently available absorbable hemostats was approved for marketing either through the NDA process or through processes required for Class III medical device regulation. Approval of these devices in general surgical indications has been based on extensive preclinical and clinical evaluations demonstrating their ability to induce hemostasis, remain intact long enough to prevent re-bleeding, and to be absorbed completely. Further approval of some devices in specific indications, such as urologic, neurologic or ophthalmologic surgery, has required additional preclinical and human studies in relevant surgical models, further ensuring patient safety. The safety and efficacy of currently available absorbable hemostats is evidenced by the limited number of adverse events reported in the literature or to the FDA.[11]

Rationale for Reclassification

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 are amendments to the MDA. The MDUFMA directed the FDA to regulate medical devices in the "least burdensome" manner possible based on available safety and efficacy information. Based on the long history and safety, the limited number of reported adverse events, and an understanding of the potential risks to health associated with the use of absorbable hemostats, the FDA first discussed reclassifying these devices to Class II regulatory status in 2002.[12] At that time, the FDA said it would seek to amend the name and identification of this group of devices, identifying an absorbable hemostatic agent as "an absorbable device intended to produce hemostasis by accelerating the clotting process of blood during surgical procedures."

Class II devices are those that cannot be classified into Class I because the general controls that regulate Class I devices do not provide sufficient reasonable assurance of safety and efficacy. Instead, Class II devices are regulated using both general controls and special controls, which may include guidelines, performance standards, post-marketing surveillance, clinical data, labeling, tracking requirements, and other requirements designed to provide assurance of safety and efficacy.[13]

The FDA's General and Plastic Surgery (GPS) Devices Advisory Committee discussed the proposed reclassification at a meeting in July of 2002.[14] Several members of the panel indicated that, in the absence of specific examples of the types of controls or guidance documents that would be implemented to ensure the safety and efficacy of absorbable hemostats approved as Class II medical devices, they were unable to recommend reclassification at that time. Discussion also focused on the broad definition of absorbable hemostats and how Class II regulations might be applied to future products that meet the definition but do not have the longstanding history of safety and efficacy of the currently approved devices. Additionally, questions were raised as to whether a single set of controls or guidance documents could be used to assure the safety and efficacy of absorbable hemostats composed of varied materials and produced via multiple manufacturing processes. The panel voted 4 to 3 to table the vote on reclassification until it could review a detailed proposal for special controls and guidance documents that would address its concerns.[15]

In July 2003, a second panel of the GPS Advisory Committee was constituted and convened to review issues related to devices intended to ablate or remove breast tumors. In an effort to resolve matters that remained pending before the committee, the proposal

to reclassify absorbable hemostats was revisited as well. Although the FDA had not yet developed the detailed controls and guidance documents requested by the previous panel, an outline of the type of information that would be covered by such documents was provided, including: general product codes and regulations; potential risks to health and measures to mitigate these risks; material descriptions and performance characterizations; manufacturing information; sterility; biocompatibility; and animal and clinical trial data. The members of this panel determined that the inclusion of these types of information in a detailed guidance document would be sufficient to assure safety and efficacy of absorbable hemostats regulated as Class II devices, and voted unanimously to recommend reclassification, even in the absence of the detailed control and guidance document requested by the 2002 panel.[16]

The different recommendations of the 2002 and 2003 panels may have resulted from the different areas of expertise assembled to address the specific issues of each meeting. The 2002 panel was convened specifically to discuss the proposed reclassification of absorbable hemostats from Class III to Class II devices. The 2003 panel, however, was convened to address the ablation or removal of breast tumors, and took up the issue of reclassification as a secondary objective. Given the FDA's effort to constitute panels that provide expertise related to the key issues discussed at each advisory committee meeting, it is possible that the members of the 2002 panel may have had more extensive expertise and, consequently, greater familiarity with the issues related to the safety and efficacy of absorbable hemostats compared with the 2003 panel.

Current Status of the Reclassification Process

In October of 2006, the FDA issued a formal proposal to reclassify absorbable hemostats as Class II medical devices or proposed a guidance document that would help to assure the safety and efficacy of new absorbable hemostats approved under Class II regulations. Given, however, that the reclassification proposal seems likely, a group of physicians with significant expertise in several relevant surgical specialties and hemostatic physiology gathered in an Absorbable Hemostat Consensus Conference to discuss the potential impact of reclassification and to develop consensus recommendations that may form the foundation of relevant special controls and guidance documents for use in the Class II regulation of these devices.

METHODS

Participants

The consensus panel consisted of seven physicians from around the United States who routinely use a variety of hemostatic agents, including absorbable hemostats, in their medical/surgical practices. Participants' experiences encompassed the use of absorbable hemostats in academic medical centers, private practices and the armed forces. Areas of expertise represented by the participants included general vascular surgery, urology, cerebral vascular surgery, hematology, transfusion medicine, trauma surgery and clinical trials of hemostatic devices.

Development of Consensus Recommendations

The development of consensus recommendations was guided by a list of specific questions developed by the chair of the meeting (Lawson). Each question was used to stimulate debate and discussion of issues related to the proposed reclassification of absorbable hemostats as Class II medical devices. Responses to each question were proposed by members of the panel and refined by the group until all seven participants agreed on a recommendation.

RESULTS

Question 1: What kind of pre-clinical and/or clinical testing would be needed for new products to assure their safety and efficacy? If clinical trials are needed, how should they be designed? How would informed consent be obtained for investigating new surgical products that potentially offer no benefit over existing products?

The panel considered several strategies for generating sufficient data to demonstrate safety and efficacy of new absorbable hemostats, including preclinical testing, clinical testing, post-marketing surveillance and Phase IV clinical trials. Immediate agreement was reached on the need for animal data demonstrating efficacy and biocompatibility (e.g. safety, toxicity, absorption, degradation) equivalent to the currently approved devices in the class. The types of animal models in which such studies should be conducted were discussed, with specific reference to hemostatic models in spleen, large veins, arteries and brain. Panel members acknowledged, however, that such specification was unduly burdensome. Rather than identifying specific models that would be required for preclinical studies of absorbable hemostats, the panel agreed that demonstration of safety and efficacy in a "relevant" animal model of hemostasis would provide sufficient data to assure patient safety while giving wide latitude to developers of new devices in the class.

Significant discussion centered on the participants' desire to speed the availability of new devices while ensuring patient safety. Post-marketing surveillance programs that would gather information on outcomes and adverse events associated with new devices were considered. Although such programs can provide important data about the performance of these devices in real-life surgical settings without imposing the need for

extensive clinical trials, they may not present a complete or accurate picture of the safety and efficacy of new devices. This is due to the largely voluntary nature of these programs as well as the difficulty in distinguishing between device-related adverse events and adverse events that are a routine risk of any surgical procedure. Combined, both of these factors often lead to under-reporting of adverse events in post-marketing studies and thus, concluded the post-marketing studies would not, on their own, provide sufficient data to assure that a new absorbable hemostat was safe and effective in humans.

Phase IV clinical trials also were considered as a mechanism for the post-approval gathering of human safety and efficacy data. However, several members of the panel who had direct experience in conducting Phase IV trials noted that these trials are difficult to conduct from a practical standpoint. Hospitals do not have the financial resources to support them and patient enrollment can be slow. Thus, recommending Phase IV trials in the absence of other human clinical data could create a situation in which new devices might used for extended periods of time before reliable safety and efficacy data become available.

While recognizing the importance of developing recommendations consistent with the idea of a "least burdensome" regulatory pathway, the panel agreed that patient safety is paramount. Several participants felt strongly that patient safety could only be assured through human clinical trials. There was general agreement that the size and scope of these trials would not need to rise to the level of a full-scale clinical development program, and that demonstration of safety and efficacy equivalent to currently approved devices would ensure patient safety. As with the recommendation on

preclinical data, participants agreed that such trials should be conducted in clinically relevant models that assess time to hemostasis, transfusion requirements and survival.

Several members of the panel have addressed the issue of informed consent through participation in clinical trials of other surgical hemostatic devices. Based on their experiences in this area, they believed that obtaining informed consent to conduct trials of new absorbable hemostats would not be difficult or problematic.

Question 2: If new hemostasis products are tested only for specific types of surgery, are they likely to be used off-label in other surgeries as well? Does this pose a patient risk?

The panelists' expertise in various surgical sub-specialties enabled a discussion of the unique hemostatic challenges associated with several surgical indications. For any surgical procedure, the health and hemostatic potential of the patient, the physical location of the surgical field and the types of tissues involved determine how hemostasis is managed. As a result, absorbable hemostats may be held to different performance standards based on the type of surgery in which they may be used. For example, the neurosurgeon on the panel indicated that the standards for pyrogenicity and biocompatibility of absorbable hemostats are greater in neurosurgical settings compared with other surgical indications due to the increased sensitivity of neurologic tissue and the significant, long-lasting damage that can occur in response to inflammation of this tissue. The urologist in the group highlighted the need for absorbable hemostats used in urologic settings to be evaluated for obstructive or calculogenic potential when used in bladder surgery.

Several members of the panel noted that swelling or migration of absorbable hemostats in the post-operative period may cause post-surgical complications if the devices are placed in confined spaces or in areas where nerves or blood vessels pass through confined bony spaces. In these settings, swelling may compress or damage nerves or vessels, with potentially serious consequences.

Participants agreed that off label-use of approved devices was likely, especially considering the very broad indications for currently marketed products. A discussion of the performance requirements in specific surgical indications exemplified the diverse needs and priorities associated with a given type of surgery. One example presented was the different degree of tolerance for oozing or re-bleeding in cardiac surgery compared with neurologic surgery. In the former setting, a limited amount of oozing or re-bleeding is not likely to compromise patient safety or surgical outcome. However, in the latter scenario, even small amounts of oozing or bleeding can give rise to serious adverse events and poor patient outcomes. Another example was the potential for absorbable hemostats to induce the formation of bladder stones when used in certain urologic surgeries. Pediatric surgical procedures were also discussed in the context of special indications that might warrant exclusion, however, the panel generally agreed that their concerns about creating a permanent constriction in a tissue that might later need to grow could readily be addressed through labeling and did not require special approval consideration. Participants noted that the current paradigm for regulating absorbable hemostats as Class III medical devices provides for a general surgical indication that excludes opthalmic, neurologic and urologic surgeries unless additional data demonstrating safety and efficacy in these settings is provided.

Panel members considered the value of recommending that new devices be approved in specific indications based on relevant preclinical and clinical data. However, the group agreed that only a few indications warranted specific demonstration of safety and efficacy and felt confident that patient safety could be assured through approval of new devices in general surgical indications with exclusions for opthalmic, neurologic and urologic surgeries. Approval in these specified areas would require data from animal and human studies conducted in relevant models. This recommendation is consistent with the existing Class III medical device regulations and the proposed Class II regulations for absorbable hemostats.

Question 3: Can clinical issues be foreseen by defining a product by its use rather than its physical composition?

Both the current and proposed definitions of absorbable hemostats are very broad and based on the function of the device rather than on specific product attributes. Under the proposed reclassification, it is possible that new devices could be approved in the class even if they are novel materials, act through novel mechanisms of action or have unique product attributes that are not supported by the long history of safety and efficacy of the currently approved devices in the class. This creates the potential to expose patients to absorbable hemostats that have not been extensively evaluated in controlled, clinical trials, which may impact patient safety and surgical outcome.

The majority of the discussion around this particular issue centered on the FDA's broad definition of absorbable hemostats and on the importance of the historical safety and efficacy of currently approved devices as part of the rationale for reclassification.

Panel members envisioned several devices that would meet the functional definition of the class but would lack a significant body of safety and efficacy data. One example of this type of device would be a chemically modified form of chitosan. Chitosan currently is used as a non-absorbable hemostat, and is not identified as a member of the class of absorbable hemostatic agents that are the focus of the proposed reclassification. However, an oxidized form of chitosan might be bioabsorbable, thus qualifying for inclusion in the class even in the absence of substantial safety and efficacy data.

The panel also considered the likely development of wholly new materials, unrelated to the currently approved devices, which could be both hemostatic and absorbable. Although the FDA could recognize such devices as new technologies and regulate them as Class III devices, the absence of specific language in the definition of the class creates the potential for such a device to be approved without rigorous examination in clinical trials. While the adoption of the panel's recommendation to include clinical data in the guidance document would provide a modicum of assurance that devices approved through Class II mechanisms were safe and effective, panel members retained a high level of concern that the proposed definition of the class created an opportunity for a gradual erosion of the current standards that have helped to ensure patients safety for decades.

Discussion also centered on the FDA's definition of absorbable hemostats and the value of developing a more specific or limited definition of these devices. The group acknowledged that regulators and end-users of these devices define them in different contexts and that a definition suitable in the regulatory arena may not be informative in a

surgical setting. For example, absorbable hemostats that contain a biologic component, such as fibrin or thrombin, are subject to separate regulatory requirements even though surgeons use them interchangeably with devices defined as absorbable hemostats. Thus, while the FDA differentiates among various classes of absorbable hemostatic agents based on their composition, surgeons are more likely to consider them from a mechanistic standpoint.

With this in mind, two alternative definitions for these devices were developed. The first provides a mechanistic definition for the absorbable hemostats that are now under consideration for reclassification. This definition identifies an absorbable hemostat as a device that induces hemostasis, does not contain active clotting factors and is bioabsorbable. The second definition is designed to help differentiate those devices composed of materials for which there is a long history of safety and efficacy from new devices that meet the FDA's functional definition but have not extensively been tested in humans. Thus, the identification of a Class II absorbable hemostatic agent would be an absorbable device intended to produce hemostasis by accelerating the clotting process of blood during surgical procedures *and is composed of material that has demonstrated safety and efficacy in prospective, randomized, controlled clinical trials*. This language would then provide a mechanism to ensure that absorbable hemostats based novel technologies that meet the functional definition would still be regulated as Class III medical devices.

Question 4: Are there new or emerging products or technologies that could interact with hemostasis products?

Absorbable hemostats are used in the context of other medical therapies and hemostatic agents. The mechanisms of action of the currently approved absorbable hemostats are well characterized, enabling physicians to understand the impact of medical therapies, such as anti-coagulant and anti-platelet agents, on the function of these devices.

The panel identified several commonly used medical therapies that may cause coagulopathy and thus impact the function of absorbable hemostats. As an example, the mechanism of action of the currently approved absorbable hemostats is platelet-dependent. In patients taking anti-platelet medications, such as aspirin and clopidogrel bisulfate, platelet function may be sufficiently reduced so as to render these devices ineffective at inducing hemostasis. In this particular example, the mechanism of action of the devices is sufficiently understood that an educated physician should be able to determine how to use them appropriately in the context of a patient's medical history and drug status.

However, with the more limited data that would be required for approval of new devices under Class II regulation, the mechanism of action of a new device might not be particularly well characterized. The absence of such data could make it more difficult for physicians to understand how other commonly used therapies might effect hemostatic function of the device, potentially compromising patient safety. Participants agreed that the mechanism of action of new devices should be evaluated in preclinical studies and should be highlighted in the device's label and packaging insert. Information about potential interactions with commonly used therapies also should be included.

Moreover, the panel acknowledged that including this information with the currently approved devices would be beneficial. It has been the panel's collective experience that, while this information is available in the literature, surgeons who use these devices may not be familiar with the data. Navigating the increasingly complex landscape created by the approval of both new devices and new medical therapies requires robust data on which physicians can base their hemostatic strategies

Question 5: What types of educational or training programs would surgeons require in order to ensure the safe use of new hemostatic products entering the market?

Panelists indicated that the safety and efficacy data of the currently approved absorbable hemostats, which were generated through the Class III approval process, enable them to make reasonable decisions about how they use these devices in their practices. The group noted that product comparisons may become more difficult if new absorbable hemostats are approved on less robust data than the currently approved devices. Several participants also voiced concern about the impact of hospital purchasing policies on their access to absorbable hemostats with longstanding histories of safety and efficacy. It has been the experience of some panel members that economic considerations play a significant role in determining which products are purchased and stocked in hospital dispensaries, oftentimes with limited input from the end users of these products and devices. They envisioned a scenario in which absorbable hemostats with which they have years of experience might, for economic reasons alone, be replaced by a similar but non-identical device that might have different safety, efficacy and performance characteristics. Participants also raised concern about the possibility that

end-users of these devices might not even be aware that such a switch had been made. The group agreed that a program to alert end-users about the change in regulatory status of absorbable hemostats and to educate them about the practical consequences of the reclassification would be helpful in maintaining physicians' ability to develop appropriate surgical hemostatic strategies.

In their routine practice, participants have observed that the level of understanding of the mechanism of action of currently approved absorbable hemostats and their interaction with commonly used medical therapies is not optimal. The approval of new devices and additional drugs will increase the level of complexity of the surgical hemostatic landscape and expand the amount of data with which physicians using these devices will need to be familiar. The panel members agreed that proactive educational initiatives are more effective at transferring knowledge than providing information through a package insert or publishing data in medical journals.

In addition to providing users with information about the physiologic function of new devices, educational programming also should include training in how to use these devices in surgical settings. A key benefit of a robust clinical development program is that it creates a base of physicians who become expert in the use of new technologies, and spread that knowledge to other users through daily interaction with their peers and presentations at medical conferences. The proposed reclassification of absorbable hemostats would significantly decrease the scope of clinical trials, thus reducing the number of physicians who will have experience with new devices approved in the future.

Several educational initiatives were discussed, including: the development of a chart or matrix indicating the interactions among various devices and commonly used drugs, which could be posted in operating rooms as a readily available reference; courses offered through professional medical associations for continuing medical education (CME) credit; inclusion of hemostatic physiology on board certification exams; the development of web-based learning modules; and a certification requirement for users of these devices.

Of the ideas proposed and discussed, the FDA has authority to require companies that manufacture the products to seek certification of the users. This could be accomplished by requiring that physicians who use these devices certify that they have been educated about their use. The responsibility for other educational programming in the area of hemostatic physiology and the appropriate use of absorbable hemostats rests with marketers of these devices, professional medical associations, medical licensing organizations and end users themselves. Although these groups cannot be required to provide this type of educational outreach, such programming would benefit physicians and patients and was unanimously endorsed by the members of the panel.

Recommendations

The panel unanimously made the following recommendations:

1. The approval of new absorbable hemostats under Class II regulation should require both animal-tested and clinical demonstration of equivalence to currently approved products with respect to safety and efficacy. Efficacy and biocompatibility should be

demonstrated in relevant animal model. Time to hemostasis, blood loss and adverse events should be assessed in human clinical trials in representative patients and procedures.

2. Approval of absorbable hemostats under Class II regulation should be for a general surgical indication, excluding opthalmic, neurologic and urologic surgeries. Approval in these excluded indications should require preclinical and clinical studies in relevant models.
3. New devices that meet the broad definition of absorbable hemostats but lack an established history of safety and efficacy should be considered novel technologies and regulated through Class III processes.
4. The hemostatic mechanism of action of new devices should be evaluated in preclinical studies. Labels and package inserts should highlight the device's mechanism of action and provide information about potential interactions with commonly used drugs.
5. Professional medical associations should include hemostatic physiology modules on board certification exams and provide ongoing educational opportunities for physicians to enhance their expertise in this area. Additionally, the FDA may wish to consider requiring users of absorbable hemostats to certify that they have received training and education in the appropriate use of these devices.

CONCLUSIONS

As high-volume users of absorbable hemostats, the members of the panel recognize the potential value of encouraging the development of novel devices in this class by reducing

regulatory burden and reclassifying absorbable hemostats as Class II devices. However, patient safety must remain the paramount concern of physicians and regulators alike. The use of absorbable hemostatic agents in critical situations leaves little room for failure, and warrants that new devices demonstrate substantial clinical safety and efficacy before they are broadly marketed. Adoption of the panel's recommendations by the FDA and the medical community at large provides a framework in which the objectives of spurring innovation and ensuring patient can both be achieved.

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