DE NOVO CLASSIFICATION REQUEST FOR
VASOPREP SURGICAL MARKING PEN

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Internal Tissue Marker: An internal tissue marker is a prescription use device that is intended for use prior to or during general surgical procedures to demarcate selected sites on internal tissues.

NEW REGULATION NUMBER: 878.4670

CLASSIFICATION: II

PRODUCT CODE: PDW

BACKGROUND

DEVICE NAME: VASOPREP SURGICAL MARKING PEN

SUBMISSION NUMBER: DEN130004

DATE OF DE NOVO: MAY 6, 2013

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REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The VasoPrep Surgical Marking Pen is intended for use prior to or during the harvesting and preparation of vein grafts used in bypass surgery. The pen is used to demarcate selected sites and orientation of the graft.

LIMITATIONS

Caution: Federal Law restricts this device to sale by or on the order of a physician.

WARNINGS

- The VasoPrep Surgical Marking Pen should not be used on a non-sterile surface prior to its internal use.
- The safety and performance of the VasoPrep Surgical Marking Pen has not been established in patients with a known allergy to FD&C Blue dye #1.

- The VasoPrep Surgical Marking Pen has not been tested on any internal tissue except for veins.

DEVICE DESCRIPTION

The VasoPrep Surgical Marking Pen is a single patient use sterile prescription use only marker intended for use on veins prior to or during Coronary-Assisted Bypass Graft (CABG) surgery. The marker (Figure 1) consists of a pen body, barrel, wick and cap with a wide chisel style applicator tip for delivery of ink to mark internal tissue. The formulation is non-toxic as used and is comprised of an ink material (FD&C Blue Dye #1) compounded into a carrier material (i.e., solvent). The wide chisel tip can deliver either a thin line of ink for precise marks or can be rotated 90° to deliver a wide stripe of ink.

Figure 1: VasoPrep Surgical Marking Pen

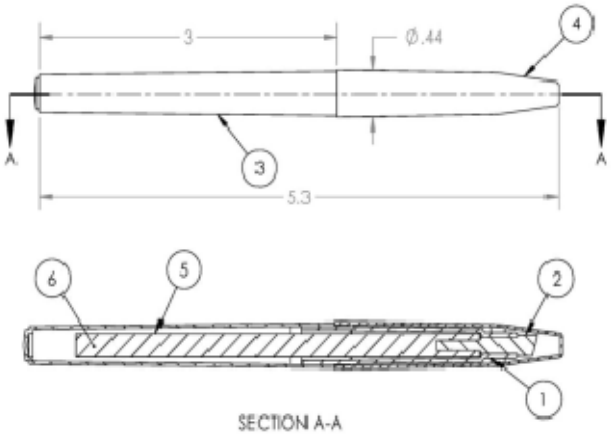

Figure 1. The device consists of a Body (1); Tip (2); Barrel (3); Cap (4); Ink Storage Wick (5); and Ink (6).

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The VasoPrep Surgical Marking Pen is comprised of three main components and are considered to be in direct contact and/or indirect contact with the patient: 1) the ink formulation; 2) the pen barrel; and 3) the wick/wicking material. These materials are well-characterized, used in medical device applications and were tested in accordance with ISO 10993-1 as indicated in Table 1 (below). The results demonstrate the VasoPrep Surgical Marking Pen is biocompatible when used as intended.

Table 1: A summary of the biocompatibility testing conducted

Test	Purpose	Acceptance Criteria	Results
Cytotoxicity (b)(4) (b)(4) (ISO 10993-5)	To test and evaluate the cytotoxicity of the marker and ink formulation.	Non-cytotoxic	Non-cytotoxic

Sensitization – Maximization Method (guinea pig) (ISO 10993-10)	To test and evaluate the potential for the marker and ink formulation to cause delayed contact sensitization.	No evidence of causing delayed dermal contact sensitization	No evidence of causing delayed dermal contact sensitization
USP Intracutaneous Reactivity (ISO 10993-10)	To test and evaluate the potential for the marker and ink formulation to cause local dermal irritant effects.	Nonirritant	Nonirritant
USP Systemic Toxicity	To test and evaluate the acute system toxicity of the marker and ink formulation.	No indications of systemic toxicity	No indications of systemic toxicity
Hemocompatibility (In vitro hemolysis)	To test and evaluate the hemocompatibility of the marker and ink formulation.	No significant hemolysis	No significant hemolysis
Material Mediated Pyrogenicity (ISO 10993-9)	To test and evaluate the pyrogencity of the marker and ink formulation.	Non-pyrogenic	Non-pyrogenic

SHELF LIFE / STERILITY / PACKAGING

A single-packed marker is packaged in a clear (b)(4) Low Density Polyethylene (LDPE)/opaque coated paper pouch that is heat-sealed with (b)(4) The single-pack marker packaging is a single sterile barrier. The single packs are then bulk-packed in a cardboard shelf carton for distribution of single markers. Shelf cartons are placed in corrugated boxes for shipping. Labels are placed on the paper side of the pouch, on the shelf carton and the shipping container.

Shelf-life and packaging integrity studies indicate a packaged, sterilized device will remain functional (i.e., tissue marking ability), non-cytotoxic and maintain a 10^{-6} SAL for 1 year. The standards and methods used are located in Table 2, below.

Table 2: A summary of the sterility and packaging testing conducted

Test	Purpose	Acceptance Criteria	Results
Sterility Testing (ISO 11137)	To test and evaluate the sterility of the marker and ink formulation.	To ensure (b)(4) gamma radiation sterilization process is an adequate dose. Devices must have a sterility assurance of at least 10^{-6}.	Meets Acceptance Criteria
Packaging Integrity (ASTM F1886 /F1886M; ASTM F1929; ASTM F88/88M)	To test and evaluate the marking ability after undergoing accelerated aging and mechanical stress.	The packaging must pass the Visual Seal Examinations; Dye Leak Test; and Peel Test.	Meets Acceptance Criteria

PERFORMANCE TESTING – BENCH

Test protocols were developed based on the results of design and clinical risk analyses of the VasoPrep Surgical Marking Pen in its intended indication for use. The original bench testing performed by the sponsor to assess the performance characteristics are summarized in Table 3.

Table 3: A summary of the performance testing conducted

Test	Purpose	Acceptance Criteria	Results
Internal Tissue Marking Ability	To test and evaluate device ability to mark human saphenous veins (HSV)	The marker shall provide a visible mark on wet or dry tissue that is 1-3 mm wide and up to 90 cm long with a single swipe. The mark shall remain visible on tissue for at least 4 hours.	Meets Acceptance Criteria
Effect of Dye on Human Vein Tissue	To test and evaluate for patency effects caused by the ink on HSV	Ex-vivo exposure to ink shall have no detrimental effect on the viability, smooth muscle contractility and endothelial-dependent relaxation of human saphenous vein grafts.	Meets Acceptance Criteria
Effect of Dye on Animal Vein Tissue	Preliminary dosing experiments to test and evaluate demarcation ability of the ink on porcine saphenous veins, at a dose that will have no detrimental effect on further HSV testing.	Application shall demonstrate ink demarcation ability on porcine saphenous veins at an amount that would have no detrimental effect on the viability, smooth muscle contractility and endothelial-dependent relaxation of human saphenous vein grafts	Meets Acceptance Criteria

Ability to mark internal tissues

Human Saphenous Vein (HSV) segments were painted on the surface with the device and placed in (b)(4) Photographs were taken with a digital camera to monitor the retention of marking on the tissue. Titration curves were generated by measuring maximum absorbance. The marker provided a visible mark on wet or dry tissue that is 1-3 mm wide and up to 90 cm long with a single swipe. The mark remained visible on tissue for at least 4 hours.

Effect of Dye on Venous Tissue

Human Saphenous Vein (HSV) were dissected free of adipose and connective tissues and divided into segments that were either left untreated (as controls) or exposed to dye prior to physiological measurements for 2 hrs. The buffer was changed to a high (b)(4) buffer which depolarizes the smooth muscle leading to contraction of functionally viable smooth muscle. Contractile responses were converted to stress normalized (b)(4) . The rings were (b)(4) To determine endothelial-dependent relaxation, the (b)(4) Maximal contractile responses to (b)(4) (b)(4) were converted to stress and endothelial dependent function were described as the percentage (%) of relaxation of the maximal (b)(4) induced contraction.

The VasoPrep Surgical Marking Pen met all design requirements for compatibility and functional use.

Effect of Dye on Porcine Venous Tissue

Dosing of FD&C Blue dye #1 was tested in porcine saphenous vein and (b)(4) was determined to be the optimal dose for color visualization.

Product Stability

The objective was to test and evaluate the performance testing on VasoPrep Surgical Marking Pens after gamma sterilization and aging (based on the proposed shelf life). Four sterilized and aged markers were tested according to protocol. The markers were gamma sterilized at the normal specified dose ((b)(4) Two real-time aged markers (the markers were stored at room temperature for at least one year after being sterilized) were shipped to multiple locations and tested for marking on wet porcine saphenous vein tissue (i.e, demarcation effectiveness) and dry paper (i.e., fluid volume). Cytotoxicity testing (b)(4) was additionally performed on accelerated-aged sterilized ink. The results (as summarized in Table 4) indicate the sterilized aged marking pens functioned as designed and that the ink is non-cytotoxic.

Table 4: Summary of the Product Stability Testing Conducted			
Test	Purpose	Acceptance Criteria	Results
Functionality (ASTM F1980)	To test and evaluate the marking ability after undergoing real time aging and shipping stress.	The marker shall provide a visible mark on wet or dry tissue that is 1-3 mm wide and up to 90 cm long with a single swipe. The mark shall remain visible on tissue for at least 4 hours.	Meets Acceptance Criteria
Cytotoxicity (ASTM F1980; ISO 10993-5)	To test and evaluate the cytotoxicity of the marker and ink formulation after undergoing accelerated aging.	The marker and contents shall be non-cytotoxic.	Meets Acceptance Criteria

TOXICOLOGICAL ASSESSMENT

Lifetime toxicity/carcinogenicity literature studies pertaining to FD&C Blue #1 dye were provided. The studies examined histology in a significant number of systemically-relevant animal tissues. The histology examined was obtained from canine, porcine and murine models for both genders and using different dye dose levels.

Several published literature articles have studied acute and/or chronic dosing of the subject dye by oral, subcutaneous and intravenous routes, demonstrating no toxicity and No Adverse Effect Levels (NOAELs) in accepted animal models at doses far in excess of that intended in the application of the Surgical Marking Pen, which is a 0.68 µg/kg one-time exposure for a 70 kg adult, representing 0.00057% of the FDA adult Acceptable Daily Intake (ADI) for FD&C Blue No. 1 of 12.0 mg/kg per day. Data from literature publications analyzing the elimination routes of FD&C Blue No.1 were also provided.

Examples of legally marketed devices containing the device dye were also provided, and include sutures, anchors and dural sealants. From these devices and the above-mentioned toxicological assessment, the risk of inadequate metabolic clearance from the body is believed to be minimal at the dose level used (i.e., 0.68 µg/kg).

LABELING

On the packaging label, the sponsor specifies prescription use only, sterility, shelf life, single-use only, not made with natural rubber latex, lot number and product catalogue number.
The labeling for the VasoPrep Surgical Marking Pen is consistent with the data and addresses all known hazards and other relevant information that could impact safe and effective use of the device. The labeling satisfies the requirements of CFR 801.109 Prescription devices.

RISKS TO HEALTH

Table 2 below identifies the risks to health that may be associated with use of Internal Tissue Marker and the measures necessary to mitigate these risks.

Table 2 – Identified Risks and Mitigation Measures	
Identified Risk	**Mitigation Measures**
Adverse tissue reaction	Biocompatibility Testing Sterilization Testing Shelf Life/Stability Testing Performance Testing Labeling
Ineffective Marking	Performance Testing Shelf Life/Stability Testing Labeling
Improper use	Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Internal Tissue Marker is subject to the following special controls:

1. The device must be demonstrated to be biocompatible. Material names and specific designation numbers must be provided.

2. Performance testing must demonstrate that the device performs as intended to mark the tissue for which it is indicated.

3. Performance data must demonstrate the sterility of the device.

4. Performance data must support the shelf life of the device by demonstrating sterility, package integrity, device functionality, and material stability over the requested shelf life.

5. Labeling must include:
   a. A warning that the device must not be used on a non-sterile surface prior to use internally.
   b. An expiration date / shelf life.
   c. Single use only labeling must be labeled directly on the device.

BENEFIT/RISK DETERMINATION

No clinical study was provided nor requested nor deemed necessary for the subject device based on the risks. The risks of the device are based on literature review, nonclinical laboratory data and tissue study data collected as described above. The subject surgical marker could provide a lower risk alternative to the present off-label use of other marking pens not intended for internal usage. However, there are potential adverse events that include, but are not limited to; infection, tissue inflammation, and mechanical failure of vessels.

The probable benefits of the device are also based on literature review, nonclinical data and tissue study data collected in a study as described above. The benefit of the subject device would be to provide a safer and effective surgical marking pen to reduce the risks associated with the off-label use of existing marking pens, which are not provided sterile nor designed and intended for CABG surgery. . The use of the device on human saphenous veins to maintain vein orientation during the procedure of coronary artery bypass grafting may help avoid twisting or torsion of the vein during the procedure. Twisting or torsion of the vein, if it occurred during CABG surgery (e.g., vein orientation), could impede early graft patency.

In conclusion, given the available information above, the data support that for the indication "The VasoPrep Surgical Marking Pen is intended for use prior to or during the harvesting and preparation of vein grafts used in bypass surgery. The pen is used to demarcate selected sites and orientation of the graft", the probable benefits outweigh the probable risks. The device provides benefits and the risks can be mitigated by the use of general and the identified special controls.

Presently, there are no available surgical marking pens specifically designed for usage on internal tissues. Marking pens that are currently used off-label have different dye formulations which may have adverse effects on saphenous vein smooth muscle and endothelium. With the use of off-label pens or no pens at all, the patency of grafted vessels can be jeopardized.

Patients are typically not aware of the use of surgical marking pens; however the data, for the subject device indicates it to be reasonably safe and effective such that patients undergoing CABG surgery would be willing to take the risk even though it is uncertain that they will achieve the benefit, because if they benefit, the benefit from maintaining vessel patency in a safe manner is substantial. Finally, the risks associated with this device, although potentially serious, should not occur in any clinically significant number for this device, and they would be expected to be lower than those currently accepted for similar treatments due to safer dye formulation.

CONCLUSION

The *de novo* for the VasoPrep Surgical Marking Pen is granted and the device is classified under the following:

Product Code: PDW
Device Type: Internal Tissue Marker
Class: Class II
Regulation: 21 CFR 878.4670