

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 878

[Docket No. 2006P-0071]

General and Plastic Surgery Devices; Reclassification of the Tissue

Adhesive for Topical Approximation of Skin Device

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify the device, tissue adhesive for the topical approximation of skin, from class III (premarket approval) into class II (special controls). Tissue adhesives for non-topical uses would remain in class III and continue to require premarket approval applications (PMAs). FDA is proposing this reclassification in accordance with the Federal Food, Drug, and Cosmetic Act (the act). Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a draft guidance document that would serve as the special control if FDA reclassifies this device.

DATES: Submit written comments by *[insert date 60 days after publication]*.

See section IX of this document for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: You may submit comments, identified by Docket No. 2006P-0071, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

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2006P-0071

NPR /

DDM

Display Date 7-2-07
Publication Date 7-3-07
Certifier D. Hawkins

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]:
Division of Dockets Management (HFA–305), Food and Drug Administration,
5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the Electronic Submissions portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No. for this rulemaking. All comments received may be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For additional information on submitting comments, see the “Comments” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number(s), found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: George J. Mattamal, Center for Devices and Radiological Health (HFZ-410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 240-276-3619.

SUPPLEMENTARY INFORMATION:

I. Regulatory Authorities

The act, as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94-295), the Safe Medical Devices Act of 1990 (SMDA) (Public Law 101-629), and the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115), among other amendments, established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

The 1976 amendments broadened the definition of “device” in section 201(h) of the act (21 U.S.C. 321(h)) to include certain articles that were once regulated as drugs. Under the 1976 amendments, Congress classified all transitional devices, i.e., those devices previously regulated as new drugs, into class III. SMDA amended section 520(l) of the act (21 U.S.C. 360j(l)) to direct FDA to collect certain safety and effectiveness information from the manufacturers of transitional devices still remaining in class III to determine whether the devices should be reclassified into class II (special controls) or class I (general controls). The legislative history of the SMDA reflects congressional concern that many transitional devices were being overregulated

in class III (H. Rept. 808, 101st Cong., 2d sess. 26–27 (1990); S. Rept. 513, 101st Cong., 2d sess. 27 (1990)).

Accordingly, in the **Federal Register** of November 14, 1991 (56 FR 57960), FDA issued an order under section 520(l)(5)(A) of the act, requiring manufacturers of transitional devices, which included tissue adhesives for use in general surgery (47 FR 2810, January 19, 1982), to submit to FDA a summary of and a citation to any information known or otherwise available to them respecting the devices, including adverse safety or effectiveness information, that had not been submitted under section 519 of the act (21 U.S.C. 360i).

Manufacturers were to submit the summaries and citations to FDA by January 13, 1992. However, because of misunderstandings and uncertainties regarding the information required by the order, and regarding whether the order applied to certain manufacturers' devices, many transitional class III device manufacturers failed to comply with the reporting requirement by January 13, 1992. Consequently, in the **Federal Register** of March 10, 1992 (57 FR 8462), FDA extended the reporting period to March 31, 1992.

Section 520(l)(5)(B) of the act provides that, after the issuance of an order requiring manufacturers to submit any information known or otherwise available respecting the devices, but before December 1, 1992, FDA was to publish regulations either leaving transitional class III devices in class III or reclassifying them into class I or II.

Subsequently, as permitted by section 520(l)(5)(C) of the act, in the **Federal Register** of November 30, 1992 (57 FR 56586), the agency published a notice extending the period for issuing such regulations until December 1, 1993. Due to limited resources, FDA was unable to publish the regulations before the December 1, 1993, deadline.

II. Regulatory Background of the Device

Transitional devices, those devices formerly regulated as drugs, were classified into class III by the statute and premarket approval was immediately required (section 520(l) of the act). The **Federal Register** of December 16, 1977 (42 FR 63472), listed transitional devices and stated the following: “The lists contained in this notice may not be an exhaustive inventory of products subject to section 520(l) of the act.” This notice did not specifically list “Tissue Adhesives.” The investigational new drug (IND) and new drug applications (NDAs) for products classified as transitional devices were shortly thereafter transferred to FDA’s Center for Devices and Radiological Health (formerly the Bureau of Medical Devices). Applications for tissue adhesives were included in this list of products transferred. (FDA did list “injectable silicone” as a transitional device in the **Federal Register** of December 16, 1977. In the January 19, 1982, **Federal Register** notice (47 FR 2810) “tissue adhesive for use in general surgery,” was included as a transitional device under “injectable silicone.” This was a typographical error as “tissue adhesives” are not a subcategory of “injectable silicone.”) Since enactment of the 1976 amendments, FDA has approved several premarket approval (PMA) applications and PMA supplements authorizing the commercial distribution of tissue adhesives in the United States.

III. Description of the Device

FDA has referred to this device, under review for reclassification, in previous notices as “tissue adhesive for use in general surgery;” however, FDA is proposing in this notice to revise the name and identification to more accurately identify the device. Under the proposal, the device proposed for reclassification into class II, would be: Tissue adhesives for the topical

approximation of skin. Tissue adhesives for the topical approximation of skin devices, which may contain cyanoacrylate as the active ingredient, are 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.

FDA is also proposing the following identification for the devices that will remain in class III: A tissue adhesive for non-topical use, including adhesives intended for use in the embolization of brain arteriovenous malformation or ophthalmic surgery, is a device used for adhesion of internal tissues and vessels.

IV. Recommendation of the Panel

On February 9, 2006, Regulatory & Clinical Research Institute, Inc. (RCRI), Minneapolis MN, submitted a petition (Docket No. 2006P-0071) to FDA to reclassify tissue adhesive for soft tissue approximation from “Class III to Class II (special controls)” (Ref. 1). On May 15, 2006, the petitioner amended its petition to include several references from the scientific literature cited in the original petition (Ref. 2). On July 18, 2006, the petitioner again amended its petition to clarify that the use it was proposing for reclassification was only the topical approximation of skin (Ref. 3).

In response to the petition, FDA consulted with the FDA’s General and Plastic Surgery Devices Panel (the Panel), regarding reclassification of this device. The Panel discussed the device at an August 25, 2006, public meeting and unanimously recommended that the tissue adhesive for the topical approximation of skin be reclassified from class III into class II. The Panel also recommended that a class II guidance document, which the Panel thought

should include several voluntary consensus standards, be the special control for the device. The Panel based the recommendations on the information provided by FDA; the presentations to the panel by the petitioner, other manufacturers, and FDA; the Panel's deliberations at the meeting; and the Panel's personal experience with the use of devices for the topical approximation of skin. The Panel did not consider the reclassification of any other use of tissue adhesives.

V. Risks to Health

After considering the information in the petition, the information presented at the Panel meeting, the Panel's recommendation, and Medical Device Reports, FDA has evaluated the risks to health associated with use of the tissue adhesive for the topical approximation of skin and determined that the following risks to health are associated with its use.

A. Unintentional bonding or product leaks into eyes

Without adequate protection of the patient's eye, the adhesive may inadvertently leak onto the eyelids when tissue adhesive is used on the skin near the patient's eye, for example on the brow or forehead. If this occurs, this can lead to sealing the eyelids shut and can require surgical intervention to remove the adhesive and any bound skin.

B. Wound Dehiscence

Wound dehiscence, the subsequent separation of the edges of the wound, i.e., incision or laceration, during recovery is a risk of all surgical procedures and treatments of traumatic wounds. Complications can arise as a result of wound dehiscence, which include re-sealing the wound and surgical revision of the wound with adhesive or sutures. These complications have the potential to delay the patient's recovery.

C. Adverse Tissue Reaction and Chemical Burns

Tissue adhesive may be associated with adverse tissue reactions, including allergy, inflammation, foreign body reactions, erythema (redness), granuloma, and the exacerbation of asthma. In addition, fumes given off by the adhesive before or during polymerization can cause chemical burns.

D. Infection

Infection of the skin or soft tissue is a risk to health associated with all surgical procedures and wound treatment. If the tissue adhesive is not properly sterilized, it may contribute to an increased risk of infection.

E. Applicator Malfunction

Inadequate packaging of the device or user error when opening the packaging can result in damage to the applicator and subsequent malfunction. If an applicator malfunctions, surgery may be extended, resulting in additional time under anesthesia, or treatment may be delayed. In addition, if the adhesive is packaged in a glass container, lacerations to the user or the patient may result if the glass breaks.

F. Delayed Polymerization

Polymerization of the adhesive may be delayed, resulting in compromise of the wound, additional time under anesthesia, or delayed treatment.

VI. Summary of the Reasons for the Reclassification

FDA believes that the tissue adhesive for the topical approximation of skin device should be reclassified into class II because special controls, in addition to general controls, would provide reasonable assurance of the safety and effectiveness of the device. FDA believes there is sufficient information to establish special controls to provide such assurance. In addition to the

potential risks to health associated with use of the tissue adhesive for the topical skin approximation device described in section V of this document, there is reasonable knowledge of the benefits of the device. Specifically, the tissue adhesive for the topical approximation of skin may prevent extended bleeding in the repair of surgical incisions and traumatic lacerations, promote healing of approximated wound edges, and reduce pain and recovery time.

VII. Special Controls

In addition to general controls, FDA believes that the draft guidance document entitled “Class II Special Controls Guidance Document: Tissue Adhesive for the Topical Approximation of Skin” (the class II special controls guidance document) is a special control adequate to address the risks to health associated with the use of the device described in section V of this document. FDA believes that the class II special controls guidance document, which incorporates voluntary consensus standards and describes labeling recommendations, in addition to general controls, provides reasonable assurance of the safety and effectiveness of the device. Elsewhere in this issue of the **Federal Register**, FDA is publishing a notice of availability of the draft class II special controls guidance document that the agency would use as the special control for this device.

The draft class II special controls guidance document sets forth the information FDA believes should be included in premarket notification submissions (510(k)s) for the tissue adhesive for the topical approximation of skin. FDA has identified the risks to health associated with the use of the device in the first column of table 1 of this document and the recommended mitigation measures identified in the class II special controls guidance document in the second column of table 1. FDA believes that addressing these

risks to health in a 510(k) in the manner identified in the class II special controls guidance document, or in an acceptable alternative manner, is necessary to provide reasonable assurance of the safety and effectiveness of the device.

TABLE 1.

Identified risk	Recommended mitigation measures
Unintentional Bonding or Product Leaks into Eyes	Bench Testing Labeling
Wound Dehiscence	Bench Testing Shelf-Life Testing Animal Testing Labeling
Adverse Tissue Reaction and Chemical Burns	Biocompatibility Animal Testing
Infection	Bench Testing Sterility
Applicator Malfunction	Bench Testing
Delayed Polymerization	Bench Testing Animal Testing

VIII. FDA's Findings

As discussed previously in this document, FDA believes the tissue adhesive for the topical approximation of skin should be reclassified into class II because special controls, in addition to general controls, provide reasonable assurance of the safety and effectiveness of the device and because there is sufficient information to establish special controls to provide such assurance. FDA, therefore, is proposing to reclassify the device into class II and establish the draft class II special controls guidance document as a special control for the device. Tissue adhesives for non-topical use will remain in class III and continue to require PMAs.

Section 510(m) of the act (21 U.S.C. 360) provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the act, if the agency determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this device, FDA believes that premarket notification is

necessary to provide reasonable assurance of safety and effectiveness and, therefore, does not intend to exempt the device from the premarket notification requirements.

IX. Effective Date

FDA proposes that any final regulation based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

X. Environmental Impact

The agency has determined under 21 CFR 25.34(b) that this proposed reclassification action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–602), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4)). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Reclassification of this device when it is used for the topical approximation of skin, from class III to class II, will relieve manufacturers of the device of the cost of complying with the premarket approval requirements in section 515 of the act (21 U.S.C. 360e). Because reclassification will reduce regulatory costs

with respect to this device, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

XII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency tentatively concludes that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement has not been prepared.

XIII. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no new collections of information. Therefore, clearance by the Office of Management

and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520) is not required.

This proposed rule designates a guidance document as a special control. FDA also tentatively concludes that the draft special control guidance document does not contain new information collection provisions that are subject to review and clearance by OMB under the PRA. Elsewhere in this issue of the **Federal Register**, FDA is publishing a notice announcing the availability of that draft guidance document entitled “Class II Special Controls Guidance Document: Tissue Adhesive for the Topical Approximation of Skin,” which contains an analysis of the paperwork burden for the draft guidance.

XIV. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XV. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Regulatory & Clinical Research Institute, Inc. (RCRI), reclassification petition, Docket No. 2006P–0071, Minneapolis MN, February 9, 2006.

2. Regulatory & Clinical Research Institute, Inc., reclassification petition, Docket No. 2006P–0071, Minneapolis MN, May 15, 2006.

3. Regulatory & Clinical Research Institute, Inc., reclassification petition, Docket No. 2006P-0071, Minneapolis MN, July 18, 2006.

4. General and Plastic Surgery Devices Panel, Transcript, pp. 199 to 207, August 25, 2006.

List of Subjects in 21 CFR Part 878

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 878 be amended as follows:

PART 878—GENERAL AND PLASTIC SURGERY DEVICES

1. The authority citation for 21 CFR part 878 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Section 878.4010 is added to subpart E to read as follows:

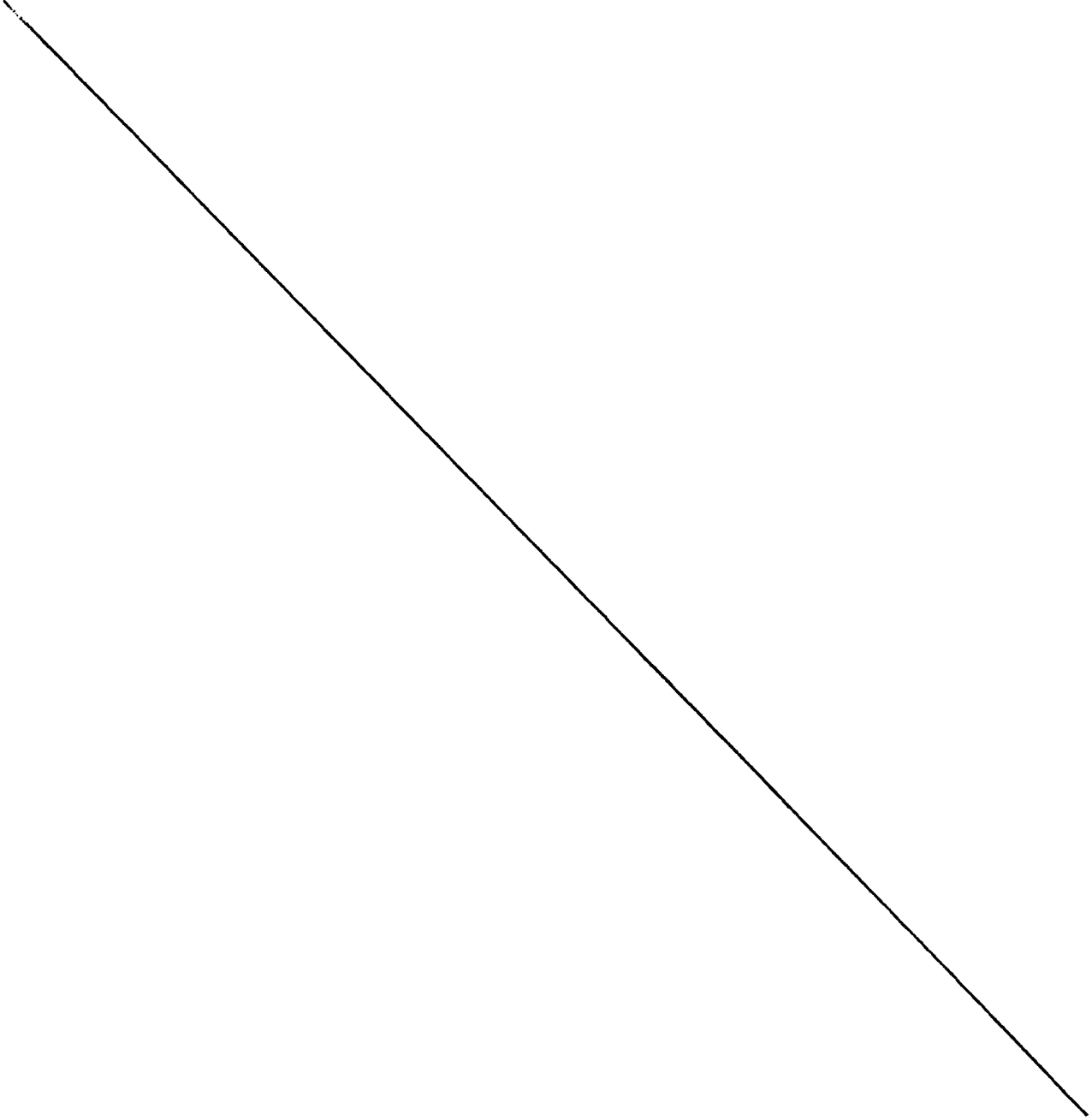
§ 878.4010 Tissue adhesive.

(a) *Tissue adhesives for the topical approximation of skin—(1)*

Identification. Tissue adhesives for the topical approximation of skin are 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.

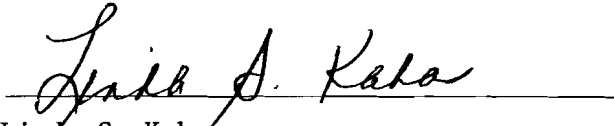
(b) *Tissue adhesives for non-topical use*—(1) *Identification*. A tissue adhesive for non-topical use, including adhesives intended for use in the embolization of brain arteriovenous malformation or for use in ophthalmic surgery, is a device used for adhesion of internal tissues and vessels.



(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.

Dated: 6-22-07

June 22, 2007.



Linda S. Kahan,
Deputy Director,
Center for Devices and Radiological Health.

[FR Doc. 07-????? Filed ??-??-07; 8:45 am]

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