U.S. FDA perspective on the regulation of cyanoacrylate polymer tissue adhesives in clinical applications

George J. Mattamal, Ph.D.

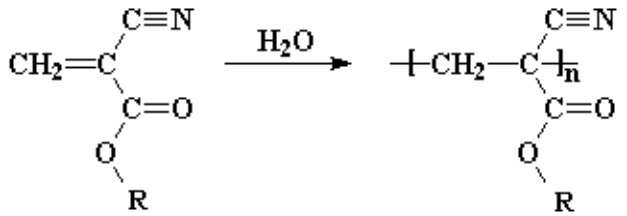
Division of General, Restorative, and Neurological Devices,
Office of Device Evaluation
Center for Devices & Radiological Health, U.S. Food and Drug Administration,
9200 Corporate Blvd., Rockville, MD 20850

INTRODUCTION

Currently, tissue adhesives and glues are an alternative technology in clinical applications that are important both to the medical industry and surgical profession. Many of these emerging tissue adhesives could modify difficult surgical procedures by stabilizing tissue surfaces through hemostasis, sealing of wounds, and fixation of tissue in areas inaccessible to staples, clips, and suture placement. Currently, physicians are relied heavily on sutures, clips, and staples which have an estimated annual worldwide market of over $ 2.5 billion for wound closure alone. There have been significant advances in this technology because of excellent clinical research and development in this field during the last 15 years. In a broad sense, tissue adhesives and glues can be categorized into biologic, composite (hybrid) biologic, synthetic and genetically engineered polymer protein glues. A biologic tissue adhesive is a natural substance consisting of blood products, for example, Fibrin Sealant (Tisseel® VH Kit). It is used as "an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery, is ineffective or impractical; also indicated as an adjunct for closure of colostomies…". Tisseel is manufactured using fibrinogen as the main ingredient (a protein from human blood that forms a clot), thrombin (another blood protein that facilitates blood clotting), bovine fibrinolysis solution, and other clotting factors or additives. An example of a composite (hybrid) biologic tissue adhesive is BioGlue Surgical Adhesive. It is a two-component (natural and synthetic substance) system consisting of purified bovine serum albumin and glutaraldehyde. It is indicated for use "as an adjunct to standard methods of achieving hemostasis (such as sutures and staples) in adult patients in open surgical repair of large vessels (such as aorta, femoral, and carotid arteries)". Synthetic tissue adhesives include cyanoacrylate tissue adhesives such as Dermabond™, Indermil™ Tissue Adhesive, Histoacryl® Blue* (*Sold widely in Canada and Europe only), and polymeric sealants such as FocalSeal-L Synthetic Absorbable Sealant and CoSeal Surgical Sealant. Genetically engineered polymer protein glues are based on protein engineering and DNA gene technology, which are still at experimental stages.

PHYSICAL AND CHEMICAL PROPERTIES OF SYNTHETIC CYANOACRYLATE ADHESIVES

Synthetic cyanocrylate 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 tooth), and soft tissue (i.e., skin, vascular tissue). Different synthetic cyanoacrylate adhesives (alkyl-2-cyanoacrylates) can be manufactured by altering the alkoxycarbonyl group (-COOR) of the molecule. Most methods involve a condensation of formaldehyde ($H_2C=O$) with an alkyl cyanoacetate ($N\equiv C–CH_2–COOR$) in presence of a base catalyst (such as piperidine) to form a low-molecular weight cyanoacrylic ester polymer, poly (alkyl-2-cyananoacrylate). This polymer is then depolymerized (cracked) in presence of a polymerization inhibitor (such as phosphorous pentoxide, nitric oxide, sulfur dioxide) at a 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 in 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 shell life of the formulation), 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).



Alkyl-2-cyanoacrylate Poly (alkyl-2-cyanoacrylate)

Figure 1. Chemical Structures of Cyanoacrylate Monomers

Table 1. Various Cyanoacrylate Adhesive Products

R	Name	Trade Name
$-CH_3$	methyl-2-cyanoacrylate	Eastman 910 Adhesive
$-C_2H_5$	ethyl-2-cyanoacrylate	Krazy Glue™
$-C_4H_9$	n-butyl-2-cyanoacrylate	Indermil™ Tissue Adhesive TRUFILL® Liquid Embolic Agent Histoacryl® Blue*
$-C_8H_{17}$	2-octyl cyanoacrylate	*Dermabond*™

*Sold widely in Canada and Europe only

Synthetic Cyanoacrylate monomers have been available since 1951; however their clinical use has been limited because ofThe potential for thermal damage and scarring to the tissues by heat generation (exothermic reaction) as they transform from monomeric to polymeric form, and Concerns about the cytotoxic or histotoxic effects of the by-products resulting from the degradation of polymer, poly (alkyl-2-cyanoacrylate), which include notably formaldehyde and the corresponding alkyl cyanoacetate, and other breakdown products. Although the polymerized cyanoacrylate monomer gains adhesion rather quickly, the curing process results in tight bonds being formed and some polymers can lack flexibility. Electronegative groups such as the nitrile (-C≡N) and alkoxycarbonyl (-COOR) groups of the alkyl-2-cyanoacrylate monomer make the monomer extremely reactive. These groups enhance anionic polymerization at ambient temperatures even with very weak bases such as water. The alkyl side chain (-R) determines the rate of degradation, rate of polymerization with release of heat in the process, toxicity, flexibility, and the properties of adhesive formed when a monomer polymerizes into a polymer. For example, earlier clinical studies revealed that when the side chain (-R) of the cyanoacrylate monomers were short, such as in methyl-2-cyanoacrylate, it polymerized quickly to give a rigid polymer matrix, poly (methyl-2-cyanoacrylate), and it degraded rapidly into corresponding alkyl cyanoacetate and formaldehyde which can led to significant histotoxicity. The degradation of polymer also depends upon the molecular weight of the polymer formed; a lower molecular weight polymer, poly (methyl-2-cyanoacrylate), degrades more rapidly into corresponding alkyl cyanoacetate, formaldehyde and other breakdown products. On the other hand, when cyanoacrylate monomers with longer alkyl chains (i.e., higher homologues), such as n-butyl-2-cyanoacrylate and 2-octyl cyanoacrylate, polymerize slowly, they form flexible polymers and degrade slowly to form fewer toxic degradation products. Accordingly, longer-chain cyanoacrylate monomers are considered to be less toxic owing to their slower degradation when compared to their shorter side chain counterparts. The formation of toxic degraded products of the polymer, poly (alkyl-2-cyanoacrylate), decreases with increase in the length of alkyl side chain (-R) and molecular weight of the polymer.

Coover discovered the adhesive properties of synthetic cyanoacrylates (alkyl-2-cyanoacrylates) in the research laboratories of Tennessee Eastman Company in 1951. Several years later, in 1958, this discovery led Eastman Kodak to the introduction of the first cyanoacrylate adhesive, methyl-2-cyanoacrylate, called Eastman 910 Adhesive, into the commercial market. In the meantime, Coover did extensive research to develop tissue adhesives based on cyanoacrylate homologs through collaboration with Ethicon Company (Somerville, NJ). Coover applied for US Food and Drug Administration (FDA) approval for one of the cyanoacrylate monomers as a tissue adhesive in 1964. He was, however, unable to obtain FDA approval, and, in 1970, he discontinued his work in medical applications of cyanoacrylate tissue adhesives. At the same time alkyl-2-cyanoacrylates such as n-butyl-2-cyanoacrylate monomer, were made in Europe, Japan, Israel, and Canada. Many clinical experiences on the use of n-butyl-2-cyanoacrylates such as Histoacryl®Blue (B. Braun, Melsungen AG, Melsungen, Germany) were reported, namely, for its clinical use

in wound closure such as for the closure of traumatic lacerations and surgical incisions. Accordingly, Histoacryl® Blue was the first cyanoacrylate tissue adhesive used clinically for closure of skin incisions in Europe and Canada in the early 1980s.

FDA REGULATORY HISTORY OF THE CLASS I, CLASS II AND CLASS III CYANOACRYLATE MEDICAL DEVICES

The US Food and Drug Administration (FDA) has approved and/or cleared a number of synthetic cyanoacrylates as Class I (exempt or not exempt), Class II, and Class III medical devices since the Medical Device Amendments of 1976 were enacted. The enactment of 1976 Amendments has expanded the role of the FDA in regulation of medical devices. The 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 [PMA]). The classes to which devices are assigned determine the type of premarketing submission or application required for FDA clearance or approval before marketing. 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) will be 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. Class I includes devices with lowest risk and Class III includes those with the greatest risk.

How Does the FDA Evaluate Class III Cyanoacrylate Medical Devices for Marketing? The FDA considers tissue adhesives as "Transitional Devices" and they are automatically classified as Class III devices by the Center for Devices and Radiological Health (CDRH), requiring premarket approval (PMA). The CDRH is one of six centers within the FDA and the other centers are the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and research (CBER), the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Veterinary Medicine (CVM), and the National Center for Toxicology Research (NCTR). At the CDRH' s Office of Device Evaluation (ODE), manufacturers present the pre-clinical, clinical, and labeling information that are required for a premarket approval (PMA) or product development protocol (PDP) application for synthetic cyanoacrylate Class III devices. Because tissue adhesives are Class III devices, they require extensive testing and evaluation for such "high-risk devices". This would include a submission of valid scientific evidence to demonstrate reasonable assurance of safety and effectiveness including laboratory, animal, and clinical data; clinical trials; panel review; and a pre-approval inspection. It should be noted that clinical evaluation of "significant risk devices" such as tissue adhesives requires an approved investigational device exemption (IDE) application in addition to institutional review board (IRB) approval.

The FDA approved three Class III PMA medical devices associated with cyanoacrylate monomers. On August 26, 1998, FDA approved the first Class III transitional cyanoacrylate tissue adhesive device for topical skin approximation, Dermabond™. It is formulated of over 90% 2-octyl cyanoacrylate monomer that is manufactured by Closure Medical Corporation, in North Carolina, USA. Following this approval, two other Class III cyanoacrylate devices were approved by the FDA. This included the first Class III neurologic embolization device formulated with n-butyl-2-cyanoacrylate monomer, Trufill® n-Butyl Cyanoacrylate Liquid Embolic System that was approved on September 25, 2000. It consists of n-butyl cyanoacrylate, ethiodized oil, and tantalum powder, manufactured by Cordis Neurovascular, Inc. in Florida, USA. On May 22, 2002, the FDA approved the second cyanoacrylate tissue adhesive for topical skin approximation, Indermil™ Tissue Adhesive. It is formulated of over 90% n-butyl-2-Cyanoacrylate monomer that is manufactured by United States Surgical, in Connecticut, USA. Aside from these Class III cyanoacrylate devices that were approved via PMA, the FDA cleared via the premarket notification process [510(k)] many Class I cyanoacrylate devices (Exempt or not Exempt), and Class II cyanoacrylate devices, such as dental cements and orthodontic bracket adhesives.

How Does the FDA Evaluate Class I, Class II Cyanoacrylate Medical Devices for Marketing? Medical devices formulated with a major component of cyanoacrylate monomers (alkyl-2-cyanoacrylates) are evaluated at the Office of Device Evaluation (ODE) of the CDRH. The ODE is one of six offices within CDRH; the other offices are as follows: Office of Surveillance and Biometrics (OSB), which monitors devices already on the market; Office of In Vitro Diagnostics (OIVD), which serves as the primary source for scientific and medical expertise on in vitro diagnostic devices with regard to safety and effectiveness; Office of Compliance (OC), which acts against firms that violate the law; Office of Communication, Education, and Radiation Programs (OCER), which communicates and educates professionals and consumers on safe use of devices; and Office of Science & Engineering Laboratories (OSEL), which performs research on device problems. Manufacturers submit premarket notification process [510(k)] submissions containing scientific data in support of Class I and Class II Cyanoacrylate devices. These submissions are evaluated at the ODE by ensuring that the medical devices are substantial equivalent to legally marketed devices and are properly manufactured with truthful labeling of the products. Class 1 and Class II devices are classified according to risk. For example, Class I device are simple and will have the lowest risk with well-established history of

safety and effectiveness (i.e., general controls), and often may be exempt from premarket notification [510 (k)]. Class II device are generally more complex, will have a moderate risk, and will be required to meet "special controls" such as guidance documents containing FDA's recommendations, performance standards, post-market surveillance, tracking requirements, labeling, and sometimes clinical data. Accordingly, for these Class II devices (and sometimes Class I), the manufacturers submit premarket notification [510 (k)] submissions, and must show that their devices are substantial equivalence to legally marketed devices in terms of intended use, design configuration, technological characteristics (or different characteristics but no new safety or effectiveness concerns), function, application, and performance. Information on preparing a 510 (k) submission for manufacturers may be found at:http://www.fda.gov/cdrh/devadvice/314.html.

I. Class I Cyanoacrylate Medical Devices. The FDA has cleared a few medical devices associated with cyanoacrylate monomers (alky-2-cyanoacrylates) as Class I devices (exempt or not exempt) under the product code 79 KMF, Liquid Bandage. Under the regulation 21 CFR § 880.5090, Liquid bandage is defined as follows:

"(a) *Identification*. A liquid bandage is a sterile device that is a liquid, semiliquid, or power and liquid combination used to cover an opening in skin or as a dressing for burns. The device is also used as a topical skin protectant. (b) *Classification.* Class I (general controls). When used only as a skin protectant, the device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to § 880.9".

II. Class II Cyanoacrylate Medical Devices. The FDA has cleared a number of Class II dental cements and orthodontic bracket adhesives in which major component was cyanoacrylate monomers (alkyl-2-cyanoacrylates).

A. Class II Dental Cements Containing Cyanoacrylates. Dental cements containing cyanoacrylates are categorized with a product code 76 EMA (Cement, Dental), and these medical devices are Class II based on 21 CFR § 872.3275. Under this regulation, dental cement is defined as follows: Dental cement other than zinc oxide-eugenol:

(1) *Identification*. Dental cement other than zinc oxide-eugenol is a device composed of various materials other than zinc oxide-eugenol intended to serve as a temporary tooth filling or as a base cement to affix dental devices such as crowns or bridges, or to be applied to a tooth to protect the tooth pulp. (2) *Classification*. Class II.

B. Class II Orthodontic Bracket Adhesives Containing Cyanoacrylates. Orthodontic bracket adhesives containing cyanoacrylates are categorized with a product code 76 DYH (Adhesive, Bracket and Tooth Conditioner, Resin) and these medical devices are Class II based on 21 CFR § 872.3750. Under this regulation, bracket adhesive resin and tooth conditioner are defined as follows: (1) *Identification*. A bracket adhesive resin and tooth conditioner is a device composed of an adhesive compound, such as polymethylmethacrylate, intended to cement an orthodontic bracket to a tooth surface. (2) *Classification*. Class II.

In summary, since 1976, the FDA has approved and/or cleared a number of Class I, Class II, and Class III devices in which the main component is a cyanoacrylate homologue. Because of the distinct differences in properties of various cyanoacrylate homologs and their formulations, these medical devices should be used appropriately as Class I, Class II, or Class III devices, depending on their clinical applications, labeling, and indications for use. Currently, many cyanoacrylate medical devices of various regulatory classes are under review by the FDA.

FDA RECOMMENDATIONS FOR TESTING OF CYANOACRYLATE TISSUE ADHESIVE FOR TOPICAL APPROXIMATION OF SKIN

On February 13, 2004, the FDA published a guidance document entitled "Guidance for Industry and FDA Staff, Cyanoacrylate Tissue Adhesive for Topical Approximation of Skin – Premarket Approval Applications (PMAs)" that may be found on FDA web site at http://www.fda.gov/cdrh/ode/guidance/1233.html. The FDA developed this guidance document based on its review experience, published scientific clinical articles, and from input from the General and Plastic Surgery Advisory Panel and manufacturers of these types of devices. The document provides guidance to regulatory personnel and manufacturers in the preparation of investigational device exemption (IDE) applications and in the development of valid scientific evidence to support premarket approval (PMA) applications for cyanoacrylate topical tissue adhesives. Specifically, this guidance document identifies important preclinical, clinical and labeling information that should be submitted in marketing applications [i.e., PMAs or product development protocol (PDPs). This document is intended to provide useful information for helping manufacturers to meet the FDA regulatory requirements. The manufacturers may consider factors such as final product release specifications, which include viscosity determination; analysis of residual content of the components of bulk formation by gas chromatography; nuclear magnetic resonance; mass spectrometry; determination of residual levels of manufacturing reagents; purity of final product; moisture determination; setting time determination; heat of polymerization determination; physical, chemical and mechanical testing; sterility testing; and stability or shelf life determination. Polymerization of the liquid cyanoacrylate tissue

adhesives is an exothermic reaction and the temperature rise in surrounding tissue is governed by the rate of curing (polymerization) and thickness of the adhesive material applied to the surgical site. Viscosity, setting time and adhesive performance of cyanoacrylate liquid monomers are major factors that define the utility of the final product. The viscosity of the liquid adhesive in the final product is a primary indicator of the stability of the final product. As cyanoacrylate adhesive formation ages, the viscosity increases owing to the transition of the monomer into polymer. This, in effect, reduces the concentration of monomer and can affect the adhesive bond formed with the underlying tissue. Thus, key adhesive properties such as the tensile strength, the tensile or overlap shear strength, the peel adhesion strength, and the impact strength, may be evaluated by performing appropriate testing on the final cyanoacrylate adhesive product. Setting time is influenced by the stability of the final product and it is the basis for specific instructions for the physician applying the product.

Aside from the general biocompatibility testing, this guidance document recommends additional animal testing of the cyanoacrylate topical tissue adhesives, such as the animal studies to evaluate the potential for delayed healing using histopathology. The FDA recommends that animal tests should represent the method of applications that will be used in human studies and that the amount of the product used in the animal study be compared that proposed for use in humans. The FDA considers that cyanoacrylate topical tissue adhesives are "significant risk devices" and that clinical studies of the same must be conducted under IDE regulation, 21 CFR Part 812. The FDA recommends a feasibility study (a small, usually non-randomized, one or two-site study), which may be used to evaluate the procedures to be used in the pivotal study, that is, refine instructions for use, and/or provide initial experience to potential investigators. The data derived from a feasibility study are critical toward meeting FDA regulatory recommendations in the design of the pivotal trial toward estimating the treatment effect, and establishing the appropriate sample size for the pivotal safety and effectiveness study.

OTHER USE OF CYANOACRYLATE ADHESIVES

A recent search of the literature revealed several references to various uses of cyanoacrylate adhesives, many of which have not been cleared and/ or approved by the FDA. For example, this includes hundreds of *Cambridge Scientific Abstracts* over the last 17 years, 295 scientific abstracts from *TOXNET* from 1966 to present, 1,638 citations from *Science Direct*, 59 abstracts from *INSPEC* from 1969 to present, 18 articles from *Health Devices Alerts Abstrac*t, and numerous other published clinical articles over a period of 30 years. These sources reveal that synthetic cyanoacrylate tissue adhesives have been used extensively as an alternative to current conventional treatments in clinical applications and studies, including applications in thoracic, gastrointestinal, neurologic, cardiovascular, ophthalmologic and vascular surgery. They also include the use of cyanoacrylates for embolization in neurologic, urologic and cardiovascular procedures and for cartilage and bone grafting procedures. For example, it was reported in the standard treatments of arteriovenous malformations (AVM) that strong adhesive force of cyanoacrylate derivatives sometimes glue the tip of the microcatheter to artery resulting in serious complications; more over, the organic solvents used to dissolve polymers cause damage to the surrounding brain tissue of AVM. It has also been reported that implantation of cyanoacrylate tissue adhesive into subcutaneous tissues can result in acute inflammatory response and foreign body giant cell reaction. Cyanoacrylates have been reported to have variable toxicity when implanted and used for procedures such as nerve and cartilage grafts. This toxicity appears to be more apparent in vascular areas but it also largely in part to the cyanoacrylate formulation used. Cyanoacrylate properties vary greatly, depending on the formulation. Therefore, before various cyanoacrylate monomers can be used successfully, their properties and the potential adverse events of each different cyanoacrylate tissue adhesive formulation must be characterized before they may be used for permanent implantation in patients. As explained here, the FDA has approved Trufill® Embolic System for aiding neurologic embolization. The safety and effectiveness of the Trufill® Embolic System device as a long-term implant has not been established. Hence, there is no current cyanoacrylate tissue adhesives approved in the United States by the FDA for long-term implantation in the human body. To design new biodegradable or bioabsorbable cyanoacrylate tissue adhesives, issues must be addressed that are pertinent to their flexibility, setting time, bond strength, heat of polymerization, viscosity, toxicity, biocompatibility, sterility, biodegradable or bioabsorbable profile, and stability or shelf life. However, animal studies have shown promise in revealing that the cyanoacrylate adhesives degrade gradually *in vivo* and are eliminated naturally by excretion, leaving no measurable levels of toxic breakdown products in the surrounding healthy tissues. These types of animal studies eventually will provide insights into the design of future biodegradable or bioabsorbable cyanoacrylate tissue adhesives that may have the potential to be implanted into the human body for clinical applications.

In summary, the long-term effects of cyanoacrylate tissue adhesives for permanent implantation in the tissues, such as vascularized tissue, are presently unknown. In the future, pre-clinical and clinical studies may ultimately shed more light on the suitability of the cyanoacrylate monomers for permanent implantation in the human body.