

FDA Summary Memo

General and Plastic Surgery Devices Advisory Committee (Panel) Meeting On August 25, 2006

Device: Cyanoacrylate Tissue Adhesive for Topical Skin approximation

Petitioner: Regulatory & Clinical Research Institute, Inc.

Subject: Docket # 2006P-0071, Petition to Reclassify Cyanoacrylate Tissue Adhesive for Topical Skin Approximation

Petition Link: <http://www.fda.gov/OHRMS/DOCKETS/dockets/06p0071/06p-0071-ccp0001.pdf>

RECLASSIFICATION PETITION SUMMARY

Regulatory & Clinical Research Institute, Inc. (RCRI) has submitted a petition (Docket # 2006P-0071, dated February 9, 2006) requesting Agency reclassification of the cyanoacrylate tissue adhesive for topical skin approximation device from Class III (Premarket Approval) to Class II (Special Controls) due to the ability of General and Special Controls to provide a reasonable assurance of safety and effectiveness. On May 15, RCRI amended the petition to include copies of representative published articles referenced in the original petition. On July 18, RCRI amended the petition with the proposed intended use for the device identification.

Currently, FDA considers tissue adhesives as “transitional devices” and they are automatically classified by Section 513(f) (1) as Class III devices by the Center for Devices and Radiological Health (CDRH), requiring PMA.

In support of reclassifying the cyanoacrylate tissue adhesive device for topical skin approximation from class III to class II, the petitioner has provided detailed information regarding the risks to health and has proposed general and special controls to mitigate the risks. The petitioner states:

“ Due to the fact that: 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/staple removal; and c) the risk of field issues is extremely low, the petitioner proposes that the application of General Controls, including Premarket Notification Procedures (21CFR807.81) which require the establishment of substantial equivalence to an already-cleared predicate and compliance with the Quality System Regulations (21CFR820) and Special Controls, including use of recognized standards and a guidance document, will be adequate to provide reasonable assurance of safety and effectiveness for tissue adhesives. Therefore, cyanoacrylate tissue adhesives should be classified as Class II medical devices.”

In accordance with Section 513(e) of the 1976 Amendments an interested person, manufacturer or importer may submit a petition to reclassify a medical device, including the reclassification of a Class III medical device into a lower regulatory class. As of the date of this memo, the FDA has not received any public comment from manufacturers, physicians, and individuals in response to the proposed reclassification.

The petitioner's rationale for down classifying this device from III to II is summarized as follows:

- The Agency has years of experience regulating this device category.
- The Agency understands the device specifications and performance characteristics (bench testing, animal testing and clinical data) needed to evaluate and control their use.
- The Agency has successfully down classified a number of similar device categories, e.g., sutures were transitional devices that were down classified to Class II.
- Down classification meets the FDA mandate to apply the "least burdensome" approach to regulating medical devices.

Regulatory History of Class III Cyanoacrylate Tissue Adhesive for Topical Skin approximation

The enactment of 1976 Amendments expanded the role of FDA in regulation of medical devices. The Food, Drug and Cosmetic Act (31 USC 306C) established three classes of medical devices depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three classes are Class I (general controls), Class II (special controls), and Class III (pre-market approval). FDA has approved and/or cleared many synthetic cyanoacrylate devices as Class I (exempt or not exempt), Class II, and Class III medical devices since the Medical Device Amendments of 1976 were enacted.

For example, FDA has cleared many Liquid Bandages made of cyanoacrylate materials, which 21 CFR 880.5090 describes as a class I device that, when used as a wound dressing, requires a 510(k) review and clearance. When used only as a skin protectant on intact skin, Liquid Bandages are Class I devices that are exempt from premarket review. FDA has cleared many Class II devices made of cyanoacrylate materials such as dental cements and orthodontic bracket adhesives. Dental cement and orthodontic bracket adhesives as described in 21 CFR 872.3275(b) are class II devices and are subject to 510(k) requirements.

FDA approved the first Class III transitional cyanoacrylate tissue adhesive device for topical skin approximation named Dermabond™ (P960052). Following this approval, two other Class III cyanoacrylate devices have been approved by FDA: a second cyanoacrylate tissue adhesive for topical skin approximation, Indermil™ Tissue Adhesive (P010002), and a Class III neurological embolization device, Trufill® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System

(P990040). (Please note that neurological embolization devices made of cyanoacrylate materials are not included in the scope of this reclassification petition.)

Cyanoacrylate medical devices are regulated as Class I (general controls; with exemptions and without exemptions), Class II (General controls and special controls), and Class III (General controls and premarket approval) depending on their design (specific chemical formulation and properties) and intended use. The classes to which devices are assigned determine the type of premarketing submission or application required for FDA clearance/approval before marketing in the U.S. If the device is classified as Class I or II, and if it is not exempt, a premarket notification [510 (k)] will be required.

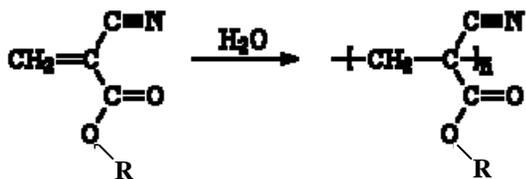
For Class III devices, a premarket approval application (PMA) is currently required. Device classification is assigned based on its *intended use* and its *indications for use*. Furthermore, classification is risk based, i.e., the risk the device poses to the patient and/or the user is a major factor in how a device is classified.

Tissue adhesives, some of which contain cyanoacrylate as the active ingredient, are class III (transitional) devices which are subject to premarket approval requirements (section 520(l) of the act (21 U.S.C. 360j(l)). Transitional devices are devices that were regulated as new drugs or antibiotic drugs prior to the enactment of the Medical Device Amendments of 1976. Specifically, transitional devices were regulated previously by the Center for Drugs, Evaluation, and Research (CDER) as new drugs or antibiotic drugs prior to the enactment of the Medical Device Amendments of 1976 to the Act[(See section 520(l) of the act; see also 42 FR 63473 (December 16, 1977) and 45 FR 58964 (September 5, 1980)]. Accordingly, sutures, tissue adhesives, absorbable hemostatic agents and other devices were transferred to the CDRH after President Ford signed the Medical Device Amendments to the Food, Drug and Cosmetic Act in 1976.

Tissue adhesives, as Class III devices, require valid scientific evidence to demonstrate reasonable assurance of safety and effectiveness, including laboratory data, animal data, clinical data, panel review, and a pre-approval manufacturing facility inspection.

As previously noted, FDA has approved 2 PMAs for cyanoacrylate tissue adhesives. Dermabond™, reviewed by this panel and approved under P960052, is formulated of approximately 94% 2-octyl cyanoacrylate monomer and is manufactured by Closure Medical Corporation, in North Carolina, USA. Indermil™ Tissue Adhesive, approved under P010002, is formulated of approximately 97% n-butyl-2- Cyanoacrylate monomer that is manufactured by United States Surgical, in Connecticut, USA.

Physical and Chemical Properties of Synthetic Cyanoacrylate Adhesives



Alkyl-2-cyanoacrylate

Poly (alkyl-2-cyanoacrylate)

Synthetic cyanoacrylate adhesives (alkyl-2-cyanoacrylates or alkyl- α -cyanoacrylates) are a family of liquid monomers consisting of the alkyl esters of 2-cyanoacrylic acid. They polymerize at room temperature in an exothermic reaction, releasing heat in the process, on contact with a small amount of water or basic fluid to form polymers, Poly (alkyl-2-cyanoacrylates). They form strong adhesive bonds with a variety of substrates such as wood, metal, hard tissue (i.e., bone and enamel), and soft tissue (e.g., skin). Most recognize the adhesive property of cyanoacrylates due to their commercialization as so-called super glues. Different synthetic cyanoacrylate adhesives (alkyl-2-cyanoacrylates) can be manufactured by altering the alkoxy carbonyl group (-COOR) of the molecule. Most methods involve a condensation of formaldehyde ($\text{H}_2\text{C}=\text{O}$) with an alkyl cyanoacetate ($\text{N}\equiv\text{C}-\text{CH}_2-\text{COOR}$) in presence of a base catalyst (such as piperidine) to form a low molecular weight cyanoacrylic ester polymer, poly (alkyl-2-cyanoacrylate). This polymer is then depolymerized (cracked) in presence of a polymerization inhibitor (such as phosphorous pentoxide, nitric oxide, sulfur dioxide) at high temperature by heating to distill off the liquid cyanoacrylate adhesive monomer, alkyl-2-cyanoacrylate. It is further purified by several consecutive fractional distillations, eliminating reactants and any unused materials that may cause premature polymerization. The liquid cyanoacrylate monomer is then stabilized with a free radical inhibitor, such as hydroquinone, which is a free-radical trap preventing re-polymerization. Finally, various cyanoacrylate adhesive formulations can be manufactured by varying viscosity, spreadability, set time, bond strength, degradation rate, and other physical, chemical and mechanical properties of the cyanoacrylate monomers.

Over 90% of cyanoacrylate adhesive formulations will be of the pure liquid monomer, alkyl-2-cyanoacrylate. The other formulation components are added to obtain appropriate performance of the desired final products. They include stabilizers (to prolong shelf life of the formation), polymerization inhibitors (to delay in the transition from liquid formulation to solid polymer), and plasticizers (to maximize strength and flexibility of the polymer after application such as in the case of topical skin application products).

Intended use/Indications for Use of the Two Approved Class III Cyanoacrylate Tissue Adhesives for Skin approximation

The approved two Class III transitional cyanoacrylate tissue adhesive for topical skin approximation devices are intended for the closure of topical incisions and simple traumatic lacerations. Specifically they have the following intended use/indications for use:

Table 1: Cyanoacrylate Tissue Adhesive for Topical Skin Approximation Indications for Use

Product Name	Manufacturer	PRODUCT CHARACTERISTICS	PRODUCT INDICATION
DermaBond P960052 Approved on Aug. 26, 1998	Closure Medical Corp.	94.166% 2-Octyl cyanoacrylate, 5.65% Acetyl tri-n-butyl citrate (plasticizer), 0.0037% D & C Violet #2, colorant), a few ppm of stabilizers for the monomer	<i>“... for topical application to hold closed easily approximated skin edges from surgical incisions, including punctures from minimally invasive surgery and simple thoroughly cleansed trauma-induced laceration. Dermabond may be used in conjunction with but not in place of subcuticular sutures.”</i>
Indermil Tissue Adhesive P010002 Approved on May 22, 2002	United States Surgical	97.0% n-Butyl-2-cyanoacrylate, 3.0% of stabilizers for monomer such as Butylated Hydroxyanisole	<i>“... for the closure of topical skin incisions including laparoscopic incisions and trauma-induced laceration in areas of low skin tension that are simple, thoroughly cleansed, and have easily approximated skin edges. Indermil may be used in conjunction with but not in place of deep dermal stitches.”</i>

Device Description/Principle of Operation of Two Approved Class III Topical Cyanoacrylate Tissue Adhesive Devices for Topical Skin Approximation.

Dermabond (P960052) is a sterile, liquid tissue adhesive containing a monomeric (2-octyl cyanoacrylate) formulation and the colorant D & C Violet #2. It is provided in a single-use applicator containing 0.5 gram liquid formulation in a blister pouch. The applicator is comprised of a crushable glass ampule contained within a plastic vial with attached applicator tip. As manufactured, a chemical initiator is incorporated into the tip applicator.

Indermil Tissue Adhesive (P010002), is also a sterile, liquid topical adhesive composed of a monomeric (n-Butyl-2- Cyanoacrylate) formulation. It is supplied in a 0.5g single patient use, plastic ampule. Each ampule is sealed within a foil packet so the exterior of the ampule is also sterile.

Both devices, Dermabond and Indermil Tissue Adhesive, remain liquid until exposed to water or water-containing substance/tissue, after which it cures (polymerizes) and form a film that bonds to the underlying surface. The devices are not absorbed by the skin or underlying tissue, but it sloughs from the wound as re-epithelization of the skin occurs, providing sufficient time for healing (typically 5-10 days). Accordingly, these two topical Class III cyanoacrylate tissue adhesive devices are not permanently implanted into the human body.

The proposed reclassification of Cyanoacrylate Tissue Adhesive for Skin Approximation from Class III to Class II

The proposed reclassification by the petitioner is based on a history of safe and effective use of these devices and the scarcity of adverse events reports in the published medical articles as well as the risks to health reported in the FDA's Medical Device Reporting System.

a. Published medical articles

Section 7.1 of the reclassification petition provides the results of a review of the published literature and summarizes the clinical use of the device from 119 articles. The May 15 Amendment, which is provided on the CD ROM, provides complete copies of articles that are representative of the total number summarized in the original petition submission. The articles demonstrate that cyanoacrylate tissue adhesive is a safe and effective method of tissue closure for surgical procedures and laceration repair.

However, a few articles, such as Harold et al (Ref. 50) and Van Den Ende et al (Ref. 116), report that Butyl cyanoacrylate tissue adhesive was inferior to sutures when reporting dehiscence. Harold reported on closing 5mm trocar incisions using either 2-octyl cyanoacrylate tissue adhesive, sutures or tapes, and concluded that patients had higher dehiscence rates as well as inferior scar formation and more pain when 2-octyl cyanoacrylate tissue adhesives were used. The authors speculate that this could be due to tension of the abdominal trocar wounds. However, majority of the clinical articles report that the use of cyanoacrylate tissue adhesives is faster than, and provide equivalent closure compared to conventional closure techniques (sutures, staples). Copies of these and other articles are provided in the enclosed CD ROM.

b. Risk to Health Reported in the FDA's Medical Device Reporting Systems

In addition to the petitioner's review of adverse event reports presented in the petition, FDA reviewed the FDA Medical Device Reports (MDR) and Manufacturer and User Facility Device Experience (MAUDE) databases as well as the FDA Enforcement Reports to identify the risk associated with cyanoacrylate tissue adhesive devices (product code MPN) for topical skin approximation. The MDR database contains reports on devices which may have malfunctioned or caused a death or serious injury. These reports were received under both the mandatory Medical Device Reporting Program (MDR) from 1984 - 1996, and voluntary reports until June 1993. MAUDE data represents reports of adverse events involving medical devices. The data in this database consists of voluntary reports since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996. The cyanoacrylate search covers the time period from August 27, 1998 to June 13, 2006.

In order to quantify the risks to health associated with the cyanoacrylate tissue adhesives for topical skin approximation (product code MPN), 287 adverse events have been identified from the Manufacturer User Facility and Distributor Experience (MAUDE) database. All duplicated reports were removed from the search results in order to identify unique events.

**Table 2: Summary of MDR Data for Topical Cyanoacrylate Tissue Adhesive Devices
August 26, 1998 – June 13, 2006**

Reported Problem	N (% of events)
<i>User Error (n=214)</i>	
Unintentional Bonding of Eyelids	172 (59.9%)
Wound dehiscence	35 (12.2%)
Product leakage into eye with no bonding	4 (1.4%)
Chemical burn from fumes	1 (0.3%)
Patient removed adhesive	1 (0.3%)
Blindness	1 (0.3%)
<i>Infectious Process (n=49)</i>	
Infection	43 (14.9%)
Abscess	3 (1.0%)
Febrile reaction	1(0.3%)
Necrosis	1(0.3%)
Excessive wound drainage	1(0.3%)
<i>Immune reaction (n=12)</i>	
Erythema	5 (1.7%)
Allergic reaction	5 (1.7%)
Asthma exacerbation	1(0.3%)
Granuloma	1(0.3%)
<i>Product Issue (n=11)</i>	
Broken vial resulting in injury	7 (2.4%)
Polymerization too slow	2 (0.7%)
Applicator Malfunction	1(0.3%)
Sterility compromised	1(0.3%)

Source: MAUDE database

The most prevalent adverse event reported was eye bonding (60%), which the manufacturers reported as a result of user error, since the functional performance of the device was not out of specification. In most cases, these adverse events resolved using a petroleum based product to slowly dissolve the cyanoacrylate. In 8 out of 172 cases, according to the reporter, the patient sustained a corneal abrasion. In 4 out of 172 cases, the patient was placed under general anesthesia to resolve the problem.

The second most frequently reported adverse event was infection with 43 out of 287 adverse events. The third most frequently reported adverse event was wound dehiscence with 35 out of 287 adverse events. Upon review of the adverse event reports, it was found, that dehiscence and infection were post-operative complications (or post-use of product) that could be attributed to a variety of factors such as type of laceration, wound cleansing procedure, or the patient's condition prior to device application and may not be a result of the device itself. The adverse events of infection and wound dehiscence involved several different types of surgery: craniectomy, laminectomy, oophorectomy, hysterectomy, breast biopsy, breast augmentation, reconstructive skin surgery, suprafacial parotidectomy, femoral endartectomy, cesarean section, myomectomy, hernia repairs, bunion surgery, and implantation of an intracardiac device. In

most cases, it appears the cyanoacrylate was used to close the skin incision but this was not always apparent from the MDR.

The majority of the adverse events were mild in severity and did not result in permanent impairment to the patient. One exception was a reported case where an epileptic patient suffered an eye laceration during a seizure. The patient developed blindness following the use of the device. It has not been ascertained how the cyanoacrylate may have been involved in this case.

The review of the MDR and MAUDE databases suggest that the risk of significant clinical adverse events when using the device is low and consistent with the events reported in the published literature and the Summary of Safety and Effectiveness Data (SSED) documents for the two PMA approved skin approximation adhesives. The petitioner's recommended method of amelioration for the most prevalent adverse event reported (eye bonding) is that these types of health risks could include clinician training and labeling.

Risk Mitigation

Table 3 below presents the risks of cyanoacrylate tissue adhesive for topical skin approximation medical devices identified via published medical articles, PMA Summary of Safety and Effectiveness Data (SSEDs for approved Dermabond and Indermil devices), and MDR/MAUDE databases, along with the proposed mitigating regulatory controls. Please note that the risks and controls in Table 3 have been developed by grouping similar risks listed in Section 9.3 of the petition. If a decision is made to down classify these devices, new tissue adhesives for topical skin approximation would be developed and tested in accordance with the standards and Special Controls guidance document based on current guidance document to demonstrate substantial equivalence.

**Table 3: Potential Risks and Controls Associated with Cyanoacrylate Tissue Adhesives
For Topical Skin Approximation**

POTENTIAL RISK	REGULATORY CONTROL
Unintentional eye bonding or product leakage into eyes	Device Labeling, Bench Testing
Wound Dehiscence	Device Labeling, Bench Testing, Clinical Data
Adverse Tissue Reaction	Device Labeling, Biocompatibility Testing, Animal Studies
Infection due to Improper Sterilization	Bench Testing, Quality Systems Regulation (QSR)
Applicator malfunction	Device Description, Bench Testing, QSR
Fumes caused chemical burns	Device Labeling, Biocompatibility Testing, QSR
Vial broke and cut finger	Device Labeling, Bench Testing
Polymerization too slow	Bench Testing, Animal Studies, QSR
Sterility compromised	Bench Testing, QSR

Proposed Reclassification

The petitioner is proposing that the cyanoacrylate tissue adhesives for topical skin approximation may be reclassified to a lower classification (Class II, special controls). These devices have been regulated by CDRH since 1998. The risk associated with these types of tissue adhesives for topical skin approximation products are identified in Table 2. The petitioner believes that all of these minor potential risks can be addressed via general controls and a special controls guidance document that would be developed to replace the existing guidance document titled "Guidance for Industry and FDA Staff, Cyanoacrylate Tissue Adhesive for Topical Skin Approximation – Premarket Approval Applications (PMAs)" dated 2/13/2004. Special controls may also include published ASTM test methods (a copy of the current guidance document and 4 FDA-recognized ASTM standard test methods are enclosed in your panel binder). The recently published four (4) American Society for Testing and Materials (ASTM) standard test methods for soft tissue adhesives such as cyanoacrylate tissue adhesive devices are intended to provide a means for comparison of the adhesive strengths of tissue adhesives for use as surgical adhesives or sealants on soft tissue:

- ASTM F2255-05 Standard Test Method for Strength Properties of Tissue Adhesives in Lap-Shear by Tension Loading
- ASTM F2256-05 Standard Test Method for Strength Properties of Tissue Adhesives in T-Peel by Tension Loading

- ASTM F2258-05 Standard Test Method for Strength Properties of Tissue Adhesives in Tension
- ASTM F2458-05 Standard Test Method for Wound Closure Strength in Tissue Adhesives and Sealants

Present CFR Listing for Tissue Adhesives for Topical Skin Approximation for the Code of Federal Regulations:

Presently, cyanoacrylate tissue adhesives for topical skin approximation devices are not listed in 21 CFR.

Petitioner's Proposed Intended Use for cyanoacrylate tissue adhesives for topical skin approximation:

Cyanoacrylate tissue adhesives for topical skin approximation devices are intended for topical closure of surgical incisions, including laparoscopic incisions, and simple traumatic lacerations that have easily approximated skin edges. Cyanoacrylate tissue adhesives for topical skin approximation may be used in conjunction with, but not in place of, deep dermal stitches.

Petitioner's Proposed Classification:

Class II (special controls). The special control for the class II device would be a guidance: "Class II Special Controls Guidance Document: Cyanoacrylate Tissue Adhesive for Topical Skin Approximation; Guidance for Industry and FDA."

Class II Special Controls Guidance Document:

If a decision is made to reclassify the device to Class II with special controls, the special controls are usually a guidance document. The guidance document: "*Class II Special Controls Guidance Document: Surgical Sutures; Draft Guidance for Industry and FDA*", issued on June 3, 2003, is provided in your panel binder as an example of a Class II special controls guidance document for a transitional device, suture, that was reclassified from Class III to Class II. The petitioner's proposed draft Class II special controls guidance document for the topical cyanoacrylate tissue adhesive devices intended for soft tissue approximation would be very similar to the example suture special controls guidance document provided, with the exception that specific device information and risks and mitigations would be different.

For the proposed cyanoacrylate tissue adhesive for topical skin approximation devices guidance document, Chapters 1 through 4 would be mostly boilerplate language except for references to the device type and regulatory background. As proposed by the petitioner in Section 9.2, the current guidance on cyanoacrylate tissue adhesives would be renamed to be a Class II special control guidance and the device description (containing chemistry and manufacturing information), mechanical properties (bench testing), biocompatibility, animal data, shelf life, sterility, clinical studies and labeling sections would remain.

Please note that the labeling section of the current PMA guidance on tissue adhesives for skin approximation contains information for physicians on methods to reduce the risk of cyanoacrylate inadvertently sealing the eyelid. However, based on the number of MDRs regarding this adverse event, the agency believes that stronger wording may be appropriate for the labeling section of guidance for cyanoacrylate tissue adhesives. A warning regarding use of the device on or near the eye may be warranted, for example:

Use of cyanoacrylate tissue adhesive near the eye has inadvertently caused some patient's eyelids to be sealed shut. In some of these cases, general anesthesia and surgical removal has been required to open the eyelid. When closing facial wounds near the eye, please position the patient so that any runoff of adhesive is away from the eye. The eye should be closed and protected with gauze. Prophylactic placement of petroleum jelly around the eye, to act as a mechanical barrier of dam, can be effective at preventing inadvertent flow of adhesive into the eye. The cyanoacrylate tissue adhesive will not adhere to skin pre-coated with petroleum jelly. Therefore, avoid using petroleum jelly to any skin area where tissue adhesive is intended to adhere.

The Least Burdensome Provisions of FDAMA:

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

One of the concepts central to this “least burdensome” approach to the regulation of medical devices is to review devices at the Class level (Class I, Class II, Class III) where they will receive an appropriate level of oversight in accordance with what is known about the safety and effectiveness of the device type. Syntactic cyanoacrylate medical devices have been on the market since the 1976 and cyanoacrylate tissue adhesive for topical skin approximation devices since the 1998. The petitioner believes that Class II, Special Controls, is the appropriate regulatory level for these devices because how to assess their effectiveness and the complications are well understood. More than just risk is taken into account when devices are classified. An understanding of the methods to assess safety and effectiveness is a central factor in the classification of medical devices. Other cyanoacrylate Class II devices that are considered to have high risks associated with their use are dental cements (product code 76 EMA, Cement, Dental) and orthodontic bracket adhesives (Product code 76 DYH, Adhesive, Bracket and Tooth Conditioner, Resin). Sutures were Class III transitional devices that were reclassified in the early 1990s.

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