

CLOSURE

MEDICAL CORPORATION®

1123 6 15 10 10:11

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

August 9, 2006

**RE: Docket Number 2006P-0071: Comments Regarding the 513(e) Petition for
Reclassification of Tissue Adhesives for Soft Tissue Approximation**

Closure Medical Corporation (Closure) appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) on the petition filed by Regulatory & Clinical Research Institute, Inc. (RCRI) requesting reclassification of cyanoacrylate tissue adhesives from class III to class II. Closure strongly believes that the tissue adhesives described in RCRI's petition do not meet the standard established by the Federal Food, Drug, and Cosmetic Act for reclassification because (1) cyanoacrylate tissue adhesives do not constitute a generic type of medical device, and (2) the publicly available, valid scientific evidence does not demonstrate that there exist adequate controls to assure safety and effectiveness of such a generic device. Closure therefore believes that FDA should deny RCRI's petition.

Provided below is a discussion of the basis for Closure's request, followed by a list of questions for consideration by the Plastic and Reconstructive Surgery Devices Advisory Panel scheduled for August 25, 2006.

I. BACKGROUND

In the United States, there have only been two cyanoacrylate topical tissue adhesive devices approved by FDA for wound closure, DERMABOND (P960052) in August 1998 and INDERMIL (P010002) in May 2002. Both of these products are regulated as class III, premarket approval (PMA) devices, and were approved based on meeting PMA requirements for establishing valid scientific evidence of device safety and effectiveness

2006P-0071

C 1

5250 GREENS DAIRY ROAD RALEIGH, NC 27616
PHONE 919 876 7800 FAX 919 790 1041
www.closuremed.com

through controlled clinical evaluations subject to rigorous scientific scrutiny and in-depth scientific review of product chemistry and manufacturing processes subject to pre-approval inspection by FDA. Because the Agency considers tissue adhesives significant risk devices, clinical evaluations for both products required Investigation Device Exemption (IDE) approval and were randomized, prospective, statistically powered, pivotal studies that included a variety of wound types to establish device safety and effectiveness.

While both of these currently approved devices are cyanoacrylate-based products, there are many differences between them. The basic starting materials are different (butyl versus octyl cyanoacetate), as well as the chemical processing conditions and controls during manufacture of the liquid adhesive. Chemical stabilizers utilized in the adhesive formulation are not the same, nor are the systems that control polymerization of liquid adhesive during use, which is critically important to the safety and effectiveness of these devices. As an example of how differences in technologies of the two seemingly similar, approved cyanoacrylate tissue adhesives result in tangible differences in these products, the stabilization package and initiator system for DERMABOND allow the product to be stored at room temperature and used without further preparation, whereas INDERMIL, the only other FDA approved cyanoacrylate tissue adhesive, requires refrigerated storage and warming prior to use due to the difference in the stabilization system and adhesive initiation constraints.

A petition for reclassification of a medical device will be considered by FDA as a petition for reclassification of “all substantially equivalent devices within the same generic type.”¹

FDA defines a “generic type of device” to mean:

a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.²

¹ 21 C.F.R. § 860.120(b).

² Id. § 860.3(i).

The variations in technologies between the only two approved cyanoacrylate tissue adhesive devices, manifest in the simple example discussed above, make these devices too different to be considered the same “generic type of device”.

Previous device reclassifications, and resulting court cases, reveal the factors that must be considered in determining whether a group of medical devices is sufficiently generic to be down-classified from class III. The generic device finding is fact-specific, and when complex variations exist within a type of medical device, adequate standards cannot be established across the entire class. In upholding FDA’s decision to not reclassify rigid gas permeable (RGP) contact lens from class III to class II, the court noted that:

[g]iven the countless conceivable combinations of ‘polymer formulation and manufacturing processes,’ and the corresponding variations in lenses’ ‘nontoxicity, biocompatibility, [and] light transmission,’ the FDA could not conclude that mere membership in the family of ‘RGP lenses’ clinched any particular lens’ safety and effectiveness.”³

Further, according to FDA, any alteration in the manufacturing and design variables of the type of lens at issue would lead to “a unique new lens whose safety and effectiveness are unknown and, without thorough clinical testing, unknowable.”⁴

From another perspective, the reclassification of devices similar to tissue adhesives, such as methyl methacrylate bone cements, has not resulted in effective regulation of these reclassified products. Rather, such reclassifications have created a generation of devices with limited regulatory oversight and questionable assurance of safety and clinical performance. Reclassification of these devices, which are similar to cyanoacrylate tissue adhesives (i.e., a liquid formulation that polymerizes to a solid *in situ*), resulted in increased risk to patients, unclear benefits, and an insufficiently controlled, mainly self-regulated industry.

The current FDA guidance document, *Cyanoacrylate Tissue Adhesive for the Topical Approximation of Skin – Premarket Approval Applications (PMA)*⁵ proposed by the RCRI petition as the primary source of Special Controls, provides guidance for the

³ Contact Lens Mfrs. Ass’n v. Food & Drug Admin., 766 F.2d 592, 597 (D.C. Cir. 1985).

⁴ Id. at 601 (citing 47 Fed. Reg. 53,404, 53,411 (1982)).

⁵ FDA guidance document available at <http://www.fda.gov/cdrh/ode/guidance/1233.pdf>

development of “valid scientific evidence” that is essential to provide data, for evaluation in a PMA review process, of safety and effectiveness of a specific, individual cyanoacrylate tissue adhesive device. Key sections of the guidance document (e.g., chemistry, manufacturing, clinical studies) require compliance with PMA requirements, which cannot be enforced or inspected by FDA as part of the Premarket Notification [510(k)] process applicable to class II.

FDA can only reclassify a generic type of medical device when the controls for the lower class are sufficient to ensure the general safety and effectiveness of the device. The Agency has historically maintained that proponents of reclassification bear the burden of demonstrating, through “publicly available, valid scientific evidence,” both “that the device’s present classification is inappropriate and that the proposed classification will provide reasonable assurance of the device’s safety and effectiveness.”⁶ Class II devices must be, or be able to be, subject to special controls.⁷ Though FDA can permit reclassification into class II without existing performance standards,⁸ there must be enough publicly available information to establish performance standards, such as special controls.⁹ A class III device can only be reclassified into class II if it is determined that “special controls in addition to general controls would provide reasonable assurance of safety and effectiveness of the device and there is sufficient information to establish special controls to provide [such] assurance.”¹⁰

Courts have upheld FDA’s requirement that petitioners requesting reclassification prove by “valid scientific evidence” that controls can be established across the generic class of the medical device.¹¹ In denying reclassification of RGP contact lenses, FDA found that “even if . . . information could be gathered for the purpose of establishing a ‘performance

⁶ Contact Lens Mfrs at 699 (citing 48 Fed. Reg. 56,788, 56,799 (1983)).

⁷ 21 C.F.R. § 860.3(c)(2) (2004).

⁸ Ethicon, Inc., 763 F. Supp. at 390 (D.C. 1991) (citing 21 C.F.R. § 860.3(c)(2)).

⁹ See Medical Device Regulation: The FDA’s Neglected Child, An Oversight Report on FDA implementation of the Medical Device Amendments of 1976, Report of the Subcommittee on Oversight and Investigations of the H. Comm. on Energy and Commerce, 14 (Comm. Print 1983).

¹⁰ 21 C.F.R. § 860.130(c)(1). Class II status is not appropriate when conformance with a performance standard will not guarantee safety and effectiveness. See Contact Lens Mfrs., 766 F.2d at 599.

¹¹ See, e.g., Contact Lens Mfrs., 766 F.2d at 599; Gen. Med. Co. v. Food & Drug Admin., 770 F.2d 214, 219 (D.C. Cir. 1985).

standard' and measuring new lenses against it, conformity with the standard would not guarantee that a lens would function safely and effectively."¹²

As mentioned above, DERMABOND and INDERMIL were approved in 1998 and 2002 respectively, and there have been no other tissue adhesive devices approved since that time. Therefore, there is no record of the guidance (issued in 2004) or the ASTM standard test methods (issued in 2005), which the RCRI petition proposes serve as Special Controls, being applied in the development or approval of a new device. As a result, there is no evidence to support that use of this guidance or these methods will be adequate to establish the clinical safety and functionality of new tissue adhesive devices.

II. COMMENTS REGARDING RECLASSIFICATION PETITION

This portion of Closure Medical's response to the RCRI petition cites specific sections of the petition to provide additional information that we feel is relevant and should be considered together with the other information provided.

1) INDICATION FOR USE (Pages 4 and 5 of 74)

Petition: The petition cites a previous version of the indication statement for the DERMABOND product, which ends with the sentence "DERMABOND adhesive may be used in conjunction with, but not in place of, subcuticular sutures."

Comments: The indication for use currently approved for all DERMABOND products ends with the sentence "DERMABOND adhesive may be used in conjunction with, but not in place of, deep dermal stitches."

2) ADVERSE EVENTS (Section 2.5, page 6 of 74)

Petition: The petition lists infection, dehiscence with need for retreatment, acute inflammation, and allergic reaction as potential adverse events for tissue adhesives.

Comments: This section fails to identify other adverse events that are reported for tissue adhesives. As documented in Attachment E of the RCRI petition, the events reported in

¹² Contact Lens Mfrs., 766 F.2d at 597 (citing 48 Fed. Reg. at 56,780-81).

the MAUDE database¹³ for tissue adhesives include the following categories. These are the leading categories of adverse events listed in order of frequency:

- Eye bonding
- Wound Dehiscence
- Infection
- Allergic Reaction
- Erythema

Additional adverse event categories not identified in the petition, but that have been reported by Closure Medical, include:

- Foreign Body Reaction
- Excessive Scarring

The total number of adverse events for tissue adhesives identified from the MUADE database in the petition is 296.

It is important to consider all categories of adverse events reported for tissue adhesives when considering the impact of reclassification. The clinical performance of any new device must be evaluated for its potential to produce adverse events. The only way to truly measure this potential is through clinical validation using controlled, randomized clinical studies.

3) SUMMARY OF REASONS FOR DOWNCLASSIFICATION (Section 6.0, page 11 of 74)

Petition: The petition states “a) the risk of significant clinical adverse events when using tissue adhesives is low; b) the benefits include effective wound closure, faster closure time, improved cosmesis, less-invasive/less-tissue trauma, no secondary dressing, and no suture removal; and c) the risk of field issues is extremely low.”

Comments: The inherent nature of the cyanoacrylate materials that are the basis for the two currently approved devices (DERMABOND and INDERMIL) does not account for the safety record cited in the RCRI petition. Rather, the low risk attributed with the use of these tissue adhesives cited in a) and c) above is the result of the effective controls enforced through class III PMA requirements. For manufacturing processes, this means

¹³ MAUDE database at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM>.

establishing valid scientific evidence that process conditions and quality controls will ensure a consistent material is produced. For clinical performance, this means validating the device for its intended use through well-controlled clinical studies, which establish safety and effectiveness.

Again, the characteristics required for effective wound closure are not inherent in these materials. It is only the rigorous evaluation required by the PMA system that has ensured the effectiveness of the two existing tissue adhesive products. Without these controls in place, there is increased risk of adverse events due to the lack of sufficient data to ensure safe, effective, and consistent clinical performance. The current level of device performance cannot be assured with the reduced controls associated with down-classification.

4) SAFETY/EFFECTIVENESS OF TISSUE ADHESIVES (Section 7.0, Page 12 of 74)

Petition: The petition provides a literature review of the published information regarding the performance of cyanoacrylate adhesives. From this search, the benefits cited are categorized by benefits of effective wound closure, faster closure time, improved cosmetic outcome, non-invasive, less tissue trauma, no secondary dressing, and no suture/staple removal. Also cited are the summaries of safety and effectiveness for the two approved tissue adhesive devices.

Comments: Closure does not dispute the safety and effectiveness of cyanoacrylate tissue adhesives as they are currently regulated. Published data and PMA Summaries of Safety and Effectiveness cited in the reclassification petition substantiate the benefits provided by the two currently approved products. When devices are developed, manufactured, and clinically validated according to class III device requirements, objective scientific evidence of their safety and effectiveness is established and consistent clinical performance is assured. Also, publishing a summary of safety and effectiveness is required as part of approval of all class III PMA devices. The mere fact that these summaries exist does not mean that they are intended to serve as the basis for reclassification.

Secondly, citing the many benefits of the two currently approved devices has no bearing on the use of the regulatory controls proposed by the RCRI petition. The existence of

this information does nothing to validate the ability of the proposed Special Controls to ensure that new devices will perform as well as those cited in the literature. As previously mentioned, there have been no new devices approved since the FDA guidance or standard methods were published, so these controls have never been employed for device approval. Therefore, there is no assurance that the proposed controls will result in new devices that can provide the same level of benefit cited in the RCRI petition.

5) REGULATORY CONTROL OF RISKS (Section 9.0, page 20 of 74)

Petition: The petition proposes that reclassification of tissue adhesives can be based on application of General Controls, including Premarket Notification to establish substantial equivalence to existing devices, combined with the application of Special Controls, which include the use of standardized tests and a guidance document. The specific guidance called out by the petition is the FDA guidance document *Cyanoacrylate Tissue Adhesive for the Topical Approximation of Skin – Premarket Approval Applications (PMA)*.

Comments: A closer examination of this proposal reveals that it is unmanageable within the 510k system, due to the complexity of chemistry and manufacturing controls for these products and the requirements for compliance to PMA regulations cited in the proposed guidance. Because of the inability of Special Controls to accommodate the requirements of the guidance, down-classification will not result in effective regulation of tissue adhesive devices and therefore should be abandoned.

Allowing for the determination of device effectiveness through substantial equivalence as provided by General Controls is inappropriate for tissue adhesives. The Safe Medical Devices Act of 1990 (SMDA) originally considered the use of data from one approved PMA to support the approval of other devices. SMDA included the four-of-a-kind rule for use of data in PMA submissions that allows the Agency to use data from any approved PMA application one year after approval after FDA had approved the fourth device of a kind. The Center for Devices and Radiological Health (CDRH) never applied the four of a kind provision. But CDRH did use its authority under SMDA to reclassify

extracorporeal shock lithotrippers from class III to class II¹⁴, a decision that was supported in part by data from five previously approved PMA applications.

In the case of topical tissue adhesives that are the subject of the RCRI petition, there have only been two PMAs for cyanoacrylate skin adhesive products approved for use by FDA, DERMABOND (P960052) in August 1998 and INDERMIL (P010002) in May 2002. Both have been regulated as class III, PMA devices and were approved based on meeting PMA requirements for establishing valid scientific evidence of device safety and effectiveness through controlled clinical evaluations and in-depth scientific review of product chemistry and manufacturing processes by the CDRH Office of Device Evaluation. As part of the PMA process, pre-approval inspections of the manufacturing facilities for these devices were conducted to confirm compliance to the manufacturing requirements for class III devices. Also as previously noted, there many differences in the chemical formulations, initiator systems, and other characteristics of the two currently approved devices.

Even in consideration of the unused SMDA four-of-a-kind rule, there has not been sufficient data collected by the Agency for tissue adhesive products to allow reclassification of these devices; there is not a sufficient regulatory history to allow implementation of Special Controls. The exclusion of manufacturing and trade secret information from the provisions of the current six-year rule precludes the Agency from use of this data for the purposes of reclassification, even though this information is central to assuring the consistent clinical performance of tissue adhesive devices. In short, it is impossible to judge the adequacy of the proposed controls based on a sample of only two PMA devices reviewed and approved by FDA.

Another important regulatory detail to consider regarding down-classification of tissue adhesives is the fact that if the reclassification petition is approved and Special Controls are adopted by FDA, they can be used as the basis for clearance of other materials as tissue adhesives, not solely cyanoacrylate adhesives. However, the FDA guidance document that has been proposed as the basis for Special Controls for tissue adhesives was developed specifically for PMA approval of devices using cyanoacrylate technology.

¹⁴ 64 Fed. Reg. 5987, (1999).

It is scientifically unsound to assume that the controls developed for cyanoacrylate adhesives can be applied to any other technology with fundamentally different chemical processes, even if these were regulated as PMA devices.

Because the controls being proposed were not in place for the currently approved products and have not been employed for device review and approval, it has not been demonstrated that the proposed guidance or ASTM standard methods are sufficient to adequately control cyanoacrylate adhesives, even through PMA approval.

III. COMMENTS REGARDING THE PROPOSED SPECIAL CONTROLS

This section evaluates the requirements of the FDA guidance document *Cyanoacrylate Tissue Adhesive for the Topical Approximation of Skin – Premarket Approval Applications (PMA)*, which has been proposed along with four standard test methods as the basis of Special Controls for regulation of tissue adhesive devices. Specific sections of the guidance are discussed regarding their applicability to the control of tissue adhesive devices. Also discussed is the applicability of the standard tests proposed in the petition for determining the mechanical characteristics of the polymerized adhesive.

1) COMMENTS REGARDING THE FDA GUIDANCE DOCUMENT

1.1) Chemistry

Guidance: The guidance directs that all materials used in the chemical processing or formulation of tissue adhesive products be provided in an “approved PMA” regulatory format. The guidance recognizes the critical nature of the starting materials, processing aids, and formulation components to ensure a consistent tissue adhesive formulation. The guidance also recommends that by-products of material decomposition be identified and quantified, citing that these degradation products can be cytotoxic or histotoxic leading to adverse patient outcomes. Also, critical performance attributes of the adhesive, such as heat of reaction, setting time, and tensile strength, can be adversely affected by minor changes in the quality or source of starting materials.

Comments: While the general concepts of the chemical manufacturing process for cyanoacrylate adhesives are commonly known within industry (synthesis, cracking, distillation), the quality and purity of the resulting adhesive product are dependent on the

specific materials used and the process controls that are applied. Tight control must be applied to limit the levels of trace impurities or trace additives (such as inhibitors and stabilizers) in every component used in the chemical process. The potential affects of cross-contamination in the chemical processing can result in toxicity as well as performance problems with the medical adhesive device. The sources and affects of this contamination for cyanoacrylate adhesive manufacturing are described in detail in Attachment 1. This attachment contains the professional opinions of two recognized polymer chemist experts who have intimate knowledge of these chemical processes and broad-based industry experience for production of these materials.

Within industry, the specific materials and chemical processing conditions for cyanoacrylate adhesives are the subject of proprietary trade secret information due to the precise conditions that must be applied for each process. The proprietary nature and fundamental differences of manufacturing methods and chemical components between cyanoacrylate device manufacturers do not allow for standardization, as would be required for effective regulation as class II devices. Even the basic starting materials are different for the two currently FDA approved skin adhesives (octyl- versus butyl-cyanoacrylate). Due to highly specialized conditions and proprietary nature of these processes, it is not possible for these materials and manufacturing conditions to be codified as part of Special Controls.

1.2) Manufacturing

Guidance: The guidance document directs that manufacturing systems for topical tissue adhesives adhere to the FDA guidance, *Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and PMA Staff*.¹⁵ Compliance to this guidance depends on regulation of these devices through PMA applications, which require supplements and annual reporting to establish and maintain scientifically valid evidence of safety and effectiveness for the device over its lifetime as a medical product.

It should be noted that these requirements apply not only to the chemical processes for producing the liquid formulation as highlighted above in the Chemistry section, but also to the manufacturing processes that govern the assembly of the liquid adhesive into its

¹⁵ FDA guidance document available at <http://www.fda.gov/cdrh/comp/guidance1140.pdf>.

applicator and subsequent packaging of the finished device. All these processes are recognized by FDA in the guidance document as being integral to device safety and effectiveness and therefore require compliance to PMA standards to ensure consistent device performance.

Comments: If tissue adhesives are down-classified to class II, there would be a lowered regulatory burden for providing this vital manufacturing information. Manufacturing controls are not routinely scrutinized at the same level as for PMA devices during Agency review of 510k notifications. Because of the critical nature of manufacturing controls for tissue adhesives, review of any marketing application for these devices should include data to demonstrate the ability of the manufacturing processes to assure repeatability and consistency. The thorough review of manufacturing processes that is required for a PMA application is necessary to assure device safety for tissue adhesive products.

PMA approval also requires successful completion of an FDA inspection of the manufacturing facility for the new device to verify compliance to PMA and QSR standards. **A pre-approval inspection is not a requirement for 510(k) clearance of new devices. Review of manufacturing information for a class II device is likely only to be only a review on paper rather than an actual audit of the manufacturing facility.**

Manufacturing changes to class II 510(k) devices are also minimally regulated after initial market clearance. The FDA guidance document *Deciding When to Submit a 510(k) for a Change to an Existing Device*¹⁶ does not directly address the need to file manufacturing changes, only broad changes to materials or device specifications. The ability to change device design under 510(k) regulation provides a great degree of flexibility to make changes without submitting a regulatory filing. This makes change control an even greater concern associated with down-classification of tissue adhesives because, as illustrated by the expert opinions in Attachment 1, even minor changes in chemistry or manufacturing processes can have a major impact on device safety and functionality. Again, because control of manufacturing changes for tissue adhesives is

¹⁶ FDA guidance document available at <http://www.fda.gov/cdrh/ode/510kmod.html>.

essential to ensuring device safety and effectiveness, clearance of these products as 510k devices is inappropriate.

1.3) Mechanical Properties

Guidance: The FDA provides a limited number of mechanical tests in the guidance as examples for characterization of cyanoacrylate tissue adhesive products.

Comments: These test only measure individual aspects of mechanical performance of the device or the applicator, and are not indicative of the overall biomechanical performance of the device as it is used clinically. There are no standardized test methods available to measure biomechanical strength of tissue adhesives that have been directly correlated to clinical performance. No standard methods exist for measuring tissue adherence, durability, thermal skin reaction, or the affect of the adhesive film on underlying microbial growth or healing, which are all key attributes of clinical performance.

1.4) Biocompatibility

Guidance: In the guidance, FDA recommends that biocompatibility testing be performed according to the FDA-modified *Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing*¹⁷ for tissue adhesive devices.

Comments: This is a widely accepted standard for biocompatibility testing and successful completion of the prescribed tests provides some assurance of device safety. These tests are only one aspect of the safety assessment of a new device, however, and clinical evaluation is also required to confirm device safety as it is intended to be used on a patient.

Over the history of regulatory oversight for skin adhesive products, FDA has continuously highlighted concerns regarding cyanoacrylate safety and biocompatibility. Many times, these concerns have focused on the safety of the material with regard to impurities from the manufacturing process, the toxicity potential of stabilizing agents and other additives, and the toxicity potential of degradation products. As discussed in the

¹⁷ FDA guidance document available at <http://www.fda.gov/cdrh/g951.html>.

chemistry and manufacturing sections above, tight control of the chemical components and processing conditions are critical to ensure biocompatibility. These conditions are not only key for initial product batches used to produce samples for biocompatibility testing, but must be strictly maintained from batch to batch after device commercialization to ensure the safety of the product over time. The 510(k) process, which does not afford this level of manufacturing control and allows the broad ability to make changes, cannot guarantee the safety these devices. Only the conditions of PMA approval for control and reporting of manufacturing changes is capable of ensuring the continued biocompatibility of tissue adhesive products.

1.5) Animal In Vivo Performance

Guidance: Animal models have been used to estimate clinical wound closure strength and durability, and the FDA guidance does suggest completing in-vivo test results as a precursor to final confirmation of device performance through clinical evaluation. The FDA states in the guidance document that performance tests in animals are only recognized as methods for providing “proof of concept” and cannot stand on their own as representative of clinical performance. Animal models on their own are not recognized by FDA as appropriate or sufficient to validate the clinical performance of these devices.

Comments: We concur with the assertions made by the FDA guidance. Animal studies alone are not sufficient represent the conditions of product use. Clinical evaluation is required to validate the safety and effectiveness of tissue adhesive devices.

1.6) Shelf Life

Guidance: FDA recommends in the guidance that shelf life testing be conducted to establish the expiration date to be included on device labeling.

Comments: Over the history of FDA regulation of cyanoacrylate skin adhesives, the Agency has emphasized the need to produce real-time stability data to establish the shelf life of the device, and this requirement is again underscored in the guidance. The protocols for conducting these real-time studies have been reviewed and approved as part of the PMA process. By contrast, a formal review of stability data is not routinely required for class II premarket notifications. Due to the importance recognized by FDA

for providing data to establish the shelf life of tissue adhesive devices, Special Controls would not be appropriate for these products.

There are a myriad of factors that can impact the stability of tissue adhesive devices, as discussed in Attachment 1, and each currently marketed product incorporates unique systems to address stability issues. For example, the stabilization package and initiator system for DERMABOND products allow them to be stored at room temperature and used without further preparation. These stabilization and initiator systems are proprietary. INDERMIL, the only other FDA approved device, requires refrigerated storage and warming prior to use due to the difference in the stabilization system and adhesive initiation constraints. Because of these design variations, which are significantly different between the only two currently approved devices and that would be unique for each new skin adhesive product introduced, it is not possible for Special Controls to be adequate to address each potential chemical system that could be employed.

1.7) Clinical Studies

Guidance: In the FDA guidance, the Agency clearly acknowledges that topical tissue adhesives are considered significant risk devices and directs that all new products comply to Investigational Device Exemption regulation¹⁸ for design and conduct of clinical studies. The FDA guidance highlights many “confounding variables” relative to clinical outcomes that cannot be adequately assessed by the in-vitro and in-vivo methods outlined in other sections of the guidance. Variables identified by FDA whose impact on safety and effectiveness can only be evaluated as part of a controlled clinical study are:

- Anatomic location of wound
- Size of wound (length, width, and depth)
- Age of wound
- Wound type and etiology
- Wound classification (clean, clean-contaminated, contaminated)
- Signs of infection and inflammation

Evaluation of device performance with respect to all these confounding variables can only be achieved as part of a well-controlled clinical study of device performance.

¹⁸ 21 C.F.R. Part 812

Comments: Because widespread clinical use of cyanoacrylates tissue adhesives for wound closure remains a new and recent area of application, the accumulation of clinical data for establishing the safety and effectiveness of these devices remains important, as recognized by FDA. The guidance goes into a greater level of detail in this section, describing inclusion and exclusion criteria, study design, study endpoints, assessment tools, as well as information to be included in case report forms. All these requirements suggested by FDA describe a randomized, controlled, pivotal clinical evaluation that must be executed to demonstrate the clinical safety and effectiveness of the device.

The need for controlled clinical evaluation of tissue adhesive products is echoed by medical professionals who use these products. As illustrated in Attachment 2, an expert opinion provided by Dr. William Spotnitz, Professor of Surgery and Director of the Surgical Therapeutic Advancement Center (STAC) at the University of Virginia, the clinical evaluation of tissue adhesives in well-controlled studies is the only way of assuring the performance and safety of these products. Through his work at STAC, Dr. Spotnitz has evaluated the majority of both topical and internal sealants currently marketed in a variety of applications, and is insistent that only clinical evaluation of these products can provide the type of validation required to demonstrate device performance.

Historically, clinical studies performed for clearance of 510(k) devices, when required at all, are typically single-arm studies that provide only a gross evaluation of device performance. Demonstration of substantial equivalence requires a significantly lower burden of evidence than that required for a demonstration of safety and effectiveness.

Also, these devices function by transitioning from a liquid to a solid form after they are applied to the skin. This active transition that is central to device functionality makes these devices unique, and as discussed in the chemistry and manufacturing sections, a large number of factors can influence the polymerization reaction. Therefore, introduction of new tissue adhesive devices should require a clinical demonstration of safety and effectiveness, not substantial equivalence, to validate the chemical formulation and delivery system employed.

2) ASTM STANDARD TESTS

Petition: The petition lists four ASTM standards for measuring the performance of tissue adhesive devices, and suggests that these are adequate for control of the manufacture of tissue adhesives.

Comments: The standard tests proposed by the petition are all of recent origin, most were published in 2005. There are no data available that these methods are effective in predicting clinical performance of tissue adhesive devices. These tests were not employed by the PMA holders for the two currently approved devices, therefore there is no correlation between the outcomes of these tests and the clinical performance exhibited by these devices.

The reclassification petition does list a method, ASTM F2458-05, that is designed to use porcine skin as the substrate for strength testing. While this method does come closer to a true biomechanical test, it only measures strength in one dimension, and does not address durability, thermal skin reaction, or other potential effects of tissue adhesives on healing.

Also, the existence of these methods does not validate their correlation to performance of these devices. ASTM merely offers a service to publish methods for the purpose of standardization. Simply publishing a method does not provide any validity of the measurements taken by the method to have any bearing on clinical performance of the device.

**IV. OUTCOMES OF A PREVIOUS RECLASSIFICATION: METHYL
METHACRYLATE (MMA) BONE CEMENT**

1) REGULATORY HISTORY OF MMA BONE CEMENTS

Methyl methacrylate (MMA) bone cements are medical devices introduced as transitional (NDA/PMA) devices according to the Medical Devices Act of 1976. Several products were approved by the Agency as NDA/PMA devices, the approved marketing applications for the devices are listed below.

N17004	P810020
N17003	P960001
N17755	P970010
N18466	

It should be noted that there were seven PMA devices approved before reclassification was considered.

PMMA bone cements were down-classified to class II by FDA on October 14, 1999 with the implementation of Special Controls allowed for class II medical devices, which were codified on July 17, 2002.¹⁹ Subsequent to reclassification, a significant number of Premarket Notifications were reviewed and cleared by the Agency. These are listed below.

K993836	K031430	K041656
K001160	K030902	K043403
K002652	K030903	K050855
K000943	K030904	K050854
K010586	K033509	K051532
K013755	K030086	K051496
K014199	K033563	K050085
K021715	K033382	K053003
K021499	K033596	K053445
K023012	K022688	K053198
K022251	K032945	
K023103	K031673	

Even with the reduced requirements associated with 510(k) notifications, the administrative burden did not necessarily decrease, but may have actually increased after

¹⁹ 67 Fed. Reg. 46,852 (2002)

reclassification of these devices. Many of these notifications were made due to changes in device design specifications, new formulation components, and new delivery systems.

2) MANUFACTURING CONTROLS

The controls set forth in the FDA guidance document for MMA bone cements, *Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement; Guidance for Industry and FDA*²⁰ are based on 510(k), class II device requirements. This was the standard acknowledged by down-classification, and has been the standard for device regulation since October 1999.

As has been discussed previously in this document, the chemical processes for production of bone cements are similar to those for cyanoacrylate tissue adhesives and there is also similarity with regard to device functionality (i.e., a liquid that polymerizes to a solid *in situ*). Therefore it is reasonable to assume that if regulatory requirements for commercialization of tissue adhesives are reduced to class II, some of the same effects on product quality would result. Also, it could be expected that a similar increase in the number of 510(k) premarket notifications for new devices would ensue.

3) ADVERSE EVENTS

Events reported in the MAUDE database for PMMA bone cements are summarized in the Table below, and illustrated graphically in the following Chart. As documented from the database, the number and severity of these events have increased in the years since down-classification. The reduced level of regulation under class II may not have been the sole cause for this increase, but it cannot be discounted as a contributing factor.

It is important to note that rates of adverse event reporting for PMMA bone cements just prior to down-classification are similar to those for tissue adhesive products today.

²⁰ FDA guidance document available at <http://www.fda.gov/cdrh/ode/guidance/668.html>.

Chart: Bone Cement Adverse Event Frequency by Year

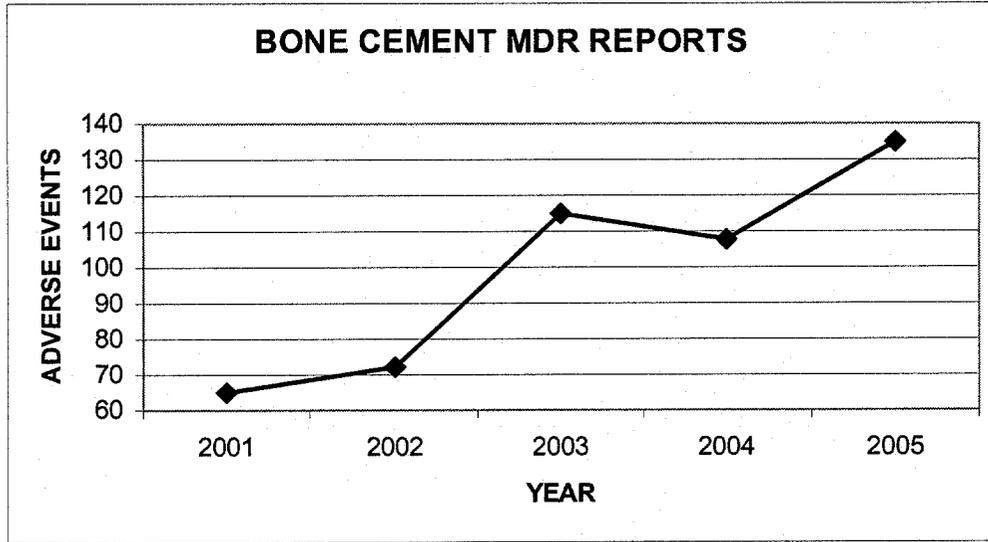


Table: Bone Cement Adverse Event Summary

Year Event Occurred	MDR Reported Events for Bone Cement (source: MAUDE database)					Total
	Death	Life Threatening Injury/Permanent Disability	Injury with Intervention	Setting Performance	Other	
2001	15	4	35	8	3	65
2002	17	3	42	8	2	72
2003	16	2	72	8	17	115
2004	28	6	46	14	14	108
2005	18	4	81	15	17	135

Significant increases in the “other” category beginning in 2003 include reports of applicator parts being implanted in patients, injuries to physician and nursing staff, breaches of sterility in the operating room due to device packaging failures, among others. These types of failures, together with increased reports of setting failures, are indicative of insufficient control of the processes intended to ensure device safety and effectiveness.

The spike in deaths recorded in 2004 may have also had a link manufacturing controls. Adsorption of residual monomer during veterinary applications of PMMA bone cement

have been associated by Pohler²¹ and others with a life threatening drop in blood pressure, sometimes resulting in fatality. The deaths reported in the MAUDE database are almost exclusively due to this type of patient reaction to the injection of the bone cement during the procedure. Within minutes of introduction of the bone cement, there is a significant drop in blood pressure and the patient does not recover. Variability in manufacturing conditions due to inadequate process controls can result in increased levels of residual monomer in these products (see Attachment 1), and therefore may have contributed to the sudden increase of fatal events that occurred in 2004.

While the severity of the outcomes for MDR reportable events for cyanoacrylates may not be as extreme as death or life threatening injury, the similarity of chemistry and manufacturing methods of tissue adhesives to those of PMMA bone cements provides sufficient evidence that a similar increase in reportable events could easily result from the down-classification of tissue adhesive devices. The complexity of the controls required to guarantee repeatability of each chemical process batch to batch, the quality systems required to control the source and quality of the starting materials, process aids, and formulation components, and the level of validation required to ensure device performance should be reflected in the level of regulatory oversight assigned to these products.

²¹ Pohler, O., "Degradation of Metallic Orthopedic Implants in Biomaterials", Rubin, L (Ed.), Biomaterials in Reconstructive Surgery, St. Louis, CV Mosby, 1983.

V. PROPOSED PANEL QUESTIONS

Closure wishes to express its appreciation for the work of the panel and we hope that the panel members have been provided sufficient opportunity to review this document and are familiar with its contents prior to rendering a decision regarding the reclassification petition. To summarize, the main points we have made in our opposition to the reclassification petition are:

- Due to the complexity and uniqueness of the manufacturing processes, chemical formulations, and delivery systems, and the need for clinical safety and effectiveness data for each individual tissue adhesive device, these cannot be considered a “generic type of device.” Only class III requirements can adequately regulate these devices.
- To date, there have only been two PMA tissue adhesive devices reviewed and approved by FDA, both via the class III PMA process. This is not a sufficient number to judge the adequacy of any proposed controls or their applicability to other chemical systems and manufacturing systems that could potentially be employed for tissue adhesive products. There is not valid scientific evidence of sufficient controls to assure safety and effectiveness of tissue adhesives as class II devices.
- The regulation of tissue adhesive devices cannot be effectively achieved through the Special Controls proposed in this petition, because no provisions exist for class II devices to meet class III device requirements.
- The Special Controls suggested by the petition were not in place at the time of review of the only two cyanoacrylate tissue adhesive devices currently approved, therefore there is no evidence of the effectiveness of these controls to guarantee the introduction of safe and effective tissue adhesive products, even as PMA devices.
- Down-classification of similar devices has not resulted in effective regulation, but has increased risk to patients and reduced confidence in the safety and effectiveness of these devices.

In consideration of the discussions of the reclassification petition herein, the following questions are proposed for the Panel.

- 1) FDA has approved only two cyanoacrylate tissue adhesives as PMA devices. In light of the history of reclassification, do these two applications provide sufficient evidence to down-classify tissue adhesives?
- 2) Is the level of regulation afforded by the 510k process sufficient to ensure proper qualification of new products (which may or may not be cyanoacrylate-based adhesives) and ensure their consistent compliance to the requirements of the guidance?
- 3) Without the controls afforded by the PMA system of device approval and file maintenance, what controls are in place to insure against the rise in MDR reportable events that have been observed for PMMA bone cement?
- 4) Should the public be expected to accept an increased risk of adverse events for tissue adhesive products in order to accommodate down-classification of these devices?

This concludes Closure Medical's comments regarding the RCRI petition for reclassification of tissue adhesives. We look forward to discussion of these issues at the Plastic and Reconstructive Surgery Devices Advisory Panel scheduled to meet on August 25, 2006.

Sincerely,



W. Thomas Stephens
Director, Regulatory Affairs
Closure Medical Corporation