

# **Guidance for Industry and FDA Staff**

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## **Cyanoacrylate Tissue Adhesive for the Topical Approximation of Skin - Premarket Approval Applications (PMAs)**

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Office of Device Evaluation**

# Preface

## Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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# **Cyanoacrylate Tissue Adhesive for the Topical Approximation of Skin - Premarket Approval Applications (PMAs)**

*This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.*

### **1. Introduction**

This guidance document addresses only class III cyanoacrylate tissue adhesives intended for the topical approximation of skin and identifies important preclinical, clinical, and labeling information that should be submitted in premarket approval applications (PMAs) or product development protocols (PDPs). This guidance is not applicable to class I or class II cyanoacrylate devices and may have limited applicability to specific intended uses for cyanoacrylate tissue adhesives such as those encountered in ophthalmic surgery.<sup>1</sup>

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<sup>1</sup>Devices composed of cyanoacrylate may be regulated as class I, II, or III devices depending on their design (specific chemical formulation and properties) and intended use. FDA has classified certain cyanoacrylate devices as liquid bandage or dental cement devices. Liquid bandage, described in 21 CFR 880.5090 is a class I device, which when used to cover an opening in the skin or as a dressing for burns, is subject to premarket notification (510(k)) requirements of the Federal Food, Drug, and Cosmetic Act (the act)). However, when used only as a skin protectant, these are exempt from the 510(k) requirements. Dental cement, described in 21 CFR 872.3275(b) is a class II device and is subject to 510(k) requirements.

Additionally, tissue adhesives, some of which contain cyanoacrylate as the active ingredient, are class III (transitional) devices subject to premarket approval requirements (section 520(l) of the act (21 U.S.C. 360j(l))). Transitional devices were regulated 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).

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FDA developed this guidance document based on its review experience, published scientific literature, and input from the General and Plastic Surgery Devices Advisory Panel and manufacturers of these devices. This guidance document serves as a supplement to other FDA publications on PMA, PDP, and IDE applications and should not be construed as a replacement for these documents.<sup>2</sup>

### **The Least Burdensome Approach**

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the “A Suggested Approach to Resolving Least Burdensome Issues” document. It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **2. Device Description**

Cyanoacrylate adhesives are a family of monomers. They polymerize at room temperature in an exothermic reaction on contact with a small amount of water or a basic fluid to form strong adhesive bonds with a variety of substrates. Different cyanoacrylate adhesives can be manufactured by altering the alkoxycarbonyl group of the molecule. Various cyanoacrylate formulations can be manufactured by varying viscosity, setting time, bond strength, degradation rate, and other physical and mechanical properties of the cyanoacrylate monomers. These properties define the adhesive performance and utility of the final product.

We recommend that you provide the following in your device description:

### ***Viscosity and Ease of Expression***

Viscosity of the liquid adhesive in the final product is a primary indicator of the stability of the subject device. As cyanoacrylate formulations age, the viscosity increases due to the transition of the monomer into polymer. This, in effect, reduces the concentration of monomer and can affect the adhesive bond formed with underlying tissue. Also, if viscosity is too great, then it

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<sup>2</sup> For general information about these applications, see the following CDRH Device Advice websites: PMAs (21 CFR Part 814), <http://www.fda.gov/cdrh/devadvice/pma/>; PDPs (section 515(f) of the act (21 U.S.C. 360e(f)), [http://www.fda.gov/cdrh/devadvice/pma/app\\_methods.html](http://www.fda.gov/cdrh/devadvice/pma/app_methods.html), and IDEs (21 CFR Part 812), <http://www.fda.gov/cdrh/devadvice/ide/index.shtml>.

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will be exceedingly difficult to express it through applicator tip. In other words, the ease of expression is affected by the stability of the viscosity of the final product.

### ***Setting Time***

Setting time is the amount of time required for the device to polymerize sufficiently for the wound edges to stay together without assistance. The setting time is also an indicator of the time to achieve maximum temperature from the introduction of the product formulation from the applicator to the test device. The stability of the final product influences the setting time. The instructions to the physician about applying the product are based on setting time.

### ***Bond Strength***

Bond strength directly affects the ability of the device to hold the wound edges together. Please see also Section 5.

### ***Degradation Rate***

Degradation rate is an indicator of the possible toxicity of the adhesive. The hydrolytic degradation of polymers (e.g., cyanoacrylate polymers) to smaller oligomers involves a hydrolysis reaction and release of formaldehyde. Formaldehyde as a by-product of cyanoacrylate hydrolytic degradation and the resultant cytotoxic or histotoxic effects have been reported and documented in research and medical journals (Trott, 1997). Please see also Section 3.

### ***Chemical Components***

The identity of the chemical components of the device should also include any alkoxy carbonyl groups present (see also Section 3).

### ***Packaging Components***

The description of packaging components should include any special or designated device applicator or glass ampoule, and if present, the applicator tube, vial, or tip.

## **3. Chemistry**

FDA recommends that you identify all materials used to comprise the finished device. You may supply this information by reference to a Master Access File (MAF) or other approved PMA or regulatory submission, if you include the appropriate letter of authorization. FDA recommends that you provide a Certificate(s) of Analysis and/or a Materials Safety Data Sheet(s) for all chemicals used in the manufacturing of the final product.

Specifically, for each material or component in the device, we recommend that you provide the following chemical information:

- chemical name
- chemical abstracts service number
- trade name
- structural formula

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- molecular formula and molecular weight
- source and purity (if the information is not included in a MAF).

We also recommend that you provide hydrolytic degradation study data to identify the amount of any by-products of material decomposition. Hydrolytic degradation of polymers (e.g., cyanoacrylate polymers) to smaller oligomers involves a hydrolysis reaction. Release of formaldehyde as a by-product of cyanoacrylate hydrolytic degradation and the resultant cytotoxic or histotoxic effects have been reported and documented in research and medical journals (Trott, 1997). Specifically, the degradation products of cyanoacrylate adhesives could accumulate in tissues and lead to significant histotoxicity characterized by both acute and chronic inflammation. The literature shows that the rate of formation of the formaldehyde decreases with increase in the length of alkyl groups and the molecular weight of the cyanoacrylate polymers (Trott, 1997).

Therefore, to identify the amount of any by-products of material decomposition, we recommend that the hydrolytic degradation study monitor the amounts of:

- formulation additives
- monomer impurities
- degradation products

We recommend that you report results for these by-products of material decomposition present in saline extract at 50°C for a period of 15 days via Gas and/or Liquid Chromatography. The analytical procedure should be sensitive to ppm level. We generally recommend that you collect data from three or more production lots.

The polymerization of cyanoacrylate is an exothermic reaction. The amount of heat generated is governed by the rate of curing (polymerization) and the thickness of the device applied to the surgical site. The heat generated can create a sensation of warmth or heat and cause discomfort in the patient. Therefore, we recommend that you provide the heat of polymerization data and the method used to determine the heat of polymerization.

## **4. Manufacturing**

We recommend that you follow the guidance, **Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff** <http://www.fda.gov/cdrh/comp/guidance/1140.pdf>. In addition to the general recommendations for PMAs in that guidance, we recommend that you submit the information described below for cyanoacrylate tissue adhesives intended for the topical approximation of skin.

### *Manufacturing Process Flow*

We recommend that you provide a description of the manufacturing process for the device, in a step-by-step flow sheet format, from incoming materials to final products. You should include

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accompanying text to identify the purpose of each step, the components/materials used, and the quality control procedures used. We recommend that your manufacturing process flow include:

- all non-reactants and reactants (including catalysts, curing agents, and intermediate precursors) for all device components
- the monomer production
- bulk formation
- cracking
- distillation
- sterilization of the product monomer
- cyanoacrylate formulation (by adding stabilizers, modifiers, inhibitors, thickeners, plasticizers, adhesion promoters, dyes or colorants, etc.)
- bottling
- ampoule filling
- assembling
- final packaging.

### ***Final Product Release Specifications***

We recommend that you provide information about final product release specifications. You should identify the test method and point during manufacture when testing was conducted. We recommend that you explain your release criteria by comparing the release criteria to the levels at which effectiveness are reduced. Examples of final product release specifications include:

- viscosity determination
- analysis of residual content of the components of bulk formation by gas chromatography, nuclear magnetic resonance, mass spectrometry, etc.
- purity of final product
- moisture determination
- setting time determination
- physical and mechanical testing
- stability/shelf life determination
- sterility.

## **5. Mechanical Properties**

FDA recommends that you conduct mechanical testing to evaluate the ability of the polymerized adhesive to provide enough bond strength to hold the wound edges together without manual



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approximation. We recommend that you evaluate the following key adhesive properties of the polymerized adhesive in accordance with appropriate testing on your final cyanoacrylate topical tissue adhesive product:

- tensile strength
- tensile or overlap shear strength
- peel adhesion strength
- impact strength.

Other mechanical testing that may provide additional supporting information for your application includes:

- adhesive expression force test to evaluate the average force to express the adhesive through the porous applicator tip
- test method for water vapor transmission of materials to determine moisture vapor transmission rate (MVTR) of the adhesive product.

## **6. Biocompatibility**

FDA recommends that you conduct biocompatibility testing as described in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing**, <http://www.fda.gov/cdrh/g951.html> for implanted devices contacting tissue for 24 hours to 30 days.

As a note, the subchronic implantation study duration should mimic the proposed use of the material. The test material should be implanted at or near the proposed site of use. The animals should be monitored for systemic toxicity, as well as for local effects at the application site. You should also assess macroscopic pathology and histopathology.

## **7. Animal In Vivo Performance**

Aside from the general biocompatibility testing described in Section 6 above, we recommend that you also provide additional animal testing of your cyanoacrylate topical tissue adhesive to address the issues discussed below.

### *Delay/Prevention of Healing*

Inflammation and the replacement of soft tissue with fibrous tissue are expected outcomes of the normal healing process. Therefore, FDA recommends that you conduct animal studies to evaluate the potential for delayed healing using histopathology.

### *Performance*

FDA recommends that you assess the performance characteristics of the device in the appropriate animal model(s) to provide “proof of concept.” In other words, the animal study

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should suggest that there is a reasonable premise for effectiveness in the human. FDA generally recommends a porcine model; however, other models may be more appropriate for your device. The study should represent the method of application that will be used in human studies. You should compare the amount of the product used in the animal study to that proposed for use in humans. You should also provide a brief discussion of the rationale for, and the limitations of, the animal model used.

## **8. Shelf Life**

We recommend that you conduct shelf life testing to support the expiration date in the labeling of your device. We generally recommend that shelf life testing assess the stability of the adhesive in three production lots. Stability studies should monitor the critical parameters of your final finished device to assure safe and effective device performance during its entire shelf-life. We recommend that your assessment of stability include parameters such as the purity of the materials, water content, setting time (sec), viscosity (cps), color, and sterility and that you describe these parameters in your application.

After you qualify the package configuration, we recommend that you assess the initial integrity of your final finished package and its ability to maintain that integrity.

We recommend that you perform stability testing on representative aged samples at time zero and at several intervals during the real time study. For example, for a 12-month real time stability study, we recommend that you place samples of the finished, packaged device on stability trials at the storage temperature recommended in your labeling. We recommend that you test the device at 1, 3, 6, 9, and 12-month intervals to assess stability at each of these points.

Accelerated shelf life testing should be supported and validated by real-time shelf life testing. The validity of the accelerated stability testing relies on the assumption that the mechanisms of product inactivation and decomposition remain the same at elevated temperatures that simulate testing at lower temperatures for longer times according to the assumptions of thermodynamics. However, because there is no validated accelerated testing method and because of the reactive nature of polymers such as cyanoacrylates, the usefulness of predicting an expiration date from accelerated stability studies remains unclear. Thus, the validity of an accelerated stability study is generally confirmed by a real time stability study performed at the labeled product storage temperature(s). Therefore, if you include accelerated shelf life testing, you should also include information that demonstrates the role of accelerated stability testing in predicting the expiration date. We recommend that this information include a discussion of various inactivation and decomposition pathways for polymerization as a function of time. We also recommend that the results of real-time stability studies illustrate the value of accelerated stability testing in predicting an expiration date of at least one year.

## **9. Sterility**

FDA recommends that you provide sterilization information in accordance with the Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA,

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<http://www.fda.gov/cdrh/ode/guidance/361.html>. The device should be sterile with a sterility assurance level (SAL) of  $1 \times 10^{-6}$ . Although that guidance addresses sterility reviews for devices subject to premarket notification, we believe those recommendations are appropriate for cyanoacrylate tissue adhesives discussed in this guidance.

## **10. Clinical Studies**

FDA believes that cyanoacrylate topical tissue adhesives addressed by this guidance document are significant risk devices as defined in 21 CFR § 812.3(m).<sup>3</sup> Therefore, clinical studies of cyanoacrylate topical tissue adhesives must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. In addition to the requirement of having an FDA-approved IDE, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50). We encourage early interaction with the review division before or during the development of an IDE protocol or to discuss clinical data collected outside the US.<sup>4</sup> Please also refer to the guidance documents “**Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)**,” <http://www.fda.gov/cdrh/ode/guidance/310.html> and “**Pre-IDE Program: Issues and Answers**,” <http://www.fda.gov/cdrh/ode/d99-1.html>.

### *Feasibility Study*

The purpose of a feasibility study is to obtain preliminary clinical assessments of the safety and some evidence of effectiveness of the device. The feasibility study is typically a small, usually non-randomized, one- or two-site study. The feasibility study may be used to evaluate the procedures to be used in the pivotal study, refine the intended patient population, refine the design of the device, refine instructions for use, and/or provide initial experience to potential investigators. The data derived from a feasibility study are used to design the pivotal trial, estimate the treatment effect, and establish the appropriate sample size for the pivotal safety and effectiveness study.

FDA recommends a feasibility study only when there is insufficient preliminary experience with the particular cyanoacrylate monomer or device formulation for the proposed intended use, or a need to refine clinical study parameters before committing to a pivotal study. If you have not committed to a particular formulation, or otherwise plan to conduct a feasibility study, specific tissue adhesive device-related issues that may be addressed in the feasibility study include:

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<sup>3</sup> See also “**Significant Risk and Nonsignificant Risk Medical Device Studies**,” <http://www.fda.gov/cdrh/d861.html>.

<sup>4</sup> The Pre-IDE Program is a way for sponsors of IDEs to submit preliminary information for comment by the review division before submitting an IDE. We encourage you to submit preliminary information, clinical protocol design, pre-clinical testing, results of your feasibility studies, etc., if you wish to obtain FDA guidance, before initiating your studies or while preparing of your IDE application.

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- method of delivery and placement
- polymerization time
- site to site variability
- handling characteristics of the device
- slough time
- preliminary training needs for device use
- wound care needs before, during and after device application
- associated wound infection or altered wound-healing
- pain or discomfort caused by the heat of polymerization.

### ***Pivotal Study***

FDA recommends that you address the following items during the development of your pivotal study:

#### **A. Inclusion and Exclusion Criteria**

Inclusion and exclusion criteria should completely and objectively identify significant patient and wound variables that characterize the study population, capture the effect of major covariates expected to be encountered by marketed product use, and allow assessment of device use under anticipated market conditions.

Inclusion and exclusion criteria should address patient age, race, and co-morbidities that may affect wound healing and assessment of device use, for example:

- nutritional status
- hemodynamic instability
- immune-status as to medications
- evidence of systemic infection
- organ failure or chronic disease
- wound healing history, such as keloid formation.

Inclusion and exclusion criteria should also address information specific to the wound itself, such as:

- wound type
- location
- etiology
- duration

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- condition
- depth of dermal penetration.

### **B. Study Design**

You should incorporate a randomized study design to minimize the introduction of bias. Your design should take into account the effect of randomizing wounds or patients on the statistical power of the study. If you choose to randomize wounds, you should explain the method of choosing the study wound and assuring that sufficient numbers of patients and wound types are enrolled per cohort to allow assessment of covariates. The number of participating geographical sites and physician specialty types should be sufficient to allow assessment of learning curve and potential variations associated with each geographic site and physician specialty.

We recommend concurrent - control trials. These trial designs typically provide the strongest evidence in support of device performance. Sutures, staples, adhesive strips, or other cyanoacrylate tissue adhesives that are legally marketed in the United States for the same intended use as your device are appropriate control devices. You should define the control device for your study; your choice should be guided by the standard of care for the target wound and population, and be appropriate to your study design.

You should address the potential for investigator bias to the greatest extent possible in the clinical study plan. We believe the most effective method of addressing bias includes independent review of photographs to assess wound healing. You should be careful to ensure that the photographs are of sufficient quality to allow consistent and accurate scoring of wounds according to a validated scale. FDA suggests you follow a standardized photography protocol in collecting and assessing these photographs. You should include methods to assess and address inter-rater variability in the photography protocol.

You should prospectively define the period of follow-up and frequency as well as methods of evaluation. These should be appropriate for the endpoint(s) being evaluated.

### **C. Endpoints**

You should describe and objectively define all safety and effectiveness endpoints. Primary endpoints should include clinically significant outcome measures (e.g., wound cosmesis) at a pre-defined timepoint. Safety is a primary endpoint that includes dehiscence, infection, inflammation, pain, and adverse events. FDA recognizes the clinical significance of decreasing procedure time. Parameters such as ease of application and time to closure may be measured as secondary endpoints.

### **D. Assessment Tools**

You should provide a rationale supporting your choice of assessment tools and evidence that these tools are validated for the proposed use. Validation can be presented from

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published, peer-reviewed literature or included in your clinical study plan. An assessment tool that has been validated for evaluating the cosmetic outcome of acute skin wound after closure is the Modified Hollander Cosmesis Scale (Singer, et al., 1998).

### **E. Case Report Forms**

You should provide case report forms that are designed to capture all pertinent information at each time-point in the study. These time-points are:

- patient enrollment
- initial treatment
- re-treatments
- patient follow-ups
- last patient follow-up at study completion.

Case report forms should provide an objective record of:

- inclusion and exclusion criteria
- baseline demographics
- baseline wound characteristics
- treatment
- follow-up
- endpoint parameters
- anticipated adverse events
- the investigator's specialty and training history for this clinical trial.

Case report forms should provide an objective record of the confounding variables. Confounding variables that should be recorded are identified below.

#### **Confounding Variables Associated with the Wound**

For collecting information about potentially confounding variables associated with the wound, the case report forms should include:

- number of wounds
- type (e.g., simple, stellate, complex)
- etiology (e.g., traumatic laceration, surgical incision, excision)
- anatomic location, specifically as to joints, mucus membranes, and dependent surfaces
- size (length, width, and depth of dermal penetration)

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- age (of the wound, i.e., time from injury to closure)
- condition (e.g., presence of crushed, hypo-perfused or devitalized tissue, foreign bodies in the wounds that could not be removed)
- classification at presentation (e.g., clean, clean-contaminated, contaminated, dirty)
- signs of infection and/or inflammation (e.g., wound pain, erythema, edema, warmth, drainage, itching, dehiscence).

### **Confounding Variables Associated with the Patient**

For collecting information about potentially confounding variables associated with the patient, the case report forms should include:

- age
- body mass index (BMI)
- American Society of Anesthesiologist (ASA) score
- vital signs (e.g., blood pressure, heart rate, respiratory rate)
- race
- concurrent medications

### **Confounding Variables Associated with the Procedure**

For collecting information about potentially confounding variables associated with the procedure, the case report forms should include:

- site on the body
- duration as defined in the protocol
- concomitant medications (anesthetics, cleansing agents, antibiotics)
- details of preparation for closure (e.g., wound position, lavage, debridement, anesthesia, hemostasis, closure of dermal and subdermal layers)
- use of adjuncts (e.g., non-randomized device, adhesive strips, covers, ointments)
- concomitant procedures.

### **Confounding Variables Associated with Prescription Devices**

For devices intended for prescription use, i.e., those that will be applied by the clinical investigator, the case report form should include:

- investigator success with device use

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- patient compliance with wound care instructions

#### **Confounding Variables Associated with Non-Prescription Devices**

For devices intended for non-prescription use, i.e., those that will be applied by the patient, the case report form should address the patient's ability to:

- recognize wounds that are candidates for device use
- follow instructions for wound preparation, device application, and follow-up wound care.

The case report form should also address the investigator's assessment of patient performance.

#### **F. Statistical Methods**

You should provide a comprehensive statistical plan. We recommend that you refer to the general statistical guidance entitled, "**Statistical Guidance for Clinical Trials of Non-Diagnostic Medical Devices**," available at [www.fda.gov/cdrh/ode/ot476.html](http://www.fda.gov/cdrh/ode/ot476.html) for additional information.

## **11. Labeling**

Labeling must comply with the requirements of 21 CFR Part 801 before a device is introduced into interstate commerce. In addition, labeling for prescription devices must comply with 21 CFR § 801.109. Labeling recommendations for cyanoacrylate adhesives in this guidance are consistent with the requirements of part 801. We recommend that you also refer to general labeling guidance, **Device Labeling Guidance**, March 8, 1991 (G91-1) <http://www.fda.gov/cdrh/g91-1.html>.

#### **A. Instructions for Use**

We recommend that you provide detailed instructions for wound preparation and device application. These instructions should reflect the experience gained in preclinical and clinical studies and include post-operative wound care. The instructions should also describe techniques for tissue separation and device removal, in the event of inadvertent bonding.

#### **B. Precautions**

We recommend that the labeling provide precautions about the inappropriate use of these devices, for example:

Cyanoacrylate tissue adhesives should not be used:

- in the presence of infection
- in the presence of ongoing bleeding



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- in the presence of incomplete debridement
- on mucosal or hair covered surfaces.

Cyanoacrylate tissue adhesives should not be used on wounds that are:

- wet
- dirty
- complex
- not easily approximated
- non-acute
- poorly perfused
- located in areas where device run-off into unintended sites cannot be prevented.

When increased risk or decreased benefit is anticipated based on available information or not adequately evaluated based on the inclusion and exclusion criteria of your study design, this information should be listed in the labeling, for example:

- the use of this device on or around the eye has not been studied
- the potential risk of runoff into unintended areas for low viscosity products.

## **12. References**

Singer AJ, Hollander JE, Valentine SM, Turque TW, McCuskey CF, Quinn JV: Prospective, randomized, controlled trial of tissue adhesive (2-octylcyanoacrylate) vs. standard wound closure techniques for laceration repair. Stony Brook Octylcyanoacrylate Study Group. *Academic Emergency Medicine* 1998;5:94-9.

Trott, A. Cyanoacrylate tissue adhesives: an advance in wound care. *Journal of the American Medical Association* 1997; 277(19):1559-1560.