



Healthcare

**United States
Surgical**

United States Surgical
150 Glover Avenue
Norwalk, CT 06856

Main: 203-845-1000
www.tycohealthcare.com

August 9, 2006

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

Re: Docket Number 2006P-0071/CCP1

Response to "513(e) Petition for Reclassification, Tissue Adhesive for Soft Tissue Approximation."

To Whom It May Concern:

The attached document is being submitted to the FDA Center for Devices and Radiological Health (CDRH) in response to the "513(e) Petition for Reclassification, Tissue Adhesive for Soft Tissue Approximation," (hereafter referred to as "the Petition") submitted by the Regulatory & Clinical Research Institute, Inc. on February 9, 2006, in accordance with Section 513(e) of the Federal Food, Drug, and Cosmetic Act (hereafter referred to as "the Act"). United States Surgical is respectfully requesting that the attached document be posted to the noted docket for CDRH consideration when reviewing the Petition.

As the sponsor of PMA 010002 for Indermil® Tissue Adhesive, it is the position of United States Surgical, a division of Tyco Healthcare Group LP, that an insufficient body of evidence exists for Tissue Adhesives for Soft Tissue Approximation, Product Code "MPN," to be reclassified as Class II medical devices in accordance with Section 513(a)(1)(B) of the Act. The basis for this position is the knowledge acquired over years of PMA preparation, including the sponsorship of a 1,092 patient clinical trial, followed by four years of commercial distribution in the U.S. All work related to Indermil® Tissue Adhesive has been conducted in partnership with its manufacturer, Henkel Ireland Limited of Dublin, Ireland. Formerly known as Loctite Ireland, Ltd., Henkel Ireland Limited is widely regarded as a world leader in cyanoacrylate manufacture.

In consideration of the insufficient body of evidence to support this proposed reclassification, United States Surgical is recommending the denial of the 513(e) Petition for Reclassification of Tissue Adhesives for Soft Tissue Approximation.

Sincerely,

Philip M. Steinborn
Vice President, Regulatory and Clinical Affairs
United States Surgical, a division of Tyco Healthcare Group, LP

att.

United States Surgical, a division of Tyco Healthcare Group, LP
Response to "513(e) Petition for Reclassification,
Tissue Adhesive for Soft Tissue Approximation."
Docket Number 2006P-0071/CCP1
August 9, 2006

This document is respectfully submitted to the FDA Center for Devices and Radiological Health (CDRH) in response to the "513(e) Petition for Reclassification, Tissue Adhesive for Soft Tissue Approximation," (hereafter referred to as "the Petition") submitted by the Regulatory & Clinical Research Institute, Inc. on February 9, 2006, in accordance with Section 513(e) of the Federal Food, Drug, and Cosmetic Act (hereafter referred to as "the Act").

As the sponsor of PMA 010002 for Indermil[®] Tissue Adhesive, it is the position of United States Surgical, a division of Tyco Healthcare Group LP, that an insufficient body of evidence exists for Tissue Adhesives for Soft Tissue Approximation, Product Code "MPN," to be reclassified as Class II medical devices in accordance with Section 513(a)(1)(B) of the Act. The basis for this position is the knowledge acquired over years of PMA preparation, including the sponsorship of a 1,092 patient clinical trial, followed by four years of commercial distribution in the U.S. All work related to Indermil[®] has been conducted in partnership with its manufacturer, Henkel Ireland Limited of Dublin, Ireland. Formerly known as Loctite Ireland Ltd., Henkel Ireland Limited is widely regarded as a world leader in cyanoacrylate manufacture.

In addition to Indermil[®] Tissue Adhesive, this document shall make reference to the one other approved PMA under product code "MPN," Dermabond[®] Tissue Adhesive (P960052), manufactured by Closure Medical Corporation of Raleigh, North Carolina.

1.0 All Topical Cyanoacrylate Adhesives Are Not Created Equal

In order to support the reclassification of cyanoacrylate tissue adhesives, the Petition attempts to create the perception Indermil[®] Tissue Adhesive (a butyl cyanoacrylate) and Dermabond[®] Tissue Adhesive (an octyl-cyanoacrylate) are alike in Section 2.8 on the "Similarity of Tissue Adhesive Medical Devices" by making the claim that, *"All currently-approved cyanoacrylate adhesives have the same basic chemistry and the same basic mechanical properties."*

However, the Petition contradicts itself in the earlier "Device Description," Section 2.1, which states, *"Butyl and Octyl cyanoacrylate tissue adhesives differ in that butyl tissue adhesives, with their smaller molecular size provide higher tensile strength but are less flexible than the lower tensile strength but more flexible octyl materials. Butyl materials also polymerize faster than octyl cyanoacrylates."*

It is our position that the lack of differentiation in the Petition among various cyanoacrylates is due to a lack of knowledge and experience in the development, testing, and manufacturing of these materials. The following will highlight the reasons why all Topical Cyanoacrylate Adhesives (TCAs) are not created equal, and the reasons why these differences can translate into increased risk to the patient.

1.1 The Differences Among TCAs

The two currently-approved tissue adhesives that have successfully completed the PMA process represent different chemical formulations and possess different mechanical properties that cannot in any way be perceived as representative of general category of cyanoacrylates, which includes methyl, methoxy, ethyl, allyl, iso-butyl, n-butyl, hexyl, heptyl, iso-octyl, and n-octyl variations, in addition to many others. The smaller chain monomers (methyl and ethyl) are considered to be more toxic due to the potential for formaldehyde release from breakdown products and the potential for exothermic reactions that cross the threshold of pain. The larger chain monomers have a higher potential for impurities due to the high boiling points needed to distill the material. While some monomers have toxicity and reactivity profiles that would make them unsuitable for use in their pure form, all of these monomers can be used to create composite blends.

Furthermore, due to differences in proprietary formulations, each TCA can have different acidic stabilizers, free-radical stabilizers, plasticizers, levels of impurities, means of activation, temperature storage conditions, and viscosity. While design verification testing may confirm the initial specifications, each of these product attributes must be properly managed in order to ensure that the specifications are met and that the risk of injury to the patient (in terms of exothermic reaction, dehiscence, and cosmesis) is minimized.

With the exception of butyl and octyl cyanoacrylates, and references made to iso-butyl cyanoacrylate, the Petition fails to acknowledge any other existing or potential formulations. It makes no mention of acidic stabilizers that can affect the cure time, causing exothermic burns if not properly managed, and no mention of plasticizers that can alter the mechanical properties of the adhesive. While the Petition does mention the general category of free radical stabilizers, one specific and commonly-used free radical stabilizer, hydroquinone, can be converted to 1, 4-benzoquinone -- a potential carcinogen that may not be detected during an initial toxicology screening.

We assert that the general safety and effectiveness of all TCAs, a class of materials that extends far beyond butyl and octyl, cannot be reasonably assured on the basis of the premarket approval of a single formulation of butyl (containing mostly cyanoacrylate with trace levels of stabilizers) and a single formulation of octyl (containing a plasticizer and a viscosity modifier which must be expressed through a separate initiator), when the two formulations are vastly different from one another.

1.2 TCA Differences Confirmed By The ASTM Standards

Each of the ASTM International standards cited in the Petition for the purpose of evaluating the mechanical properties of cyanoacrylates contains disclaimers that provide further evidence that all cyanoacrylates are not alike.

F2255-05 Standard Test Method for Strength Properties of Tissue Adhesives in Lap-Shear by Tension Loading:

- *"The complexity and variety of individual applications for tissue adhesive devices, even within a single indicated use (surgical procedure) is such that the results of a single-lap shear test are not suitable for determining allowable design stresses without thorough analysis and understanding of the application and adhesive behaviors."*
- *"This test method may be used for comparing adhesives or bonding processes for susceptibility to fatigue and environmental changes, but such comparisons must be made with great caution since different adhesives may respond differently to varying conditions."*

F2256-05 Standard Test Method for Strength Properties of Tissue Adhesives in T-Peel by Tension Loading:

- *"The complexity and variety of individual applications for tissue adhesive devices, even within a single indicated use (surgical procedure) is such that the results of a T-peel test are not suitable for determining allowable design stresses without thorough analysis and understanding of the application and adhesive behaviors."*
- *"This test method may be used for comparing adhesives or bonding processes for susceptibility to fatigue and environmental changes, but such comparisons must be made with great caution since different adhesives may respond differently to varying conditions."*

F2258-05 Standard Test Method for Strength Properties of Tissue Adhesives in Tension:

- *"The complexity and variety of individual applications for tissue adhesive devices, even within a single indicated use (surgical procedure) is such that the results of a tensile test are not suitable for determining allowable design stresses without thorough analysis and understanding of the application and adhesive behaviors."*

F2458-05 Standard Test Method for Wound Closure Strength in Tissue Adhesives and Sealants:

- *"This test method may be used for comparing adhesives or bonding processes for susceptibility to fatigue and environmental changes, but such comparisons must be made with great caution since different adhesives may respond differently to varying conditions."*

2.0 The Continued Need for Clinical Trials

Since the exothermic reaction of TCAs can lead to the sensation of pain or discomfort by the patient, the clinical setting remains the definitive means of evaluating this adhesive property. Also, cosmesis, cited by the Petition as "an important long-term outcome of wound repair for the patient," must be evaluated for both lacerations and incisions since there is no predictive method for this endpoint. TCAs have the potential to seep into the wound bed and trigger a foreign body response, or they can completely seal a wound and act as a barrier to exudates or lock in infection. Each of these scenarios must be accounted for, in order to reduce the potential for adverse events.

Clinical trials are necessary to evaluate the behavior of TCAs when applied near the surface of the eye or eyelid, when used on wounds of varying skin tension, or when used on patients with various co-morbidities. They also remain the most viable means of evaluating how a particular formulation should be applied: whether as a continuous film or "spot-welded" using minute drops. As with all clinical trials, each aspect has a direct bearing on the ultimate labeling of the product.

In addition to the chemical and mechanical differences between Indermil[®] and Dermabond[®], their respective clinical trials revealed differences that could not have been ascertained by preclinical testing alone. Such differences include Dermabond[®]'s warnings against applying excessive pressure on the wound with the applicator tip, and for the need to apply multiple layers of the adhesive with drying time between applications. Whereas Indermil[®] is a one-part adhesive contained in a plastic vial that must be refrigerated prior use, Dermabond[®] is a two-part adhesive contained in a glass ampule that must be crushed prior to use and the adhesive expressed through the applicator tip. The clinical setting remains the appropriate place to understand how different packaging configurations will perform.

While the downward classification of TCAs would ease the regulatory burden for manufacturers, for CDRH, the burden of PMA review would be replaced by a '510(k) with clinicals' that has a limited 90-day review clock. This trade-off would occur at a time when all of the clinical concerns related to the use of these products remain. With only two formulations of TCAs evaluated in randomized prospective clinical trials, and with the constraints of intellectual property that would likely result in the development of very different formulations by other manufacturers, the 510(k) pathway can only be regarded as atypical and insufficient to meet the scope of evaluation warranted by such devices.

3.0 The Complexity of TCA Manufacture

While surgical sutures have a long medical history spanning thousands of years, the use of cyanoacrylates was first reported in 1959 and their primary use remains in industrial applications. The downward classification of TCAs would provide an opportunity for both medical device and industrial manufacturers to enter the marketplace with little or no prior experience in the making of medical grade cyanoacrylates.

While Henkel (Ireland) Limited remains primarily a manufacturer of industrial adhesives, Indermil[®] Tissue Adhesive is distilled at the specially-constructed, fully CGMP-compliant, Henkel Biomedical Facility, which was designed and staffed by both medical and technical experts with the sole intent of producing medical-grade TCAs. Each of the manufacturing processes, cleaning

processes, environmental controls, quality controls, and validations were developed with the intent of meeting the level of FDA scrutiny mandated by high risk devices. To date, the facility has undergone 3 comprehensive FDA audits with no 483 Inspectional Observations.

While the standards of CGMP compliance would not change with the downward classification of TCAs, the level of FDA scrutiny would diminish without the benefit of extensive information about a manufacturer's facilities and procedures, synthesis and formulation methods, and purification steps that is provided in a PMA, but not in a 510(k). Companies would be allowed to make potentially significant changes to their manufacturing processes or even to the product's formulation without submitting a new 510(k), whereas these changes would likely require either a PMA supplement or at least prior notification to FDA in the case of manufacturing changes. In addition, the frequency and depth of pre- and post-market FDA audits could also diminish. As a result, such audits may fail to capture subtleties of medical-grade TCA manufacture, whether practiced by experienced professionals, or overlooked by inexperienced industrial or medical device manufacturers.

For example, the Henkel Biomedical Facility has documented over 54 separate Validation Master Plans, Installation Qualifications, Operational Qualifications, Process Capability Studies, and Specification Studies above and beyond the reaction, cracking, and purification steps used to manufacture the bulk adhesive. Each of these plans, qualifications, and studies is dedicated to the production of a single liquid that undergoes an exothermic chemical reaction *during the procedure*. Simply stated, there is only one chance to get it right. While a sampling audit is the only practical way to evaluate such a system, the interrelationships among each aspect of the system could not be captured solely during a routine audit.

4.0 The Continued Need to Regulate TCAs as Class III Medical Devices

While topical cyanoacrylate tissue adhesives were initially considered by the FDA to be "transitional devices" that received an automatic Class III designation, we contend they should remain Class III medical devices under section 513(a)(1)(C) of the Act for the reasons stated below. [Note: Underlining has been added for reference purposes only.]

For reference, Section 513(a)(1)(C) of the Act states the following:

(C) CLASS III, PREMARKET APPROVAL.—A device which because—

(i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and

(ii)(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (II) presents a potential unreasonable risk of illness or injury, is to be subject, in accordance with section 515, to Premarket approval to provide reasonable assurance of its safety and effectiveness.

If there is not sufficient information to establish a performance standard for a device to provide reasonable assurance of its safety and effectiveness, the Secretary may conduct such activities as may be necessary to develop or obtain such information.

4.1 With Regard to Section 513(a)(1)(C), Part (i)(II) of the Act

Due to the differences among TCAs, the complexity of TCA manufacture, and the continued need for clinical trials, we contend that insufficient information exists to determine that special controls would provide reasonable assurance of the safety and effectiveness of topical tissue adhesives under the "MPN" product code.

A) The "MPN" Product Code:

It is our position that the "MPN" product code provided a convenient means of grouping Indermil® and Dermabond® in the early stages of the product category, but it has fostered the perception that all cyanoacrylates are alike. When compared with the regulatory evolution of other well-known devices, it becomes apparent why such treatment is over-reaching and premature. For example:

Since both currently-approved tissue adhesives have been compared to sutures (Class II devices) in prospective, randomized clinical trials, one must ask:

"Would CDRH accept the statement that, 'All currently-cleared sutures have the same basic chemistry and the same basic mechanical properties?'"

B) CDRH Oversight of TCA Manufacturers:

The downward classification of TCAs would translate to less FDA oversight of a manufacturing process that remains complex and exacting. The two currently-approved TCAs have been manufactured by companies with long histories of producing safe and effective medical devices, however, with downward classification must come the expectation that industrial or medical device manufacturers with little or no experience will attempt to enter the marketplace.

One must ask: "Has CDRH gained sufficient expertise in the auditing and evaluation of all potential cyanoacrylate manufacturers on the basis of evaluating two companies that are both experienced in the production of safe and effective medical devices?"

C) CDRH Review of TCA Submissions:

According to the FDA Guidance Document, "FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment" of October 8, 2003, the decision goal for an Original PMA is 320 days from the date the PMA is filed. The downward classification of TCAs would curtail the review time for new submissions from 320 days to the 90 days of FDA review time required by a Traditional or Abbreviated 510(k).

According to the "Stakeholder Meeting to Discuss the Possible Implementation of Two Review Performance Goals in the Medical Device User Fee and Modernization Act of 2002; Public Meeting -- May 22, 2006," CDRH reported that its goal for FY'07 is to complete 80% of 510(k)s final decisions within 90 days of FDA review time.

One must ask: "Would the downward classification of TCAs add further delay to an already overburdened system for review?" or "Does CDRH have a reasonable expectation that the review of TCAs (including clinical data) can be completed in 90 days without compromising patient safety?"

D) The Development of a "Performance Standard"

Section 513(a)(1)(C) of the Act states:

If there is not sufficient information to establish a performance standard for a device to provide reasonable assurance of its safety and effectiveness, the Secretary may conduct such activities as may be necessary to develop or obtain such information.

Each of the four ASTM International standards cited in the Petition regarding Lap-Shear by Tension Loading (F2255-05), T-Peel by Tension Loading (F2256-05), Strength Properties (F2258-05), and Wound Closure Strength (F2458-05), includes the following disclaimer:

"This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate

safety and health practices and determine the applicability of regulatory limitations prior to use.”

The ASTM International standards, by their own admissions, do not provide reasonable assurance of their respective attributes of safety per Section 513(a)(1)(C) of the Act. In addition, critical aspects such as the clinical safety of exothermic reactions and the clinical effectiveness of a given TCA on a wound’s cosmetic appearance have not been addressed.

4.2 With Regard to Section 513(a)(1)(C), Part (ii)(II) of the Act

To reiterate, Section 513(a)(1)(C), Part (ii) of the Act states the following:

(C) CLASS III, PREMARKET APPROVAL.—A device which because—

(ii)(I) [it] is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (II) presents a potential unreasonable risk of illness or injury, is to be subject, in accordance with section 515, to Premarket approval to provide reasonable assurance of its safety and effectiveness.

We contend that the broad category of cyanoacrylates presents a potential unreasonable risk of injury, and as such, should continue to be subject to Premarket approval in accordance with Section 515 of the Act, for the following reasons:

- While the primary mode of action of TCAs is wound closure, the *primary mode of operation* subjects the patient to an exothermic chemical reaction during the procedure. While initial design specifications can be set below a given threshold, the risk of injury lies in the ability to consistently manufacture the product to the initial design specifications.
- As a wound closure device, the manufacture of TCAs is critical to ensuring that adequate adhesive strength is applied during the critical wound healing period. While two very specific formulations of TCAs have been approved, their differences demonstrate that not all cyanoacrylates are alike, and the manufacture of other formulations must be carefully controlled in order to avoid dehiscence.
- In addition to the concerns raised by exothermic reactions, if applied improperly, TCAs have the potential to seep into the wound bed, trigger a foreign body response, and impair healing. They can also seal a wound and act as a barrier to exudates or lock in infection. The Petition states cosmesis is "an important long-term outcome of wound repair," and as such, the formulation and manufacturing of TCAs are critical to ensuring that the long-term effects of this wound closure method are minimized.

4.3 TCAs: Significant Risk vs. Non-Significant Risk

A) With Regard to Overall S&E and FDA Experience:

On February 13, 2004, CDRH published the "Guidance for Industry and FDA Staff: Cyanoacrylate Tissue Adhesive for the Topical Approximation of Skin -- Premarket Approval Applications (PMAs)" (hereafter referred to as "the Guidance Document"), which would likely serve as the Special Controls for the "MPN" product category.

The Guidance Document, published on February 13, 2004, states the following:

"FDA believes that cyanoacrylate topical tissue adhesives addressed by this guidance document are significant risk devices as defined in 21 CFR § 812.3(m)."

One must ask, "What has changed since CDRH stated this position?"

- 97 of 121 (or 80%) of the literature references cited in the Petition were published prior to the publication of the Guidance Document. The remaining 24 literature references describe studies that were similar to those published prior to the publication of the Guidance Document.
- No further PMAs have been approved by CDRH in product category "MPN" since the publication of the Guidance Document, providing CDRH with no further experience in the evaluation of TCAs.
- The PMA supplements submitted by the two current PMA holders have generally focused on packaging issues, with the exception of a high viscosity formulation of Dermabond[®]. The formulation of Indermil[®] has not changed since its original PMA approval.
- Other cyanoacrylate devices such as liquid bandages, skin protectants, and dental cements, carry different intended uses than those submitted under the "MPN" product code.

B) With Regard to Investigational TCA Devices:

According to the FDA Blue Book Memo entitled "Significant Risk [SR] and Nonsignificant Risk [NSR] Medical Devices Studies," October 1, 1995:

"If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA."

The Petition makes numerous references to the risks posed by cyanoacrylates. For example, in Section 6.0 on the "Summary of Reasons for Downclassification":

- "... the risk of significant clinical adverse events when using tissue adhesives is low";
- "... the risk of field issues is extremely low"; and finally,
- "The remaining sections of this petition will discuss how these known risks are controllable...."

One must ask: "If all TCAs in the 'MPN' product code were lowered to Class II and deemed a 'Nonsignificant Risk,' is CDRH prepared for a scenario whereby a newly developed product, which is part of a class of materials that has the potential to cause exothermic burns, provide inadequate closure strength, impede the healing process, or lead to poor cosmesis, could bypass the IDE process and move directly to use in patients?" We believe that this scenario is unacceptable from the standpoint of patient risk.

Conclusions

In response to the "513(e) Petition for Reclassification, Tissue Adhesive for Soft Tissue Approximation," submitted to the FDA Center for Devices and Radiological Health by the Regulatory & Clinical Research Institute, Inc. on February 9, 2006, we contend that all cyanoacrylates are not created equal, and that the general safety and effectiveness of all TCAs cannot be reasonably assured on the basis of a single formulation of butyl and a single formulation of octyl.

We also contend that the downward classification of TCAs would leave insufficient review time for clinical data, when all of the clinical concerns related to the use of these products remain. With only two formulations of TCAs on the market, and with the constraints of intellectual property that would likely result in the development of very different formulations by other manufacturers, the 510(k) pathway can only be regarded as atypical and insufficient to meet the scope of evaluation warranted by such devices.

While the standards of CGMP compliance would not change with the downward classification of TCAs, the level of FDA scrutiny would likely diminish. As a result, evaluations may fail to capture subtleties of medical-grade TCA manufacture, whether practiced by experienced professionals, or overlooked by inexperienced industrial or medical device manufacturers. As such, we contend that downward classification would provide for insufficient review of critical manufacturing controls and process validations.

Finally, we believe that insufficient information exists to determine that special controls would provide reasonable assurance of the safety and effectiveness of topical tissue adhesives under the "MPN" product code in accordance with Section 513(a)(1)(C), Part (i)(II) of the Act, and that TCAs in general present a potential unreasonable risk of injury under Section 513(a)(1)(C), Part (ii)(II) of the Act. As such, TCAs should continue to be subject to premarket approval in accordance with Section 515 of the Act.