

# Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Tissue Adhesive for the Topical Approximation of Skin

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This document supersedes Cyanoacrylate Tissue Adhesive for the Topical Approximation of Skin - Premarket Approval Applications (PMAs), dated February 13, 2004

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Food and Drug Administration  
Center for Devices and Radiological Health

Plastic and Reconstructive Surgery Devices Branch  
Division of General, Restorative, and Neurological Devices  
Office of Device Evaluation

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## Preface

### Public Comment

Written 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. Alternatively, electronic comments may be submitted to <http://www.regulations.gov> (<http://www.regulations.gov>). 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.

## Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to [CDRH-Guidance@fda.hhs.gov](mailto:CDRH-Guidance@fda.hhs.gov) (<mailto:CDRH-Guidance@fda.hhs.gov>) to receive a copy of the guidance. Please use the document number 1630 to identify the guidance you are requesting.

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# Guidance for Industry and FDA Staff

## Class II Special Controls Guidance Document:

### Tissue Adhesive for the Topical Approximation of Skin

## 1. Introduction

This guidance document was developed as a special control to support the reclassification of tissue adhesive for the topical approximation of skin into class II (special controls). The device is intended for topical closure of surgical incisions, including laparoscopic incisions and simple traumatic lacerations that have easily approximated skin edges . This guidance document does not apply to tissue adhesives for non-topical uses .

On August 25, 2006, the General and Plastic Surgery Devices Panel unanimously recommended that the tissue adhesive for the topical approximation of skin be reclassified into class II with special controls. This guidance is issued in conjunction with a *Federal Register* notice announcing the reclassification of this device type.

Following the effective date of a final rule reclassifying the device type, any firm submitting a 510(k) for a tissue adhesive for the topical approximation of skin will need to address the issues covered in the special control guidance document. The firm must show that its device addresses the issues of safety and effectiveness identified in this guidance, either by meeting the recommendations of this guidance or by some other means that provides equivalent assurances of safety and effectiveness.

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## 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](#)**

**[\(/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDA ModernizationAct/ucm136685.htm\)](#)**” document.

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## 2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of the tissue adhesive for the topical approximation of skin. Thus, a manufacturer who intends to market a device of this generic type must (1) conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with the tissue adhesive for the topical approximation of skin identified in 21 CFR 878.4010(a), and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This special controls guidance document identifies the classification regulation and product code for the tissue adhesive for the topical approximation of skin (Please refer to **Section 4.Scope**). In addition, other sections of this special controls guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with tissue adhesives for the topical approximation of skin and lead to a timely 510(k) review and clearance. This document supplements other FDA guidance documents regarding the content requirements of a 510(k) submission. You should also refer to 21 CFR 807.87, the guidance, **Format for Traditional and Abbreviated 510(k)s**,<sup>1</sup> and the section of CDRH's Device Advice, **How to Prepare a 510(k) Submission**.<sup>2</sup>

As described in the guidance entitled, **The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**,<sup>3</sup> a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA issues a class II special controls guidance document. Manufacturers considering certain modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

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## 3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g);

therefore, we recommend that you include a summary report. The report should describe how this special controls guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of section 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

## Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this special controls guidance document.

## Proposed labeling

Proposed labeling must be sufficient to describe the device, its intended use, and the directions for its use (21 CFR 807.87(e)). (Please refer to **Section 13.Labeling** for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

## Summary report

We recommend that the summary report contain a:

### Description of the device and its intended use

We recommend that you describe the performance specifications and, when appropriate, include detailed, labeled drawings of the device. (Please refer to **Section 6. Device Description** for specific information that we recommend you include in the device description for devices of the type covered by this guidance document.) You should also submit an “indications for use” enclosure.<sup>4</sup>

### Description of device design requirements

We recommend that you include a brief description of the device design requirements.

### Identification of the risk analysis method

We recommend that you identify the risk analysis method(s) you used to assess the risk profile, in general, as well as the specific device’s design and the results of this analysis. (Please refer to **Section 5.Risks to Health** for the risks to health generally associated with the use of this device that FDA has identified.)

### Discussion of the device characteristics

We recommend that you discuss the device characteristics that address the risks identified in this class II special controls guidance document, as well as any additional risks identified in your risk analysis.

## Description of the performance aspects

We recommend that you include a brief description of the test method(s) you have used or intend to use to address each performance aspect identified in **Sections 6-12** of this class II special controls guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.<sup>5</sup> (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

## Reliance on standards

If any part of the device design or testing relies on a recognized standard, we recommend that you include either:

- a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed or
- a declaration of conformity to the standard.<sup>6</sup>

Because a declaration of conformity is based on results from testing, you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, refer to the FDA guidance document, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA** ([/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm](https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm)).

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(I), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering certain modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a 510(k) submission for a tissue adhesive for the topical approximation of skin.

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## **4. Scope**

The scope of this guidance document is limited to tissue adhesives for the topical approximation of skin as described below in proposed 21 CFR 878.4010(a). The product code associated with this device is MPN (tissue adhesive for the topical approximation of skin).

### **Section 878.4010 Tissue adhesive.**

#### *(a) Tissue adhesive for the topical approximation of skin —*

(1) *Identification.* A tissue adhesive for the topical approximation of skin is a device intended for topical closure of surgical incisions, including laparoscopic incisions, and simple traumatic lacerations that have easily approximated skin edges. Tissue adhesives for the topical approximation of skin may be used in conjunction with, but not in place of, deep dermal stitches.

(2) *Classification.* Class II (special controls). The special control for this device is FDA's "Class II Special Controls Guidance Document: Tissue Adhesive for the Topical Approximation of Skin." See § 878.1(e) for the availability of this guidance document.

#### *(b) Tissue adhesive for non-topical use —*

(1) *Identification.* A tissue adhesive for non-topical use, including adhesives intended for use in the embolization of brain arteriovenous malformation or for use in ophthalmic surgery, is a device used for adhesion of internal tissues and vessels, and does not include the use described in paragraph (a) of this section .

(2) *Classification.* Class III (premarket approval). As of May 28, 1976, an approval under section 515 of the act is required before this device may be commercially distributed. See § 878.3.

Tissue adhesives for non-topical use include tissue adhesive for use in embolization of brain arteriovenous malformation (product code KGG) and tissue adhesive for ophthalmic use (product code LZQ) remain in class III and continue to require premarket approval. Non-adhesive agents, including injectable embolic agent, (product code MFE) are not within the scope of this guidance and continue to require premarket approval. This guidance also does not address liquid bandage devices, which are used to cover openings in the skin, as a dressing for burns, or as topical skin protectants (product codes KMF and NEC) classified in 21 CFR 880.5090. For information

regarding these devices, please contact the Plastic and Reconstructive Surgery Devices Branch of the Division of General, Restorative and Neurological Devices. This guidance also does not address tissue adhesives used as a dental cement. These devices are classified under 21 CFR 872.3275, product code EMA.

Devices used as an adjunct to standard methods of achieving hemostasis in open surgical repair of large vessels such as the aorta, femoral and carotid arteries (product code MUQ), are also not within the scope of this guidance and continue to require premarket approval. For information regarding these devices, please contact the Peripheral Vascular Devices Branch of the Division of Cardiovascular Devices at 240-276-4141.

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## 5. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the tissue adhesive for the topical approximation of skin device addressed in this guidance document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you also conduct a risk analysis, before submitting your 510(k), to identify any other risks specific to your device and include the results of this analysis in your 510(k). If you elect to use an alternative approach to address a particular risk identified in this guidance document, or have identified risks additional to those in this guidance document, then you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Unintentional Bonding or Product Leaks into Eyes	Section 7. Bench Testing Section 13. Labeling
Wound Dehiscence	Section 7. Bench Testing Section 8. Shelf Life Testing Section 10. Animal Testing Section 13. Labeling
Adverse Tissue Reaction and Chemical Burns	Section 9. Biocompatibility Section 10. Animal Testing
Infection	Section 7. Bench Testing Section 12. Sterility



Applicator Malfunction	Section 7. Bench Testing
Delayed Polymerization	Section 7. Bench Testing Section 10. Animal Testing

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## 6. Device Description

FDA recommends that you identify your device by the regulation and product code described in **section 4. Scope** and include the information discussed below.

Tissue adhesives 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. Various formulations can be manufactured that vary in viscosity, setting time, bond strength, degradation rate, and other physical and mechanical properties. Because these properties define the adhesive performance and utility of the final product, your description should discuss the molecular composition and structure of your compound. Products that include biological or drug components are generally considered by the agency to be combination products. For advice about the appropriate regulatory pathway, please contact the Office of Combination Products at 301-427-1934.<sup>7</sup>

FDA recommends that you identify all materials used to comprise the finished device. FDA recommends that you provide a Certificate of Analysis or a Material Safety Data Sheet for each chemical included in the device.

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### a. Chemistry

We recommend that you provide the following information for chemicals included in your device:

- chemical name
- chemical abstracts service number
- trade name
- structural formula
- molecular formula and molecular weight
- source and purity.

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**b. Material Characteristics of the Adhesive**

We recommend you provide the following information about the device, including your test methods:

- viscosity determination<sup>8</sup><sub>....</sub>
- analysis of residual content of the components of bulk formation by, for example, gas chromatography, nuclear magnetic resonance, or mass spectrometry
- purity
- moisture determination
- setting time determination<sup>9</sup><sub>....</sub>
- physical and mechanical testing (see 7. Bench Testing)
- shelf life determination (see 8. Shelf Life Testing)
- sterility (see 12. Sterility).

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**7. Bench Testing****a. Adhesive Strength**

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 approximation. We recommend that you evaluate the following key adhesive properties of the polymerized adhesive in accordance with appropriate testing on your device:

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

The following four test methods 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. These or equivalent methods may be used in support of the bench testing outlined above:

- 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

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## b. Degradation Rate

Degradation rate is an indicator of the possible toxicity of an adhesive material. The hydrolytic degradation of an adhesive material, such as cyanoacrylate, to smaller oligomers involves a hydrolysis reaction and release of formaldehyde. In the case of cyanoacrylate adhesives, formaldehyde as a by-product of hydrolytic degradation and the resultant cytotoxic or histotoxic effects have been reported and documented in research and medical journals. 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.<sup>10</sup>

Accordingly, FDA recommends that you provide hydrolytic degradation study data to identify the amount of any by-products of material decomposition. 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, and
- 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 the parts per million (ppm) levels.

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## c. Heat of Polymerization Study

Polymerization of an adhesive material, such as cyanoacrylate, is generally 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.

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#### **d. Other Mechanical Testing**

Your submission should include additional mechanical testing of the applicator functionality appropriate to the design of your applicator and its components.

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## **8. Shelf Life Testing**

We recommend that you conduct shelf life testing to support the expiration date in the labeling of your device. Stability studies should monitor the critical parameters of your final finished device to assure adequate device performance during its entire shelf-life.<sup>11</sup> We recommend that your testing include parameters such as the:

- purity of the materials,
- water content,
- setting time (in seconds),
- viscosity (in centipoises (cps)),
- color, and
- sterility.

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 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 you discuss 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 one year or more.

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## 9. Biocompatibility

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. You should monitor systemic toxicity, as well as local effects at the application site. You should also assess macroscopic pathology and histopathology.<sup>12</sup>

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## 10. Animal Testing

In addition to the biocompatibility testing described above, we recommend that you provide additional animal testing of your topical tissue adhesive to address the issues discussed below.

Inflammation and the replacement of soft tissue with fibrous tissue are expected outcomes of the normal healing process. Therefore, FDA recommends you conduct animal studies to evaluate the potential for delayed healing using histopathology. We also recommend your animal studies demonstrate that the fumes given off by the product itself and fumes that arise during polymerization will not cause chemical burns.

FDA recommends you assess the performance characteristics of the device in the appropriate animal model(s). 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 employed in clinical use. You should compare the amount of the product used in the animal study to the amount given in your instructions for use. You should also provide a brief discussion of the rationale for and the limitations of the animal model used.

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## 11. Clinical Studies

In accordance with the act, FDA will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies will not be needed for most tissue adhesive for the topical approximation of skin devices, FDA may recommend that you collect clinical data for a tissue adhesive for the topical approximation of skin with:

- material formulations dissimilar from designs or material formulations used in legally marketed tissue adhesives for the topical approximation of skin;
- new technology, i.e., technology different from that used in legally marketed tissue adhesives for the topical approximation of skin; or
- indications for use dissimilar from a legally marketed tissue adhesive for the topical approximation of skin.

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. The Plastic and Reconstructive Surgery Devices Branch is available to discuss any questions about clinical testing before you initiate your studies. If a clinical study is needed to demonstrate substantial equivalence (i.e., conducted prior to obtaining 510(k) clearance of the device), the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA believes that this device is a significant risk device as defined in 21 CFR 812.3(m).<sup>13</sup> In addition to the requirement of having a 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).

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## 12. Sterility

FDA recommends that you provide sterilization information in accordance with the **Updated 510(k) Sterility Review Guidance K90-1**<sup>14</sup>. The device should be sterile with a sterility assurance level (SAL) of  $1 \times 10^{-6}$ .

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## 13. Labeling

The 510(k) must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e).<sup>15</sup>

## Prescription Use

As a prescription device under 21 CFR 801.109, this device must bear the following caution statement: "Caution: Federal law restricts this device to sale by or on the order of a physician."

## Instructions for Use

We recommend that you include the following information in your instructions for use:

- adequate information on contraindications, warnings, and precautions to address the identified risks to health
- a clear explanation of the device's technological features and how it is to be used on patients.
- labeling instructions to mitigate the risks to health shown in **Section 5** of this document.

We recommend that you provide detailed instructions for wound preparation and device application. The instructions should also describe techniques for tissue separation and device removal in the event of inadvertent bonding.

## Warnings

The labeling should also include warnings that address the use of the device near the eye. For example:

When closing facial wounds near the eye with a tissue adhesive for topical approximation of skin, 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 or dam, can be effective at preventing inadvertent flow of adhesive into the eye. Use of 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 intervention has been needed to open the eyelid.

## Precautions

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

Tissue adhesives for the topical approximation of skin should not be used:

- in the presence of infection

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

Tissue adhesives for the topical approximation of skin should also 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.

In addition, the labeling should address potential interference with adherence to skin, for example:

The tissue adhesive will not adhere to skin pre-coated with petroleum jelly. Therefore, avoid using petroleum jelly on any skin area where tissue adhesive is intended to adhere.

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<sup>1</sup> See, **Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s**  
**(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm)**

<sup>2</sup> See, **Device Advice: Premarket Notification 510(k)**  
**(/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm)**

<sup>3</sup> See, **The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance**  
**(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm)**

<sup>4</sup> Refer to **Indications for Use form**  
**(http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm360431.pdf)**  
(PDF File Size: 1.03MB) for the recommended format.



<sup>5</sup> If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

<sup>6</sup> See, **Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions)** ([/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142706.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142706.htm)), .

<sup>7</sup> **Office of Combination Products** (<http://www.fda.gov/CombinationProducts/default.htm>)

<sup>8</sup> 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 a 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 will be 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.

<sup>9</sup> 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 needed 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 regarding application of the product are based on setting time.

<sup>10</sup> Quinn, J.V., Tissue Adhesives in Clinical Medicine, BC Decker Inc., 2 nd ed. 2005.

<sup>11</sup> After you qualify the package configuration, we recommend you assess the initial integrity of your final finished package and its ability to maintain that integrity. You should document the assessment in your design history file (see 21 CFR 820.30).

<sup>12</sup> See, **Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices May 1, 1995 (G95-1)** ([ssLINK/ucm080735.htm](http://www.fda.gov/oc/ohrt/irbs/devices.html#risk)).

<sup>13</sup> See Significant Risk and Nonsignificant Risk Medical Device Studies, <http://www.fda.gov/oc/ohrt/irbs/devices.html#risk>.

<sup>14</sup> See, **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA** ([/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072783.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072783.htm))

<sup>15</sup> Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance document are consistent with the requirements of part 801.

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**[Office of Compliance Final Guidance](#)**  
**[\(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070269.htm\)](#)**

**[Office of the Center Director Final Guidance](#)**  
**[\(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110228.htm\)](#)**

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**[Office of Device Evaluation Final Guidance 2010 - 2016](#)**  
**[\(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm198577.htm\)](#)**

**[Office of Device Evaluation Final Guidance 1998 - 2009](#)**  
**[\(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070272.htm\)](#)**

**[Office of Device Evaluation Final Guidance 1976 - 1997](#)**  
**[\(/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080283.htm\)](#)**

**[Office of In Vitro Diagnostics and Radiological Health Final Guidance](#)**  
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**[Office of Surveillance and Biometrics Final Guidance](#)**  
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**[Office of Science and Engineering Laboratories Final Guidance](#)**  
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**[Draft Guidance](#)**  
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**Radiation-Emitting Products Guidance**

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**Withdrawn Guidance**

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