DE NOVO CLASSIFICATION REQUEST FOR
XSTAT

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Non-absorbable, expandable, hemostatic sponge for temporary internal use:** A non-absorbable, expandable, hemostatic sponge for temporary internal use is a prescription device intended to be placed temporarily into junctional, non-compressible wounds, which are not amenable to tourniquet use, to control bleeding until surgical care is acquired. The sponges expand upon contact with blood to fill the wound cavity and provide a physical barrier and pressure that facilitates formation of a clot. The device consists of sterile, non-absorbable, radiopaque, compressed sponges and may include an applicator to facilitate delivery into a wound.
>
> **NEW REGULATION NUMBER:** 21 CFR 878.4452
>
> **CLASSIFICATION:** II
>
> **PRODUCT CODE*:* PGZ**

BACKGROUND

> **DEVICE NAME:** XSTAT
>
> **SUBMISSION NUMBER:** K130218
>
> **DATE OF DE NOVO:** JANUARY 28, 2013
>
> **CONTACT*:*** REVMEDX, INC.
> % JOHN SMITH, M. D., PH. D., REGULATORY CONSULTANT
> HOGAN LOVELLS US, LLC
> 555 13TH STREET NW
> WASHINGTON, DISTRICT OF COLUMBIA 20004
>
> **REQUESTER'S RECOMMENDED CLASSIFICATION:** II

INDICATIONS FOR USE

XSTAT is a hemostatic device for the control of bleeding from junctional wounds in the groin or axilla not amenable to tourniquet application in adults and adolescents.

XSTAT is a temporary device for use up to four (4) hours until surgical care is acquired. XSTAT is intended for use in the battlefield.

XSTAT is NOT indicated for use in: the thorax; the pleural cavity; the mediastinum; the abdomen; the retroperitoneal space; the sacral space above the inguinal ligament; or tissues above the clavicle.

LIMITATIONS

The sale, distribution, and use of XSTAT are restricted to prescription use in accordance with 21 CFR 801.109.

Limitations on device use are also achieved through the following statements included in the Instructions for Use:

> "For use by trained emergency responders"
>
> "DO NOT attempt to remove sponges from wound. Sponges must be removed intraoperatively by surgeon with the capability and equipment for achieving proximal and distal vascular control."
>
> "Assess patient for peripheral circulation and document presence of distal pulse on included casualty card. WARNING: Vascular compression greater than four hours is not recommended due to concerns related to limb ischemia."
>
> "WARNING: Triangular segments of the applicator tip may break away from applicator during treatment. If this occurs, do not attempt to retrieve it from the wound. Record number of separated applicator tips on casualty card."
>
> "XSTAT has not been tested for use in extremity wounds that are amenable to tourniquet application"
>
> "XSTAT use in conjunction with tourniquet application has not been assessed for use in extremity wounds that are amenable to tourniquet application"
>
> "Prior to wound closure, obtain plane x-ray, optimally in more than one projection. The presence of retained sponges may be easily missed on radiographic images. Thoroughly examine x-ray for radiopaque x-pattern of sponges and any triangular segments of the applicator tip that may be inadvertently retained in the wound cavity."
>
> "If sponges or applicator tip segments are identified via x-ray, carefully re-examine wound cavity and remove them. Perform and review second x-ray to confirm complete sponge and applicator tip segment removal."
>
> "The XSTAT elicited a mild pyrogenic response in biocompatibility tests. Monitor patient for rise in temperature, chills, hypotension, and septic shock."
>
> "Inhibition and enhancement validation was not performed for the LAL method to confirm that the device itself does not bind and/or block detection of endotoxin."

"Contains material derived from shellfish"

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

XSTAT consists of three sterile, syringe-style applicators containing compressed cellulose sponges with an absorbant animal-derived coating. The applicators facilitate fast delivery of the sponges into bleeding wounds. The black, telescoping handle is pulled away from the barrel of the applicator to prepare for sponge deployment. The tip of the applicator is placed into the wound track as close as possible to the source of bleeding before pushing the handle to deploy the sponges. Trained emergency responders may apply up to three applicators of sponges into junctional wounds in the groin or axilla as needed to completely pack the wound.

Each applicator houses 92 non-absorbable, expandable sponges for a total of 276 sponges per device (see Figure 1). Each sponge absorbs 3 ml of blood and a single applicator is therefore capable of absorbing approximately 300 ml. The sponges rapidly expand in length (see Figure 2) upon contact with blood or fluid to fill the wound cavity and thereby provide a physical barrier and pressure that facilitate formation of a clot. Once hemostasis is achieved, a standard occlusive dressing is applied before transporting the patient to a medical facility where surgery is performed to definitively repair the wound. The sponges are intended for temporary use up to four hours until surgical care is acquired. All sponges must be removed from wounds manually and/or with forceps by a surgeon with the capability and equipment for achieving proximal and distal vascular control. For easy detection via x-ray, one face of each tablet contains radiopaque filaments in an "x" pattern (see Figure 2). To confirm removal of all sponges and any applicator tips, a radiograph is required prior to wound closure with imaging in more than one plane recommended.

Figure 1: Photograph of one device, which consists of compressed sponges housed in a syringe-style applicator. One device consists of three applicators.

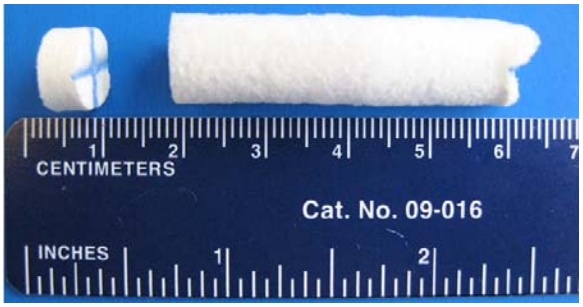

Figure 2: Photograph depicting side views of compressed and fully expanded sponges. Radiopaque filaments are attached to one end of each sponge in an "x" pattern.

SUMMARY OF NONCLINICAL/BENCH STUDIES

The sponsor conducted a series of non-clinical performance testing to demonstrate that XSTAT

would perform as anticipated for its intended use population.

BIOCOMPATIBILITY/MATERIALS

XSTAT is comprised of two main components, the XSTAT sponge and the applicator. As summarized in Table 1, these components were subjected to biocompatibility testing as recommended for a limited duration, blood contacting externally communicating device.

Table 1: Summary of Biocompatibility Tests

Biocompatibility Test	Standard	Applicator Result	Sponge Result
Cytotoxicity (MEM Elution)	ISO 10993-5:2009	PASS	PASS
Sensitization (Guinea Pig Maximization)	ISO 10993-10:2010	PASS	PASS
Irritation (Intracutaneous Reactivity Test)	ISO 10993-10:2010	PASS	Sponge passed testing in non-polar solvent, but failed in polar solvent and thus was found to be a moderate irritant in polar solvent.
Acute Systemic Toxicity	ISO 10993-11:2006	PASS	PASS
Hemocompatibility (Hemolysis Assay - Extract Method)	ASTM F756-08	PASS	PASS

Material characteristics including specifications for raw materials used in the device were assessed to support safety under anticipated conditions of use. XSTAT contains a raw material derived from an animal source. For the animal derived component, manufacturing information, material specifications, and literature were provided to support the adequacy of viral inactivation and verify that the risk for immunogenicity reactions is low.

STABILITY/STERILITY

XSTAT is labeled with a shelf life of 6 months based on testing of devices exposed to real time and accelerated aging conditions. Devices were stored on a shelf at room temperature for real-time aging with average temperature and relative humidity of 23°C and 29%, respectively (see Table 2). Devices exposed to accelerated aging conditions of 50°C for 25 days represent an equivalent of six months (ASTM F1980-07) (see Table 3). Samples were also evaluated using *in vitro* tests for applicator deployment force, sponge expansion rate, and package integrity (see Table 4) and met all product stability acceptance criteria.

Table 2: Real Time Aging Summary (6 months)

Test	Criteria	Result
Applicator Deployment Force	(b)(4) Trade Secret/CCI	PASS
Sponge Expansion Rate	(b)(4) Trade Secret/CCI	PASS

Table 3: Accelerated Aging Summary (25 days, equivalent to 6 months)

Test	Criteria	Result
Applicator Deployment Force	(b)(4) Trade Secret/CCI	PASS
Sponge Expansion Rate	(b)(4) Trade Secret/CCI	PASS

	(b)(4) Trade Secret/CCI	

Table 4: Packaging Testing on XSTAT

Test	Acceptance Criteria	Baseline Results	6 Months Real Time Aged Results
Bubble Emission Integrity (ASTM F2096)	0 fail locations. There must be no leaks.	PASS	PASS
Seal Peel Strength (ASTM F88)	All seals must have seal strength $\geq$ 1 lb/in	PASS	PASS

XSTAT is sterilized by gamma radiation to ensure a sterility assurance level of 10^{-6} according to ISO 11137. The device is not intended for re-sterilization or reuse. Based on the testing provided as described in Table 5, the subject device may elicit a pyrogenic response. To mitigate this risk, the labeling and training materials advise monitoring the patient for rise in temperature, chills, hypotension, and septic shock. Recommended device use is limited to no more than one device (3 total applicators of sponges) serving as a temporary wound packing for no longer than 4 hours. The risk of a possible pyrogenic response is acceptable considering the mitigations for the risk and the potential benefit of controlling bleeding that is otherwise non-compressible.

Table 5: Summary of Endotoxin and Pyrogenicity Tests

Test	Standard	Applicator Result	Sponge Result
Endotoxin (*Limulus* Amebocyte Lysate, LAL)	USP <85>, USP <161>	PASS (< 8.50 EU/device) Inhibition and enhancement validation was not performed for the LAL method to confirm that the device itself does not bind and/or block detection of endotoxin.	
Pyrogen (Materials Mediated Rabbit Pyrogen Test)	USP <151>	PASS	Pyrogenic response observed

PERFORMANCE TESTING – BENCH

Bench testing demonstrated that the device performs as expected under anticipated conditions of use. Testing to verify the properties and performance of the sponges included measuring the absorption capacity, extent of swelling, expansion force/pressure, mechanical properties, and radiopacity (see Tables 6 and 7). To verify ease of use and the structural integrity of the applicator, mechanical testing measured deployment forces for dry applicators as well as those immersed in liquid for 30 seconds (see Tables 8 and 9).

Table 6: Product Acceptance Criteria

Criteria Description		Characteristic	Acceptance Criteria
XSTAT Sample Testing	Minisponge Compression	(b)(4) Trade Secret/CCI	(b)(4) Trade Secret/CCI
	Minisponge Expansion		
	Functional Applicator Test		

Table 7: Performance Data for Sponges

Test	Results
Absorption Capacity	(b)(4) Trade Secret/CCI
Extent of Swelling	(b)(4) Trade Secret/CCI
Mechanical Properties	Single and Multiple Sponge Force Curves: Force measured as a function of the extent of swelling for single sponges and multiple sponges expanding in the same direction. Within a wound, the pellets will not all expand in exactly the same direction and there will inherently be void space between the sponges. The void space will in essence buffer the pressure by providing some room for pellet expansion. Load Relaxation: The sponges exhibit stress relaxation, i.e. a time-dependent decrease in force under constant compression. Stress relaxation will help to reduce the pressure in a packed wound.
Expansion Force/Pressure	Gel Wound Simulator: Testing in a wound simulator consisting of a cavity created in a gel indicated that pressures are different at different locations within a packed wound. The highest pressure observed for a model wound packed with XSTAT was 200 mm Hg, which relaxed to 150 mm Hg after 40 seconds. Cadaver: Cadaver experiments with model junctional wounds verified that the pressure inside a wound packed with XSTAT does not appear to be any higher than that for a wound packed with gauze. The equilibrium pressure after packing with XSTAT was 44 mm Hg and increased to 84 mm Hg after wrapping the wound with an ace bandage. Moving the limbs caused changes in the volume of the wound and therefore changes in the pressure.
Radiopacity (ASTM F640)	Average optical densities: background $= 0.86 \pm 0.02$, subject device $= 0.70 \pm 0.01$ With 95 percent confidence ($\alpha < 0.05$), the image background and subject device OD were significantly different ($P = < 0.001$).

Table 8: Mechanical Testing of Applicator

Scenario-based loading condition	Criteria	Rationale for criteria	RESULTS in LBS (st dev)		
			@ -18°C	@ 21°C	@ 43°C
Max force required to retract the applicator handle in high temp, low temp, and room temp conditions	(b)(4) Trade Secret/CCI	Ensures that the design provides an easy one-handed engagement of the applicator by a combat medic using a two-finger-pull with low exertion.	Pass	Pass	Pass
Max force required to deploy the applicator in high temp, low temp, and room temp conditions.		Ensures that the design provides an easy one-handed deployment of the applicator by a combat medic using palm contact and low exertion.	Pass	Pass	Pass
Min force required to generate handle failure in high temp, low temp, and room temp conditions		Ensures that the design provides safe and effective performance when engaged by a combat medic using a one-handed, two-finger pull with high exertion.	Pass	Pass	Pass
Min lateral load the applicator body can withstand at the weakest portion (distal end) in high temp, low temp, and room temp conditions		Ensures that the design provides safe and effective performance when exposed to lateral loading equivalent to 2x the weight of a typical combat medic aid bag (25 lbs).	Pass	Pass	Pass
Min force required to generate failure of the locking mechanism in high temp, low temp, and room temp conditions.		Ensures that the design provides safe and effective performance when deployed with one hand (palm contact) by a combat medic using high exertion.	Pass	Pass	Pass

Table 9: Mechanical Testing of Applicator After Immersion in Fluid

Test	Result
Deployment force after 30 sec of immersion in fluid	PASS

PERFORMANCE TESTING – ANIMAL

Three animal studies using XSTAT in swine demonstrated reasonably safe and effective use by verifying that the device controls bleeding, does not promote adverse local or systemic effects, and can be completely removed the wound. Studies to assess control of bleeding from swine femoral and subclavian arteries are described in Tables 10 and 11. An additional animal subclavian artery study was submitted within a separate device master file to which the sponsor had a letter of authorization to further support device performance. The animal studies confirmed device performance characteristics including deployment, control of bleeding, radiopacity, and retrieval as well as the impact of device use on the animals in terms of local and systemic effects.

Table 10: Swine Femoral Artery Study

Name of Study	GLP Evaluation of XSTAT Device in a Swine Femoral Model
Study Description	GLP animal study to demonstrate the performance of the XSTAT device compared to a control article, using the United States Army Institute of Surgical Research ("USAISR") standard femoral animal injury[1,2]
Number of Animals	Ten (10) animals were treated with the XSTAT device Ten (10) animals were treated with the control article.
Inclusion / Exclusion	• Inclusion: o Animal breed: Landrace cross swine o Weight at procedure: 55 - 65 kg o Age at procedure: appropriate to weight • Exclusion criteria included inappropriate vessel anatomy, persistently low MAP (<55 mmHg) prior to femoral artery injury, and significant blood loss (>300 mL) because of surgical complication or error before femoral artery injury.
Study Procedure	<u>All Wounds Prior to Randomization</u> • An incision was created (3.5 cm long) through the skin and subcutaneous tissues in the groin area directly over the right femoral artery and an approximately 3 cm section of femoral artery was exposed. • The femoral artery was covered with a small piece of gauze and bathed with 2% lidocaine HCl solution to relax the vasospasm and dilate the artery to ≥ 5 mm outer diameter • Non-traumatic vessel loops were placed proximally and distally on the femoral artery. • Using a 6.0 mm vascular punch, an arteriotomy was created. • The vessel loops were released, injury start time was recorded and the vessel was allowed to bleed freely for 45 seconds before the Test (XSTAT) or Control Article was applied. • The vessel loops were allowed to remain in the wound to facilitate hemorrhage control during test material removal. • Surgeon and device applicator were blinded to the identity of test material prior to application. • Randomization was accomplished by picking a sealed envelope that contained the name of the test material. The contents of the envelope were revealed in the surgery suite during the 45 second free bleed period. <u>Wounds Randomized to XSTAT</u> • XSTAT applied as per product label immediately following the 45-second free bleed. • XSTAT applied as quickly as possible and as many as necessary until the bleeding has stopped, or until the 5 minute limit, whichever was sooner. • If room within the wound allowed, plain gauze (i.e., S-Rolled Gauze) was packed on top of the XSTAT-filled wound.

<table>
<tr><td></td><td>

Cloth bandage used to secure XSTAT/Plain Gauze device within the wound.
Manual compression was permitted if bleeding persisted following application of the device.

<u>Wounds Randomized to Control Article</u>

Immediately following the 45-second free bleed up to 5 minutes was allowed to apply control article(s) by packing device completely into wound track using enough control article to fill the wound and contact all bleeding surfaces. More than one device may be required.
If room within the wound allowed, plain gauze (i.e., S-Rolled Gauze) was packed on top of the control article.
Cloth bandage used to secure control article within the wound.
Manual pressure applied for 3 minutes.

<u>Post-Randomization Care</u>

Resuscitation began 5 minutes post-injury (i.e., free bleed start time) by infusing approximately 500 ml of Hextend® fluid at a target rate of 33 mL/min through the jugular vein.
Resuscitation was continued, if necessary, with pre-warmed lactated Ringer's solution (LRS) infused at a target rate of 100 mL/minute, to maintain the mean arterial pressure (MAP) to at least 65 mmHg.
Following the 6-hour observation period, the Test or Control Article was removed from the wound site and the animal euthanized.
XSTAT sponges were removed from the wound site manually as well as with surgical forceps. Control article(s) were pulled out of the wound manually.
Following sponge removal and euthanasia, the wound site was imaged using a portable fluoroscopy unit. No sponges were identified in the fluoroscopic images or at necropsy.

</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Endpoints</th><th>XSTAT</th><th>Control Article</th></tr>
<tr><td>1: Bleeding Time, mean: Duration of bleeding (visible blood shed from the wound site) occurring at any time immediately following test material application until exsanguination or end of the 6 hour observation period.</td><td>0 Minutes</td><td>0 Minutes</td></tr>
<tr><td>2: Post-Treatment Blood Loss, mean (stdev): Amount of blood shed from the wound cavity during the time period following the 45 second free bleed until exsanguination or end of the 6 hour observation period.</td><td>21.7 (17.5) mL</td><td>28.3 (18.1) mL</td></tr>
<tr><td>3: Final Mean Arterial</td><td>62.0 (5.0) mmHg</td><td>64.0 (3.0) mmHg</td></tr>
</table>
</td></tr>
</table>

	Pressure (MAP), mean (stdev): Mean arterial pressure recorded just prior to exsanguination or end of the 6 hour observation period.		
	4: Survival Time, mean (stdev): Time period immediately following the 45 second free bleed during which vital signs are; MAP >20mmHg and PCO2 >15 mmHg to exsanguination or end of the 6 hour observation period.	6.0 (0.0) hours	6.0 (0.0) hours
	5: Percentage Survival: Percentage of animals surviving to the end of the study observation period (6 hours) for a given treatment, where survival was defined as the MAP >20 mmHg and PCO2 >15 mmHg.	100%	100%
	6: Wound Packing Time, mean (stdev)	1.1 (0.3) minutes	4.6 (0.5) minutes
	7: Wound Compression Time	0 minutes	3 minutes
	The presence or absence of distal limb ischemia was not assessed in this study. There was no postmortem evidence of blood tracking beneath the skin.		
Device Removal	Mean XSTAT removal time 10.5 ± 3.4 minutes. Mean control article removal time 2 ± 0.8 minutes. Neither test nor control article material adhered to the wound or were found to be retained in the wound at necropsy.		

[1]Kheirabadi BS, Arnaud F, McCarron R et al. Development of a Standard Swine Hemorrhage Model for Efficacy Assessment of Topical Hemostatic Agents. J of Trauma. 2011;71:S139-S146. [2]Littlejohn LF, Devlin JJ, Kircher SS, et al. Comparison of Celox-A, ChitoFlex, WoundStat, and Combat Gauze Hemostatic Agents Versus Standard Gauze Dressing in Control of Hemorrhage in a Swine Model of Penetrating Trauma. Acad Emerg Med. 2011;18:340-350. Acheson, E.M., et al. Comparison of Hemorrhage Control Agents Applied to Lethal Extremity Arterial Hemorrhages in Swine. J of Trauma. 2005;59:865-875.

Table 11: Swine Subclavian Artery Study

Name of Study	Evaluation of XSTAT Device in a Swine Subclavian Model
Study Description	Animal study to demonstrate the performance of the XSTAT device in a swine subclavian injury
Number of Animals	8
Inclusion / Exclusion	• Inclusion: o Animal breed: Landrace cross swine

<table>
<tr><td></td><td>

Weight at procedure: 55 - 65 kg
Age at procedure: appropriate to weight

Exclusion criteria included inappropriate vessel anatomy, persistently low MAP (<65 mmHg) prior to femoral artery injury.

</td></tr>
<tr><td>Study Procedure</td><td>

Animal anesthetized and 4.5-cm incision was created to access the subclavian artery and vein
Subclavian artery and vein transected
After 30-second free bleeding, the wound cavity was filled with the XSTAT sponges with no external pressure.
Resuscitative fluids were administered to the animal as needed to support a mean arterial blood pressure of 60 mmHg.
No additional wound care was provided during the 1-hour observation period.
Following the 1-hour observation period, the XSTAT sponges were removed from the wound site and the animal euthanized.

</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Endpoint</th><th>XSTAT</th></tr>
<tr><td>1: Animals with hemostasis at 4 min after device application.</td><td>7 / 8 (87.5%)</td></tr>
<tr><td>2: Animals with hemostasis at 60 min after device application</td><td>7 / 8 (87.5%)</td></tr>
<tr><td>3: Animal Survival at 60 min where survival was defined as the MAP > 20 mmHg and PCO2 > 15 mmHg.</td><td>8 / 8 (100%)</td></tr>
<tr><td>4: Bleeding Time, mean (StDev) Duration of bleeding occurring at any time immediately following material application until study termination</td><td>7.9 (21.1)</td></tr>
<tr><td>5: Post-TBL, mean (stdev) Amount of blood shed from the wound cavity during the time following the 45 second free bleed until study termination</td><td>331.5 (818.9)</td></tr>
</table>
The failure to achieve hemostasis in one of the animals was due to an applicator tip breaking off and falling into the wound. The location of the tip in the wound created a small gap (1 cm) that prevented sponges from accessing the point of bleeding. As a result, applicator tips are now secured with glue.
</td></tr>
</table>

PERFORMANCE TESTING – HUMAN FACTORS

Human factors testing and analysis validated that the device design and labeling are sufficient for appropriate use by emergency responders deploying the device as well as surgeons retrieving the device from wounds (see Tables 12 and 13). Human factors assessments were used to modify the labeling to promote reasonably safe and effective use of XSTAT.

Table 12: Device Deployment Human Factors Study

Name of Study	User Evaluation of XSTAT Device and Applicator Use
Study Description	A user evaluation (human factors) was completed to determine the ability of medics and civilian EMS to understand and execute instructions for using XSTAT and applying XSTAT on a simulated casualty.
Number of subjects	10

<table>
<tr><td>Inclusion / Exclusion</td><td colspan="4">Military medic or civilian EMS with no prior knowledge or experience of using XSTAT device prior to the study</td></tr>
<tr><td>Study Procedure</td><td colspan="4">• A medical-mannequin torso served as a wound model.
• The wound track—located in the upper thigh region approximately 5 cm distal to the iliac artery—had a diameter of 3 cm and a length of 8 cm and was pre-filled with 150-200 mL of saline.
• Participants were tested in a low-light environment.
• Participants were evaluated on the time needed to ready the device for use, as well as the time necessary to deploy the appropriate amount of material to stop bleeding.</td></tr>
<tr><td rowspan="12">Results</td><td colspan="4">• All participants passed the device usage criteria which involved opening the package, cocking the applicator, applying the applicator into the wound, applying the correct number of applicators, and deploying XSTAT in under 90 seconds (mean (stdev): 50.1(12.6) sec.).
• The study did not assess a user’s ability to properly diagnose a severely bleeding junctional wound in the groin or axilla not amenable to tourniquet application.</td></tr>
<tr><td>Participant</td><td>Time (sec)</td><td>User Comments</td><td>Actions Taken</td></tr>
<tr><td>1</td><td>45</td><td></td><td></td></tr>
<tr><td>2</td><td>31</td><td>Add detail on pulling/locking applicator</td><td>Revised instruction on pulling/cocking application handle</td></tr>
<tr><td>3</td><td>47</td><td>Add detail on preclinical data</td><td>Added detailed information on preclinical testing to product insert</td></tr>
<tr><td>4</td><td>70</td><td></td><td></td></tr>
<tr><td>5</td><td>43</td><td>Explain importance of direct pressure</td><td>Added detailed instructions regarding application of direct pressure and bandage</td></tr>
<tr><td>6</td><td>71</td><td></td><td></td></tr>
<tr><td>7</td><td>53</td><td></td><td></td></tr>
<tr><td>8</td><td>47</td><td></td><td></td></tr>
<tr><td>9</td><td>54</td><td>Add detail on pulling/locking applicator</td><td>Revised instruction on pulling/cocking application handle.</td></tr>
<tr><td>10</td><td>40</td><td></td><td></td></tr>
</table>

Table 13: Sponge Retrieval Human Factors Study

Name of Study / Cited Publication	User evaluation of XSTAT device removal
Study Description	A user evaluation was completed to assess the ability of surgeons to understand and execute instructions for removing XSTAT sponges from human cadaver wounds.
Number	4 surgeons; 1 cadaver; 2 wounds, 2 tests/wound.
Inclusion / Exclusion	Inclusion: civilian or military surgeon with no prior experience with XSTAT prior to the study.
Study Procedure	• Junctional wounds were made in each shoulder of the cadaver. • Saline solution was circulated through cadaver’s vasculature to simulate blood flow. • Following application of 2 XSTAT devices into the shoulder wounds,

	each surgeon was handed draft instructions for use and instructed to treat the wound.	
Endpoints/Results	**Endpoint**	**Result**
	1. Labeling clear on use of XSTAT device (Yes / No)	4 of 4 surgeons indicated 'Yes'
	2. Completed all steps in IFU without assistance (Yes / No)	4 of 4 surgeons completed
	3. IFU conveys necessity of removal of sponges, median*	4.5
	4. IFU conveys steps to assure removal, median*	4.5
	5. Effective order of removal steps, median*	4.5
	6. Ease of removal of sponges, median*	3.5
	* Scale: 1 = Poor, 2 = Fair, 3 = Acceptable, 4 = Good, 5 = Very Good	
User Comments/Actions Taken	**Comment**	**Actions Taken**
	Add reminder that all sponges must be removed before wound closure.	Package label and casualty card contain explicit instructions for surgical sponge removal
	Note approximate number of sponges per applicator on the package.	Package updated to include number of sponges per applicator

LABELING

Labeling has been provided which includes the instructions for use and an appropriate prescription statement as required by 21 CFR 801.109.

The labeling includes the following information:

- directions for use for deployment by emergency responders and retrieval by surgeons;
- warnings, cautions, and limitations needed for safe use of the device;
- information on how the device operates and the typical course of treatment;
- detailed summary of the in vivo and human factors testing pertinent to use of the device;
- appropriate imaging information to ensure complete retrieval of device;
- an expiration date/shelf life.

RISKS TO HEALTH

Table 14 below identifies the risks to health that may be associated with use of non-absorbable, expandable, hemostatic sponge for temporary internal use and the measures necessary to mitigate these risks.

Table 14: Identified Risks to Health and Mitigation Measures

Identified Risk	**Mitigation Method**
Failure to Stop Bleeding or Recurrence of Bleeding	Non-Clinical Performance Data *In Vivo* Performance Data Stability Assessment

	Labeling
Obstruction of Vital Organs	Human Factors Testing Labeling
Embolization	*In Vivo* Performance Data
Collateral Tissue Damage (e.g., paralysis, nerve damage, tissue necrosis)	*In Vivo* Performance Data Labeling
Adverse Tissue and Allergic Reactions	Material Characterization Biocompatibility *In Vivo* Performance Data Labeling
Infection (e.g., cellulitis, Toxic Shock Syndrome, sepsis)	Sterility Testing Stability Assessment
Reoperation Due to Material Retained in Body	Non-Clinical Performance Data *In Vivo* Performance Data Human Factors Testing Labeling
Sponge Deployment Failure	Non-Clinical Performance Data *In Vivo* Performance Data Stability Assessment Human Factors Testing Labeling
Improper Application Technique or Use Error	Human Factors Testing Labeling

SPECIAL CONTROLS :

In combination with the general controls of the Food, Drug & Cosmetic Act, the **Non-**

absorbable, expandable, hemostatic sponge for temporary internal use is subject to the following special controls:

1. Performance data must demonstrate the biocompatibility of patient-contacting components.
2. Performance data must demonstrate the sterility of patient-contacting components including endotoxin and pyrogenicity assessments.
3. Performance data must support device stability by demonstrating continued sterility of the patient-contacting components of the device, package integrity, and device functionality over the requested shelf life.
4. Assessment of material characteristics must be sufficient to support safety under anticipated conditions of use. Assessments must include the following:
    A. Material specifications
    B. Immunogenicity
    C. Viral inactivation for animal-derived materials
5. Non-clinical performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    A. Absorption capacity
    B. Extent of swelling
    C. Mechanical properties
    D. Expansion force/pressure
    E. Radiopacity
    F. Deployment/applicator functionality
6. *In vivo* performance data must demonstrate safe and effective use by verifying that the device performs as intended under anticipated conditions of use. Appropriate analysis/testing must demonstrate that the product: controls bleeding, does not promote adverse local or systemic effects, and can be completely removed from the wound. The following performance characteristics must be tested:
    A. Deployment
    B. Control of bleeding
    C. Radiopacity
    D. Retrieval
    E. Assessment of local and systemic effects
7. Human factors testing and analysis must validate that the device design and labeling are sufficient for appropriate use by emergency responders deploying the device as well as surgeons retrieving the device from wounds.
8. Labeling must include:
    A. Specific instructions for deployment by emergency responders and retrieval by surgeons,
    B. Warnings, cautions, and limitations needed for safe use of the device
    C. Information on how the device operates and the typical course of treatment
    D. A detailed summary of the in vivo and human factors testing pertinent to use of the device
    E. Appropriate imaging information to ensure complete retrieval of device
    F. An expiration date/shelf life

BENEFIT/RISK DETERMINATION

The risks of the XSTAT device are based on nonclinical laboratory and animal studies. The likelihood for each of the listed risks have not been quantified but are expected to be extremely low given the steps taken through the bench testing, animal testing, labeling and training that has been performed to mitigate each of the listed XSTAT device risks. The risks associated with use of the device include the following: failure to stop bleeding or recurrence of bleeding, obstruction of vital organs, embolization, collateral tissue damage, adverse tissue and allergic reactions, infection, reoperation due to material retained in body, sponge deployment failure, and improper application technique or use error.

All of the above listed serious adverse events may also result in non-serious adverse events depending on location of adverse event effect and extent of adverse event effect. As an effect of major hemorrhage, even with adequate resuscitation, significant blood loss could lead to hypothermia, coagulopathy, acidosis and late mortality through the development of sepsis and multiple organ failure. The probability of a harmful event is unknown due to the variable nature of the injury and associated injury, the need for rapid response using the device, the variations in the battlefield circumstances, and variations in the level of experience with the device and junctional injuries by the treating medic. However the risk of these adverse events is unknown but considered to be acceptable considering the benefits of device use to reduce hemorrhage associated with non-compressible, junctional bleeding in the battlefield. Signs or symptoms of many of the listed adverse events may be reversed by removing the device from the wound. The harmful events may or may not be reversible. The harmful events may be mitigated with rapid hemorrhage control and transfer to a definitive treatment facility where the device can be removed.

The probable benefits of the XSTAT device are also based on nonclinical laboratory and animal studies. Early control of bleeding is of high value to both patients and providers and can reduce the secondary effects of severe hemorrhage which include hypothermia, coagulopathy and late development of sepsis and multiple-organ system failure.

Due to an inability to perform a study involving patients with junctional bleeding secondary to battlefield injury, the studies performed were conducted in animals. The animal testing offered the advantages of reproducible testing in a standard wound, careful monitoring of device use and animal condition, standardization of resuscitation efforts, and standard post-mortem evaluation. The animal testing performed did not elucidate how benefits may vary across subpopulations. However due to the increased incidence of junctional injury in the military population and the reduced assess to definitive emergency medical care access in the battlefield, it is expected that the benefits far outweigh the risks for XSTAT device use in the military population requiring emergency treatment for junctional bleeding in the battlefield. The benefit risk profile for the civilian population—where the incidence of junctional bleeding is much less and the access to definitive emergency medical treatment is faster—is less clear.

Additional factors to be considered in determining probable risks and benefits for the XSTAT device include: the limitations of the animal study designs, clinical expertise required to use the

device, and lack of alternative treatments. The animal testing performed was conducted in a limited number of animals with axillary junctional bleeding and groin junctional bleeding but consistently demonstrated that the device can be packed in junctional wounds created in the axilla and groin to reduce hemorrhage. The animal testing was performed using a standard swine junctional bleeding model; however, the model was not adjusted to show device effect and limitations in most severe circumstances of bleeding accompanied by hemodilution or severe coagulopathy. The animal testing was performed in a controlled setting and standard junctional bleeding was created using a live animal model. The animal testing was performed both early in the device development process to inform device design changes and subsequent additional testing on the standard junctional bleeding live animal model was performed with the near final versions of the XSTAT device to demonstrate proof of concept. The testing was not statistically powered but demonstrated a trend of rapid device deployment with comparable treatment effects as control and required no manual compression. The sponsor has performed human factors testing to assess device deployment and has developed a script with key images for an instructional video. This instructional material has been carefully reviewed and appears to mitigate potential use error associated with device use and early recognition of potential adverse events associated with device use. The human factors testing demonstrated that users could apply the device to a junctional bleeding site in a mock setting. These risk mitigations have been carefully reviewed and appear to be acceptable.

In conclusion, given the available information above, the data support that for the temporary control of bleeding for non-compressible wounds in the groin and axilla, the probable benefits outweigh the probable risks for the XSTAT. Sufficient evidence has been provided to establish special controls that can adequately mitigate the risks to health for the use of XSTAT for its intended patient population. The probable benefits outweigh the probable risks for battlefield device use since junctional bleeding is more frequently encountered in the battlefield and because there are few options for obtaining hemorrhage control in austere battlefield settings where definitive healthcare facility access is limited. There is an urgent need for devices that can reduce hemorrhage from non-compressible groin and axillary junctional bleeding. Many of the listed adverse events may be reversed with expeditious treatment using the device and transfer of the patient to a facility capable of offering definitive treatment of the injury. The device provides substantial benefits and the risks can be mitigated by the use of general and identified special controls.

CONCLUSION

The *de novo* for the XSTAT is granted and the device is classified under the following:

Product Code: PGZ
Device Type: Non-absorbable, expandable, hemostatic sponge for temporary internal use
Class: II
Regulation: 21 CFR 878.4452