Guidance for Industry and FDA Staff
Class II Special Controls Guidance Document: Tissue Adhesive with Adjunct Wound Closure Device Intended for the Topical Approximation of Skin

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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. 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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Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Tissue Adhesive with Adjunct Wound Closure Device Intended for the Topical Approximation of Skin

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 was developed as a special control to support the classification of the tissue adhesive with adjunct wound closure device intended 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. The device may be used in conjunction with, but not in place of deep dermal stitches. This guidance document does not apply to tissue adhesives for non-topical uses. This guidance document is issued in conjunction with a Federal Register notice announcing the classification of tissue adhesive with adjunct wound closure device intended for the topical approximation of skin.

Following the effective date of a final rule classifying the device, any firm submitting a premarket notification (510(k)) for a tissue adhesive with adjunct wound closure device intended for the topical approximation of skin will need to address the issues covered in this special controls guidance document. However, the firm need only show that its device meets the recommendations of the guidance document or in some other way provides equivalent assurances of safety and effectiveness.

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 with adjunct wound closure device intended 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 with adjunct wound closure device intended for the topical approximation of skin identified in this guidance, 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 adhesives with adjunct wound closure device (Please refer to **Section IV. Scope)**. In addition, other sections of this special controls guidance 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 these tissue adhesives with adjunct wound closure devices and lead to a timely 510(k) review and clearance. This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87, **Format for Traditional and Abbreviated 510(k)s**[1] and the section of CDRH's Device Advice, **How to Prepare a 510(k) Submission.**[2]

3. Scope

The scope of this guidance document is limited to the following class II device type: tissue adhesives with adjunct wound closure device intended for the topical approximation of skin. The product code associated with this device type is OMD, tissue adhesive with adjunct wound closure device intended for the topical approximation of skin. This device is classified into Class II by 21 CFR 878.4011.

Section 878.4011 Tissue adhesive with adjunct wound closure device intended for the topical approximation of skin

(1) Identification. A tissue adhesive with adjunct wound closure device intended for the topical approximation of skin is a device indicated for topical application only to hold closed easily approximated skin edges of wounds from surgical incisions, including punctures from minimally invasive surgery, and simple, thoroughly cleansed, trauma-induced lacerations. It may be used in conjunction with, but not in place of, deep dermal stitches. Additionally, the adjunct wound closure device component maintains temporary skin edge alignment along the length of wound during application of the liquid adhesive.

(2)Classification. Class II (special controls). The special control for this device is FDA's "Class II Special Controls Guidance Document: Tissue Adhesive with Adjunct Wound

[1] Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)'s (Aug. 2005), available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084396.pdf

[2] How to Prepare a 510(k) Submission: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm

Closure Device Intended for the Topical Approximation of Skin." See § 878.1(e) for the availability of this guidance document.

This classification for **Section 878.4011 Tissue adhesive with adjunct wound closure device intended for the topical approximation of skin** is a separate classification from the classification for Tissue Adhesives in 21 CFR 878.4010 which include tissue adhesive for the topical approximation of skin and tissue adhesive for nontopical use. Please note: the scope of this guidance is limited to the identification given above. The following devices, for example, are not within the scope of this guidance and continue to require premarket approval: 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), devices used as dural sealants (product code NQR), and devices used as tissue adhesives for opthalmic use (product code LZQ).

4. Device Description

FDA recommends that you identify your device by the regulation and product code described in **Section 3., 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.

The adjunct wound closure device component may be manufactured from various materials. Therefore a description of the composition and structure of the adjunct wound closure device component should also be provided, together with a description of how this component interacts with the tissue adhesive to produce the final polymerized device.

Products that include biological or drug components in addition to device components are generally considered by the agency to be combination products. For advice about the appropriate regulatory pathway for such products, please contact the Office of Combination Products at 301-427-1934.[3]

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.

a. Chemistry

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

- chemical name

[3] Office of Combination Products, http://www.fda.gov/CombinationProducts/default.htm

- chemical abstracts service number
- trade name
- structural formula
- molecular formula and molecular weight
- source and purity
- chemical identity and purity of polymerization initiator
- chemical identity and purity of product stabilizer
- description of the chemistry used for device polymerization
- regulatory status of each device component (i.e., have they been previously cleared or approved)

b. Material Characteristics of the Adhesive

We recommend you provide the following information about the Adhesive:

- viscosity
- analysis of residual content of the components of bulk formation by, for example, gas chromatography, nuclear magnetic resonance, or mass spectrometry
- Purity
- Moisture
- setting time
- Pyrogenicity and sterility (see 11. Sterility)

c. Material Characteristics of the Adjunct Wound Closure Device Intended for the Topical Approximation of Skin

We recommend you provide the following information about the Adjunct Wound Closure Device:

- Appearance
- material description (i.e., chemical composition and method of component manufacture)
- dimensions (including pore size if appropriate)
- component contamination
- construction
- pyrogenicity and sterility (see 11. Sterility)
- Regulatory status (i.e., whether the skin adjunct wound closure device component has been previously cleared or approved)

5. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the tissue adhesive with adjunct wound closure device intended 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 justification to support the approach you have used to address that risk.

Identified risk	**Recommended mitigation measures**
Unintentional bonding of device due to misapplication of device, device leaking or running to unintended areas, etc.	Section 6. Bench Testing Section 12. Labeling
Wound dehiscence	Section 6. Bench Testing Section 7. Shelf Life Testing Section 9. Animal Testing Section 10. Clinical Studies Section 12. Labeling
Adverse tissue reaction and chemical burns	Section 8. Biocompatibility Section 9. Animal Testing Section 10. Clinical Studies
Infection	Section 6. Bench Testing Section 8. Biocompatibility Section 9. Animal Testing Section 10. Clinical Studies Section 11. Sterility
Applicator malfunction	Section 6. Bench Testing
Weak bonding leading to loss of approximation	Section 6. Bench Testing Section 9. Animal Testing Section 10. Clinical Studies
Delayed polymerization	Section 6. Bench Testing Section 9. Animal Testing

6. Bench Testing

a. Strength of the Skin Adjunct Wound Closure Device Component

FDA recommends that you conduct mechanical testing to evaluate the ability of the skin edge alignment component to provide enough tensile strength and bond strength to the skin to maintain skin edge alignment until application of the tissue adhesive. We recommend that you evaluate the following key properties in accordance with appropriate testing on your device:

- Peel testing
- Creep testing

- Tensile testing

The following three test methods are intended to provide a means for comparison of the strength of the skin alignment aid. These or equivalent methods may be used in support of the bench testing outlined above:

- ASTM D3330 / D3330M – 04 Standard Test Method for Peel Adhesion of Pressure-Sensitive Tape
- ASTM D3654 / D3654M – 06 Standard Test Methods for Shear Adhesion of Pressure-Sensitive Tapes
- ASTM D882 – 09 Standard Test Method for Tensile Properties of Thin Plastic Sheeting

b. Adhesive Strength of the Final Polymerized Device

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

c. 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.[4]

Accordingly, FDA recommends that you provide hydrolytic degradation study data to identify the amount of any by-products of material decomposition for the polymerized device including the skin adjunct wound closure device component. 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.

d. 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.

e. Other Testing

Your submission should include additional mechanical testing of the applicator functionality appropriate to the design of each applicator and its components, as well as the following tests:

- Viscosity: 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 bone formed with underlying tissue. Also, if viscosity is too great, then it will be difficult to express the adhesive through an 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

[4] Quinn, J.V., Tissue Adhesives in Clinical Medicine, BC Decker Inc., 2nd ed. 2005.

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.

7. 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.[5] 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,
- Sterility
- Force to express the device from the delivery applicator
- Applicator functionality

We recommend that you perform real time stability testing on representative aged samples at time zero and at several intervals during the 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 is only approriate if it is 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.

[5] 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).

8. Biocompatibility

FDA recommends that you conduct biocompatibility testing according to the requirements of ISO 10993-1:2003 and FDA Memorandum G95-1 for a prolonged contact duration (24 hours – 30 days) device in contact with breached or compromised surfaces with blood contact.[6] As a note, the subchronic implantation study duration should mimic the proposed use of the final polymerized device. 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.

Because accurate analyses of rapidly decomposing chemicals (e.g., cyanocrylate monomer, polymerization inhibitor, etc) can be difficult, please include as part of the biocompatibility discussion, information from the published toxicology literature describing the known local (i.e., topical administration) and systemic adverse reactions known to be associated with each device component. Such information should also discuss the component concentration known to elicit a toxic reaction and the corresponding concentration delivered directly to a patient's skin.

9. Animal Testing

In addition to biocompatibility testing, we recommend that you provide additional animal testing of your product 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 and wound dehiscence, including histopathology as appropriate.

FDA also recommends you assess the performance characteristics of the device in an appropriate animal model(s). FDA generally recommends a porcine model; however, other models may be more appropriate for your device depending on product composition or intended use. 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.

The conduct of preclinical animal studies should follow modern practices of humane care and use (please refer to **Appendix A**), including thorough veterinary medical record-keeping at all stages of the study, appropriate training of personnel, and adequate controls for the minimization of infections, pain and distress, and other experimental confounders. Standard operating procedures consistent with refinements, reductions, and where appropriate validated models exist, replacement, should also be implemented.[7] FDA also requires that

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6 https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.pdf

7 ANSI/AAMI/ISO 10993-2:2006;Biological evaluation of medical devices—Part 2: Animal welfare requirements

animal studies to support marketing and research applications must be conducted in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR Part 58).

10. Clinical Studies

FDA may recommend that you collect clinical data for a tissue adhesive with adjunct wound closure device intended for the topical approximation of skin in cases where:

- The material formulations are dissimilar from designs or material formulations used in legally marketed predicate devices such as tissue adhesives with adjunct wound closure device intended for the topical approximation of skin;
- There is new technology, i.e., technology different from that used in legally marketed predicate devices such as tissue adhesives with adjunct wound closure device intended for the topical approximation of skin; or
- The indications for use are dissimilar from a legally marketed predicate devices such as tissue adhesives with adjunct wound closure device intended 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).[8]

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).

11. Sterility

FDA recommends that you provide sterilization information in accordance with the **Updated 510(k) Sterility Review Guidance K90-1**.[9] The device should be sterile with a sterility

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Russell, W.M.S. and Burch, R.L., The Principles of Humane Experimental Technique. Methuen, London, 1959. Reprinted by UFAW, 1992: 8 Hamilton Close, South Mimms, Potters Bar, Herts EN6 3QD England. ISBN 0 900767 78 2

8 http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm

9 https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM109897.pdf

assurance level (SAL) of 1 x 10^{-6}.

12. 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).[10]

Prescription Use
As a prescription device, under 21 CFR 801.109, this device is exempt from having adequate directions for lay use. Labeling must include, however, adequate information for practitioner use of the device. The label of the device must bear the following 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; and
- 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 include warnings that address the use of the device near sensitive areas that could be injured or irritated by unintended bonding of the device, such as the eye.

For example:

"When closing facial wounds near the eye with a tissue adhesive with adjunct wound closure device intended 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 with adjunct wound closure device near the eye can inadvertently cause some patient's eyelids to be sealed shut. In some of these cases, general anesthesia and surgical intervention have been needed to open the eyelid."

[10] 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.

Precautions

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

"Tissue adhesives with adjunct wound closure device intended 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; and
- on mucosal or hair covered surfaces.

"Tissue adhesives with adjunct wound closure device intended for the topical approximation of skin should also not be used on wounds that are:

- wet;
- dirty;
- complex;
- not easily approximated;
- under dynamic stress (e.g., knuckles or elbows);
- non-acute;
- poorly perfused; or
- 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."

Appendix A

As stated in Section 9, the conduct of preclinical animal studies should follow modern practices of humane care and use. All animal studies should be designed based on the modern practices described in the following references.

1. Animal Welfare Act, Code of Federal Regulations, Title 9 Volume 1, 7 USC 2131-2156
    - Definitions: http://www.access.gpo.gov/nara/cfr/waisidx_03/9cfr1_03.html
    - Regulations: http://www.access.gpo.gov/nara/cfr/waisidx_03/9cfr2_03.html
    - Standards: http://www.access.gpo.gov/nara/cfr/waisidx_03/9cfr3_03.html
    - Applicable Policies: http://www.aphis.usda.gov/animal_welfare/policy.shtml

2. Public Health Service Policy on Humane Care and Use of Laboratory Animals, Office of Protection from Research Risks, NIH, Bethesda, MD, 1996: http://grants.nih.gov/grants/olaw/references/phspol.htm

3. Public Law 99-158 "Animals in Research" Health Research Extension Act of 1985 November 20, 1985. http://grants.nih.gov/grants/olaw/references/phspol.htm#Health%20Research%20Extension%20Act%20of%201985.

4. US Government Principles for the Utilization of and Care of Vertebrate Animals Used in Testing, Research, and Training. http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples.

5. Guide for the Care and Use of Laboratory Animals. National Research Council, Institute of Laboratory Animal Resources Commission on Life Sciences 1996. National Academies of Science Press, Washington, DC. http://www.nap.edu/openbook.php?record_id=5140&page=8