

## SUMMARY REVIEW MEMO

**Date:** May 17, 2011

**From:** [REDACTED] Ph.D.  
FDA/CDRH/ODE/DSORD/PRSB

**Subject:** P990004/Supplement 019  
SURGIFLO Hemostatic Matrix  
SURGIFLO Hemostatic Matrix Kit with Thrombin

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**To:** The Record

### **Reason for Supplement**

Ethicon, the sponsor, is seeking approval of the following changes to their SURGIFLO Hemostatic Matrix and SURGIFLO Hemostatic Matrix Kit with Thrombin:

1. Introduction of a new Hemostatic Matrix formulation (modified) with increased viscosity for improved handling compared to the existing Matrix formulation (marketed).
2. Redesign the application components of the kit to be more ergonomic and easily identifiable.
3. Reorganize the packaging of kit components to reduce the overall packaging size.
4. Add the prescribing information of EVITHROM Lyophilized Thrombin directly into the directions for use to form one packaging insert (reviewed by CBER)
5. Update the labeling information.

### **Review Team**

[REDACTED] Ph.D. (Commissioner's Fellow)

### **Indications for Use**

SURGIFLO Hemostatic Matrix and SURGIFLO Hemostatic Matrix Kit with Thrombin are both indicated for surgical procedures (except ophthalmic) for hemostasis, when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures is ineffective or impractical.

### **Device Description**

SURGIFLO Hemostatic Matrix consists of porcine-derived gelatin powder suspended in saline and processed to yield a paste. It is provided within a syringe along with applicator tips and

several mixing accessories. The SURGIFLO Hemostatic Matrix Kit with Thrombin adds lyophilized human thrombin and sterile water.

## **Summary of Pre-Clinical Data**

### **Biocompatibility**

The following biocompatibility tests were conducted on the Hemostatic Matrix paste:

1. Muscle implantation testing (in accordance to ISO 10993-6)

According to the conditions of the test, the Hemostatic Matrix paste was determined to be biocompatible.

The following biocompatibility tests were conducted on extractions from the syringe, applicator tips, and mixing accessories:

1. Delayed dermal contact sensitization testing (in accordance to ISO 10993-10)
2. Pyrogenicity testing (in accordance to USP <151>)
3. Cytotoxicity testing (in accordance to 10993-5)
4. Acute systemic toxicity testing (in accordance to 10993-11)
5. Intracutaneous reactivity testing (in accordance to ISO 10993-10)

According to the conditions of these tests, the syringe, applicator tips, and mixing accessories were determined to be biocompatible.

### **Identification of Leachables and Extractables**

The syringe components were extracted in both (b) (4) and (b) (4) using a test article to solvent ratio of (b) (4) g/(b) (4) ml, an elevated temperature (water: (b) (4) C, (b) (4) (b) (4) C) and reflux. The extracts were then evaporated and baked at (b) (4) C for (b) (4). The soluble extractable weight was measured and the drying process was repeated until the change in measured weight was less than (b) (4) mg. The extraction procedure was repeated on each test article until the measured change in extraction residue was (b) (4)% or (b) (4) mg. The extracts were analyzed using (b) (4) and (b) (4) for leachables/ extractables and the following materials were identified: (b) (4)

(b) (4). Toxicological information on the extracted chemical species was identified using the (b) (4) (b) (4) and (b) (4) was used to screen identified chemical species for genotoxicity. None of the identified chemical species were found to be genotoxic and there were no safety concerns at the levels observed. Additionally, heavy metal analysis showed the primary container system did not contribute significant heavy metal contamination.

### **Swelling**

Both the modified and marketed formulations of the hemostatic matrix paste were mixed with (b) (4) or (b) (4) of thrombin (from Ethicon's (b) (4), human) prior to use. An additional (b) (4) of (b) (4) (from Ethicon's (b) (4), human) was added to the mixture and a clot was allowed to form by curing the mixture for (b) (4) at (b) (4) C. The resulting clot was segmented into (b) (4) and then placed in (b) (4) ml of (b) (4) for (b) (4) hours. The clot segments were weighed before and after (b) (4) incubation and swelling was defined as the percent weight

increase of the clot. Overall the swelling range for both formulations was between 7 – 20% (marketed: 7 – 14%, modified: 9 – 20%), however in all cases the modified formulation swelled to a greater degree than the marketed formulation. These swelling values were compared to SURGIFOAM Absorbable Gelatin Powder (approved under PMA P990004/S004) prepared under similar conditions (adjusted according to its specific instructions for use) to determine the risk associated with this enhanced swelling. SURGIFLOAM Absorbable Gelatin Powder had a higher swelling range (22 – 26%) than both the marketed and modified formulation of SURGIFLO Hemostatic Matrix. Therefore, it was determined that the increase swelling did not impose additional safety concerns.

**Time to Hemostasis (TTH)**

Immediate Use Post-Mixing

The modified and marketed hemostatic matrix paste formulations were mixed with either (b) (4) of sterile saline or sterile EVITHROM topical human thrombin (provided as a (b) (4), (b) (4) IU/ml). The control device, saline wetted gauze (b) (4) samples), and the test devices (b) (4) samples/article) were evaluated using a (b) (4) model. (b) (4) (b) (4) were anaesthetized using medication that does not interact with the hemostasis process. (b) (4) defects were made in the (b) (4) to produce bleeding sites in each of the (b) (4), the (b) (4), and the (b) (4) of the (b) (4). Each bleeding site was treated with either the control or test device (b) (4) samples of each article per (b) (4). For test sites, a sufficient amount of test material ((b) (4) ml) was applied to (b) (4) bleeding surface and (b) (4) was applied over a saline soaked gauze with a (b) (4). For control site, a saline soaked gauze was applied to the bleeding surface and (b) (4) was applied (b) (4) with a (b) (4). At all sites, initial (b) (4) application started the clock for time to hemostasis measurement. (b) (4) was maintained for a period of approximately (b) (4), at which time the gauze was lifted from the treatment site. The test site was observed for a period ranging (b) (4) to (b) (4). When free (b) (4) was observed at any time during the observation period, the test material was (b) (4) (b) (4) at test sites that did not appear to (b) (4). At all test sites observed to have (b) (4), (b) (4) was applied again with a (b) (4) over the gauze and held for (b) (4). (b) (4) compressions and (b) (4) were repeated as described until hemostasis was deemed complete or a time of (b) (4) was reached. If (b) (4) was not observed during the observation period, hemostasis was deemed complete and the time to hemostasis was noted.

The results from this study were compared to a similar study conducted with the marketed product. The protocols differed slightly:

	Marketed	Modified
Initial test material applied:	0.8 – 4.0 ml	1.0 – 7.0 ml
Additional test material applied:	0.4 – 1.8 ml	0.5 – 2.0 ml
Initial observation period:	11 – 135 sec	< 60 sec
Subsequent observation period:	2 – 64 sec	60 sec

The results from both studies are reported below:

Modified Formulation + Saline:	4.201 ± 1.8621 min
Marketed Formulation + Saline:	4.373 ± 1.5496 min
Modified Formulation + Thrombin:	3.000 ± 0.0000 min
Marketed Formulation + Thrombin:	3.357 ± 0.8369 min
Gauze + Saline:	> 10 ± 0.0000 min

The one-sided 90% Clopper-Pearson Confidence Interval was used to compare the relative benefit of using thrombin vs. saline within each formulation and the relative improvement compared to the control. Both the marketed and modified paste formulations mixed with thrombin and saline achieved statistically significant improvements in time to hemostasis compared to saline wetted gauze. In both formulations, the use of thrombin did not significantly improve the time to hemostasis compared to the use of saline.

### 8 hrs Post-Mixing

The objective of this study was to evaluate the hemostatic efficacy of the modified hemostatic matrix paste when used 8 hrs after preparation with saline or thrombin. The modified hemostatic matrix paste formulation was mixed with (b) (4) ml of saline or (b) (4) ml of thrombin solution (lyophilized EVITHROM thrombin reconstituted using saline to a concentration of (b) (4) IU/ml), and either (b) (4) used or stored at room temperature for > 8 hrs prior to use. The test articles were compared to the marketed hemostatic matrix formulation with thrombin and wetted gauze (negative control). The study was performed in a (b) (4) model using a (b) (4) (b) (4) technique and the (b) (4) were anaesthetized using medication that does not interact with the hemostasis process. The effectiveness of each article (n samples/article) was assessed by time to hemostasis (TTH). Test articles were applied to the (b) (4) initially for (b) (4) followed by a (b) (4) hemostasis evaluation period. If hemostasis was not achieved, an additional (b) (4) was applied and a (b) (4) re-evaluation for hemostasis was performed. (b) (4) application/evaluation was repeated until hemostasis was achieved or the testing period reached 12 min (the failure time point).

All extended use samples were aged beyond the 8 hour time point (saline: average = (b) (4) hrs; thrombin: average = (b) (4) hrs). The average TTHs results reported in the study are as follows:

Modified Formulation + Saline + 0 hrs:	2:21 min
Modified Formulation + Saline + 8 hrs	2:05 min
Modified Formulation + Thrombin + 0 hrs:	2:00 min
Modified Formulation + Thrombin + 8 hrs:	2:00 min
Marketed Formulation + Thrombin + 0 hrs:	2:00 min
Gauze + Saline:	> 12:00 min

### **12-Month Stability**

The sponsor performed a 12-month real-time stability study in a (b) (4) °C / (b) (4) %RH environment and performed tests to show that the product remained stable during the intended shelf-life. Testing included the evaluation of physical performance of the individual components, efficacy of the paste in a (b) (4) model, and evaluation of the properties of the primary packaging material. However, the results did not include data for time-to-hemostasis testing and showed the

viscosity of the paste decreased substantially over the 12-month period. As a result, additional testing was suggested:

#### Time-To-Hemostasis

The time-to-hemostasis was evaluated to ensure the efficacy of the modified formulation did not diminish over the 12-month shelf-life period. In the results the sponsor stated all samples achieved hemostasis faster than the negative control. However, data was not provided to verify this statement. The sponsor was requested to show data to confirm the modified paste achieved hemostasis faster than the negative control and compare the time-to-hemostasis of the modified and marketed pastes. The results indicated the time-to-hemostasis of both pastes were similar and outperformed the negative control.

#### Viscosity

The viscosity of the modified formulation decreased quite dramatically over the 12-month period, changing from approximately 3300 Pa\*S to 2000 Pa\*S, which raised concerns of reduced performance. Once applied to the bleeding surface, the gelatin paste is expected to remain firmly in place as it stimulates the formation of a clot and a return to hemostasis. Therefore, the paste must maintain a certain viscosity to ensure the product acts on the intended site and does not extend into unexpected areas. The sponsor was asked to compare the viscosity of the modified formulation to the marketed formulation over a 12-month period to show this decrease in viscosity was similar in both products. The results showed that the viscosity of both products decreased over time and the modified formulation remained above the marketed formulation at all time points.

#### **Review of Proposed Labeling Changes**

The sponsor states that the following changes were made to the product labeling.

1. Addition/deletion of references to specific components of the modified and marketed device to reflect the proposed changes in device design.
2. Minor updates to the kit box format.
3. Minor updates to text format.
4. Additional text revisions/clarifications.
5. New labeling for thrombin packaging.
6. Updated and added new symbols on the packaging.
7. A recommended volume of saline to prepare the SURGIFLO Hemostatic Matrix.
8. Three new warnings.
9. Directions for use in open procedures.

10. Further directions for the preparation of thrombin.
11. Instructions on removing the components from the new packaging.
12. More specific intended use statement.
13. Addition of the prescribing information of EVITHROM Lyophilized Thrombin directly into the directions for use to form one packaging insert (reviewed by CBER)
14. Updated swelling capacity of the modified formulation.
15. A statement claiming the SURGIFLO Hemostatic matrix paste can be mixed with either saline or thrombin solution and effectively used up to 8 hours after completing the mixing procedure.

Most of the proposed changes further clarify the intent of the statements that appear in the current version of the labeling. However, there are several changes that required further supportive data or rationale from the sponsor to justify these changes. These are described in further detail below.

The sponsor added a statement claiming the SURGIFLO Hemostatic Matrix paste can be mixed with either saline or thrombin solution and effectively used up to 8 hours after completing the mixing procedure. However, scientific evidence to substantiate this claim was not provided in the original submission. In an email sent on January 31, 2011, the sponsor was requested to provide evidence that the Hemostatic Matrix paste remained effective 8 hours after mixing with either saline or thrombin solution or remove the statement from the labeling. The sponsor agreed to provide the requested additional information during a teleconference held on February 11, 2011. A study report containing this information was sent via email to the Agency on February 15, 2011. This study showed that both the SURGIFLO Hemostatic Matrix and SURGIFLO Hemostatic Matrix Kit with Thrombin were able to achieve equal Times to Hemostasis when used immediately or aged for 8 hrs. As a result, this claim was added to the labeling.

The sponsor changed the labeled swelling capacity of the SURGIFLO Hemostatic Matrix paste from 19% to 20%, however scientific evidence to support this modification was not initially provided. On January 31, 2011, the sponsor was requested, via email, to provide data showing that the modified SURGIFLO Hemostatic Matrix paste formulation has the potential to swell 20%. The sponsor agreed to provide the requested additional information during a teleconference held on February 11, 2011 and sent a study report to the Agency, via email (dated February 15, 2011), that tested the swelling capacity of the hemostatic matrix paste mixed with (b) (4), or (b) (1) ml thrombin and (b) (1) ml fibrinogen. The swelling capacity of these samples ranged from 9 – 20%. As a result, this claim was added to the labeling.

#### **Summary of Interactive Review and Correspondence**

On January 31, 2011, the sponsor was asked, via email, to provide additional information that was specifically outlined in the letter.

On February 11, 2011, the sponsor agreed, via teleconference, to address the requests for additional information outlined in the email sent on January 31, 2011 and provide the responses when available via email.

On February 15 and March 4, 2011, the sponsor sent, via email, additional information requested in the email sent January 31, 2011.

On March 7, 2011, Amendment 1 was received by the FDA containing the additional information from email correspondences on February 15 and March 4, 2011.

On March 11, 2011, a Not Approvable Letter was issued to the sponsor.

April 8, 2011, the sponsor agreed, via teleconference, to address the requests for additional information outlined in the Not Approvable Letter sent on March 11, 2011.

May 2, 2011, Amendment 2 was received by the FDA containing responses to the deficiencies outlined in the Not Approvable Letter send on March 11, 2011.

May 13, 2011, Amendment 3 was received by the FDA containing the BLA approval from CBER regarding the prescribing information of EVITHROM Thrombin.

### **Conclusion**

This supplement is being submitted to seek approval for a new formula of SURGIFLO Hemostatic Matrix and SURGIFLO Hemostatic Matrix Kit with Thrombin, which possesses increased viscosity for improved handling compared to the marketed matrix formulation. In addition the sponsor redesigned the application components of the kit, reorganized the packaging, added prescribing information of EVITHROM Lyophilized Thrombin directly into the directions for use, and updated the labeling. Standard biocompatibility tests were performed along with extractable/leachable testing to show the design changes did not affect the safety of the product. The swelling of the modified formulation did increase beyond that of the marketed formulation, however the sponsor showed this increase in swelling remained below that of SURGIFOAM Absorbably Gelatin Powder (approved under P990004/S004). To demonstrate the change in formulation did not influence the effectiveness of the product, a time-to-hemostasis was evaluated in a porcine liver model immediately post-production, at the end of a 12-month stability test, and 8 hours after mixing with saline or thrombin. Under all these conditions, the time-to-hemostasis of the modified formulation was similar to the marketed formulation. Viscosity was also measured over the 12-month stability study and shown to decrease significantly over that period of time. However, the viscosity of the modified formulation remained above the marketed formulation at all time points. The sponsor included additional labeling claims to reflect the swelling and time-to-hemostasis results. The prescribing information of EVITHROM Lyophilized Thrombin was also added directly into the directions for use (this was reviewed by CBER).

**Recommendation** – I recommend that the supplement be **Approved**.

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[Redacted], Ph.D. Date  
[Redacted], Plastic and Reconstructive Surgery Branch

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[Redacted] Ph.D. Date  
[Redacted], Plastic and Reconstructive Surgery Branch