

Stryker Sustainability Solutions' Reprocessed LigaSure Impact Curved, Large Jaw, Open Sealer/Divider: A Pre-Clinical Comparison to OM LigaSure Impact Curved, Large Jaw, Open Sealer/Divider

STUDY SUMMARY

Stryker Sustainability Solutions' (SSS) Reprocessed LigaSure Impact Curved, Large Jaw, Open Sealer/Divider devices (reprocessed LF4318) were compared to original manufacturer (OM) LigaSure Impact Curved, Large Jaw, Open Sealer/Divider devices (OM, non-reprocessed LF4318) and found to perform as well as OM devices for seal integrity (hemostasis), tissue sticking and tissue charring in an acute study. Thermal spread measurements were also found to be statistically equivalent between OM and reprocessed devices using histopathology methods. The average thermal spread depth for reprocessed devices was 2.38mm and 2.33mm for OM, and the lateral thermal spread was 2.61mm and 2.82mm, respectively. Additionally, a chronic, 21-day animal survival study was performed, which demonstrated effective long-term seal quality of the reprocessed device. The pathological gross assessment of the surviving animals demonstrated healed vascular seal sites with acceptable long-term seal quality and no indication of recent or active bleeding. In addition, there were no hemostatic complications or evidence of thermal injury to adjacent tissue attributed to use of the reprocessed device.

BACKGROUND

Advanced directed energy vascular sealing instruments have become essential with the proliferation of endoscopic procedures as well as general surgical procedures. These devices are of vital importance to providing hemostasis while sealing and dividing vessels, and can be costly as single-use instruments. With over two decades of reprocessing experience, Stryker Sustainability Solutions is the market-leader provider of reprocessing and remanufacturing services for medical devices. SSS offers innovative, cost-effective programs to help meet the resource management demands of its hospital partners, while reducing the environmental impact, in order to support advancements in responsible healthcare. SSS incorporates both internal and third-party validation of all cleaning systems and employs a rigorous validation paradigm for reprocessing even the most contaminated devices. Reprocessing of single use medical devices includes the disinfection (the process of killing pathogenic organisms or rendering them inert), cleaning, remanufacturing, functional performance testing, packaging, labeling and sterilization of a used medical device, for an additional clinical use through demonstration of substantial equivalence.

"Substantial equivalence" to a legally marketed (predicate) device is demonstrated through Premarket Notification, or 510(k) clearance, in accordance with the Food and Drug Administration (FDA) Code of Federal Regulations (21CFR Part 807).¹ Specifically, FDA draft guidance for bipolar electrosurgical vessel sealers suggests that comparative thermal spread data should be provided that includes quantitative measurement (under magnification) of the size (length, width and depth) of the thermal damage zone. After vessels are sealed with either subject or predicate (control) device, thermal damage (e.g. coagulation necrosis) should be assessed histologically to determine the distance from the edge of the seal. Similarly, the same draft guidance states that in order to assess the long-term seal quality and potential for injury to adjacent structures, a chronic animal study should evaluate device performance at a minimum of three (3) weeks post-procedure in at least five (5) animals.²

As part of the verification and validation activities to show substantial equivalence, and receiving FDA 510(k) clearance,³ multiple benchtop functional performance tests were performed with reprocessed and OM LigaSure Impact Open Sealer/Divider (LF4318) devices, such as vessel burst pressure and thermal spread measurements (evaluated with a FLIR infrared camera).⁴ However, in addition to benchtop testing, and to further demonstrate the effectiveness of the reprocessed LF4318 device, acute and chronic studies were designed and executed in a porcine model to support the FDA draft guidance, which is outlined in the succeeding discussion. In the animal studies, multiple sized vessels were sealed in vivo (both arterial and venous). Post-operative histology evaluation of thermal spread was included in the design of the acute study, whereas evaluation of long-term seal quality was designed into the chronic study. The null hypothesis was defined as no difference in performance between reprocessed and OM devices for both acute and chronic studies.

METHODS

The preclinical studies consisted of Institutional Animal Care and Use Committee (IACUC) approved protocols using a porcine model.⁵ The anatomy and physiology of the porcine model provided a tissue response to electrosurgical instrumentation similar to that of human tissues. The surgeon and pathologist were blinded as to the device identification (OM vs. reprocessed) until after all scoring, measurements and gross evaluation were completed to eliminate bias.

For the chronic animal study, a total of seven (7) subject animals (where one reprocessed device was used for each subject), plus one (1) control animal (OM device was used) underwent a splenectomy, unilateral nephrectomy and bilateral oophorectomy, and all vessels associated with the organs were sealed with a LigaSure LF4318 device (seven reprocessed plus one control). A gross evaluation was performed at day 21 to assess hemostasis of the sealed vessels and any collateral tissue changes, as appropriate.

The acute animal study was designed to compare a minimum of three (3) subject animals and three (3) control animals, where a total of six (6) porcine test systems were used. One reprocessed device was used for each subject animal and one OM device was used for each control animal. Each animal underwent procedures to seal multiple vessels of different sizes and with various physiological functions (Table 2). Device performance was assessed through thermal spread measurement, seal integrity (hemostasis), tissue charring and tissue sticking to the device distal jaws.

Vessel Type	Vessel Identification
A/V Bundle	ovarian pedicle, short gastric, splenic, uterine bundle
Artery	carotid, gastric splenic, large intestinal, rectal, renal, small mesenteric, splenic
Vein	gastric splenic, internal jugular, large intestinal, rectal, renal, small mesenteric, splenic

Table 1. Vessel type and identification

Vessel Diameter	0-2mm	2-5mm	5-7mm
Power Level	Low (1 Bar)	Medium (2 bars)	High (3 Bars)
Instructions for Use	<i>Use on isolated or small tissue bundles</i>	<i>Use with average tissue bundles</i>	<i>Use on larger tissue bundles</i>

Table 2. Generator power level assignment per vessel diameter

In the acute study, thermal spread depth and lateral thermal spread were measured postoperatively, and evaluated by an ACVP board-certified veterinary pathologist. Hematoxylin and eosin (H&E) was used for histological staining. The length (depth) of thermal spread (indicated by the double headed arrow) was measured as the distance from the outside or outer edge of the thermally injured tissue/seal (indicated by the dotted arrow) to the endpoint of thermal change (indicated by the broken arrow). The measurements were obtained from the intimal, medial or adventitial surface of the blood vessel or vascular plexus.

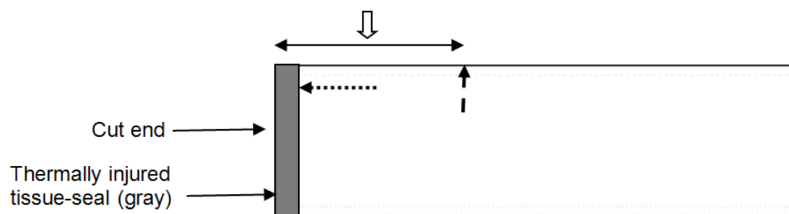


Figure 1. Depth of Thermal Spread Measurement

The width of thermal spread (indicated by the double-headed arrow) was the measured distance from the thermally injured perivascular tissue on one side of the vessel (light gray area) to the thermally injured tissue on the opposite side of the vessel. The measurement was obtained at approximately halfway between the inner edge of the thermal seal and the endpoint of the thermal injury.

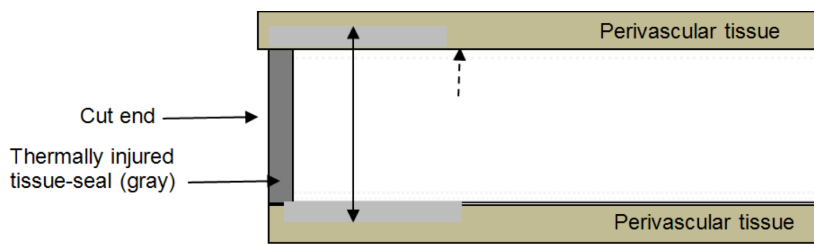


Figure 2. Lateral Thermal Spread Measurement

Depth of thermal damage and lateral spread was identified by the pathologist by one or more of the following:

- Tunica media smooth muscle cell nuclear pyknosis (shrunken dark nuclei)
- Tunica media smooth muscle cell vacuolation which was greater than the incidental vacuolation observed in the vessel wall at the opposite end from the seal.
- Cellular changes in the tunica adventitia predominately pyknosis.
- Collagen changes (denaturation, fragmentation, hypereosinophilia) in the tunica adventitia and immediate perivascular tissue.
- Perivascular changes in adipocytes, small blood vessels or small nerve fibers adjacent to the treated blood vessel.

In the acute study, seal integrity (hemostasis), tissue charring and tissue sticking were rated on a four-tiered scale by the surgeon after performing each incision[†]. For each evaluation, a test for normality was conducted on both the reprocessed and OM sample populations using an alpha level of 0.05 to determine whether each sample population is considered to be normal or non-normal. An Anderson Darling (AD) score of less than or equal to 0.75 or a P-value of greater than or equal to 0.05 indicates that the data is normally distributed. The subject and control populations for lateral thermal spread exhibited normal data and therefore a (2-sample) t-test was used to determine statistical equivalence between the sample populations. In the remaining cases, one or both sample populations exhibited a non-normal distribution, and therefore a Mann-Whitney comparison was used to determine if the two sample populations are different. A P-value of greater than or equal to (\geq) 0.05 indicates that there is not a detectable statistical difference between populations under test for both t-test and Mann-Whitney comparison tests. In some cases, a statistical hypothesis test could not be used because one or more sample population(s) consisted of the same ordinal data point. These tests used an individual plot with a 95% confidence to graphically depict the distribution of the sample populations. The raw data and detailed statistical analysis are contained in the report on file.^{5,6}

The chronic, 21-day survival study was designed to assess long-term seal quality and potential for injury to adjacent structures. Multiple vessel types and diameters per animal were sealed using reprocessed LigaSure Impact devices, across various generator power levels. All three generator power levels were represented in each animal, where the power level was assigned to be used on the various vessel diameters, ranging from 0-7mm in diameter in order to achieve the desired tissue effect, according to the device instructions for use (IFU) (Table 2).

RESULTS

Acute Study

Thermal Spread: One hundred and fifteen (115) out of 134 total vessels collected were measured for depth of thermal spread. Forty-nine (49) out of 134 total vessels collected were measured for lateral thermal spread. Some blood vessels (despite several recuts) were not suitable for acquiring measurements and therefore were excluded from analysis per the discretion of the pathologist.⁵ Fifty-six (56) data points were collected for the subject device and another 59 data points were collected for the control device for statistical comparison of thermal spread depth. Additionally, 22 data points were collected for the subject device and another 27 data points were collected for the control device for statistical comparison of lateral thermal spread.

Each specimen was microscopically measured (morphometry) by the pathologist and the data was sent to the study sponsor for statistical analysis per the protocol. There was no detectable statistical difference between the OM and reprocessed populations for either depth or lateral thermal spread (Table 1 and Table 2).

Vessel Size Range	Generator Power	Reprocessed (SSS) LF4318			OM LF4318			P-value
		Mean (mm)	SD (mm)	N	Mean (mm)	SD (mm)	N	
0-2mm	Low (1Bar)	2.01	1.28	6	1.96	0.51	8	0.48
2-5mm	Medium (2 Bars)	2.35	0.82	31	2.36	0.69	29	0.65
5-7mm	High (3 Bars)	2.56	0.65	19	2.43	0.70	22	0.50
0-7mm	All	2.38	0.83	56	2.33	0.68	59	0.96

Table 3. Depth of Thermal Spread Results Summary

Vessel Size Range	Generator Power	Reprocessed (SSS) LF4318			OM LF4318			P-value
		Mean (mm)	SD (mm)	N	Mean (mm)	SD (mm)	N	
0-2mm	Low (1Bar)	1.51	0.69	5	2.08	0.34	5	0.23
2-5mm	Medium (2 Bars)	2.86	0.91	12	2.90	1.00	15	0.92
5-7mm	High (3 Bars)	3.12	1.01	5	3.25	1.07	7	0.83
0-7mm	All	2.61	1.05	22	2.82	1.01	27	0.62

Table 4. Lateral Thermal Spread Results Summary

Histology: Figure 3 represents the manner in which the histological slides were measured for the depth of thermal tissue spread. Both images are small intestinal mesenteric artery specimens.

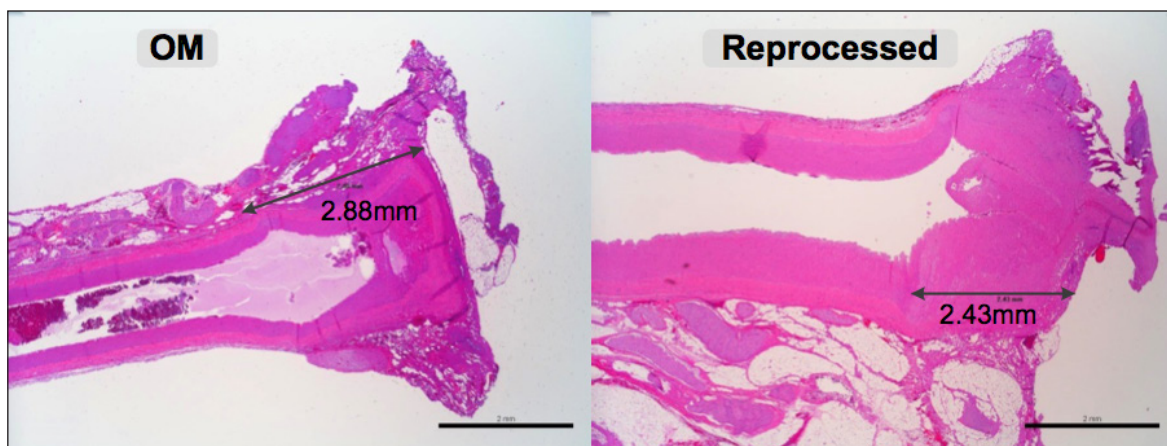


Figure 3. Representative Histological Images

Seal Integrity: Sixty-eight (68) OM and 66 reprocessed samples were evaluated for seal integrity during the surgery. There was no detectable statistical difference between the groups. Overall average seal integrity rating for both reprocessed and OM was one (1), indicating adequate seal at tissue site, with no leakage of blood (complete hemostasis) as evaluated by the surgeon, and according to the established ranking scale.† During microscopic examination (post-operatively by the pathologist), all sealed sites evaluated appeared to have microscopic seal integrity meaning that the vessel was closed or sealed and there was no evidence of hemorrhage, vascular leakage, or fibrin deposition on the ends of

the seals. Additionally, there was no loss of vascular structure such as arterial dissection or arterial/venous medial thinning observed in any site (OM or reprocessed).

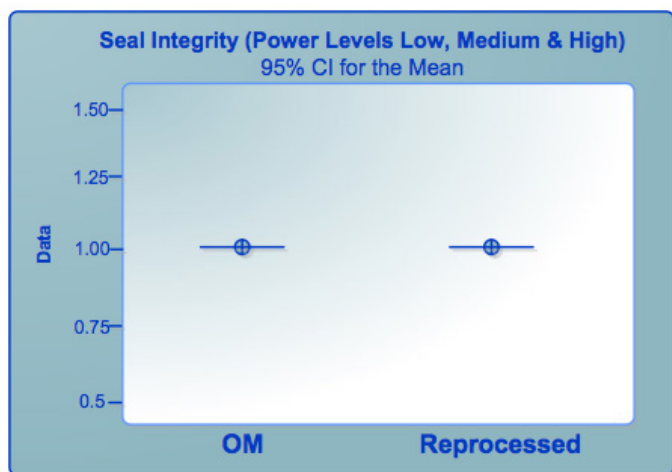


Figure 4. Seal Integrity Interval Plot with 95% CI

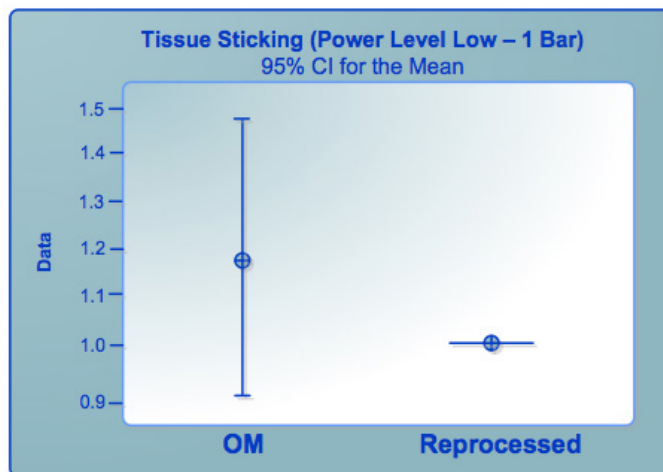


Figure 5. Tissue Sticking Interval Plot with 95% CI, Power Level: Low

Tissue Sticking: Sixty-nine (69) OM and 67 (SSS) reprocessed samples were evaluated for tissue sticking. Overall average for reprocessed ranking was 1.06 and 1.19 for OM devices. For the low power level, there was no tissue sticking observed for the reprocessed devices (average ranking was 1.00 (SSS) and 1.18 (OM)), which is graphically depicted in Figure 5[†]. However, there were two (2) instances at high and two (2) at medium power settings, where minor tissue sticking occurred to one or both jaws. For the OM devices, there were a total of 13 occasions where minor tissue sticking was observed across all power levels (average rankings: (medium) 1.06 (SSS), 1.12 (OM); (high) 1.09 (SSS), 1.29 (OM)). Overall, there was no detectable statistical difference between the OM and reprocessed samples (P-values were > 0.05).

Tissue Charring: Sixty-nine (69) OM and 67 reprocessed samples were evaluated for tissue charring. The average sample for reprocessed and OM exhibited minimal charring (refer to ranking scale in Methods section). There was no detectable statistical difference between the OM and reprocessed sample populations.

Vessel Size Range	Generator Power	Reprocessed (SSS) LF4318		OM LF4318		P-value
		Mean	N	Mean	N	
0-2mm	Low (1Bar)	1.88	8	1.36	11	0.08
2-5mm	Medium (2 Bars)	1.50	36	1.69	34	0.26
5-7mm	High (3 Bars)	1.65	23	1.88	24	0.32
0-7mm	All	1.70	67	1.61	69	0.34

Table 5. Average Tissue Charring Results Summary

Chronic Study

At 21-day necropsy, the pathological gross assessment of the surviving animals demonstrated healed vascular seal sites with acceptable long-term seal quality and no indication of recent or active bleeding. In addition, there were no hemostatic complications or evidence of thermal injury to adjacent tissue attributed to use of the reprocessed device. Two (2) of the eight (8) animals did not survive to the 21-day endpoint due to complications that were not related to either the subject or control device. The chronic study provides further assurance that the reprocessed LigaSure Impact device will perform as intended to provide acceptable long-term seal quality and is safe for human use.

DISCUSSION

Reprocessed LigaSure Impact Curved, Large Jaw, Open Sealer/Divider (SSS LF4318) were compared to brand new models (OM LF4318) during an acute animal study, in addition to a chronic animal study, which demonstrated long-term seal quality was achieved for reprocessed devices. The reprocessed devices utilized in the animal studies underwent extensive device cleaning, functional performance testing, preoperative inspection and sterilization process managed by Stryker Sustainability Solutions.

The results presented in these preclinical studies, performed on porcine models in vivo, provide further validity of the functional performance benchtop test performed,⁴ as the reprocessed devices functioned similarly to OM devices. Benchtop vessel burst pressure and thermal spread tests were evaluated on 2-7mm diameter porcine carotid and iliac vessels. Vessels sealed with the reprocessed LF4318 had vessel burst pressures that were statistically equivalent or greater than the OM. Thus the benchtop burst pressure tests, seal integrity (hemostasis) evaluated in the acute study and the long-term seal quality as evaluated in the chronic study all provide evidence of the seal integrity and quality performance of the reprocessed LF4318 being substantially equivalent to the OM.

Similarly, the results presented for thermal spread depth and lateral thermal spread via histopathology methods provide further confirmation of the functional performance benchtop thermal spread results, where infrared thermal images were recorded with a FLIR infrared camera using customized fixturing. To measure the thermal spread, FLIR images were analyzed using customized software to calculate the maximum distance from the middle of the device jaws to where the tissue surrounding the jaws reaches a temperature that would result in protein denaturation in tissue (above 60°C). Vessels sealed with the reprocessed LF4318 had thermal spread distances that were statistically equivalent or less than the OM.⁴ Thus the benchtop thermal spread tests using the FLIR infrared camera and thermal spread measured via histopathology both provide evidence of the substantial equivalence of thermal spread between the reprocessed and OM devices (LF4318).

CONCLUSION

Data from these acute and chronic in vivo studies (Tables 3-5; Figures 3-5) were provided in addition to benchtop functional performance testing, cleaning, packaging, sterilization and biocompatibility validations as part of an FDA 510(k) pre-market notification. FDA determined that after undergoing Stryker Sustainability Solutions' comprehensive reprocessing system, the reprocessed (SSS LF4318) device is "substantially equivalent" to the OM LigaSure Impact Curved, Large Jaw, Open Sealer/Divider devices.

† The 4-tiered scale used for each evaluation is as follows:

Seal Integrity/Hemostasis: 1 = "Seal at tissue site, no leakage of blood (complete hemostasis)"; 2 = "Seal at tissue site, but slight oozing of blood that stops within (≤) 1 min."; 3 = "Partial sealing of vessel, but brisk bleeding present that requires intervention"; 4 = "Incomplete sealing with uncontrolled bleeding requiring intervention".

Tissue Sticking: 1 = "No sticking, tissue falls off instrument when opened"; 2 = "Tissue sticking, minor adherence to one or both jaws"; 3 = "Tissue sticking requiring counter tension and extensive force to remove tissue"; 4 = "Tissue sticking such that tissue is damaged or torn during the removal process".

Tissue Charring: 1 = "No charring"; 2 = "Minimal charring, browning rather than blackening"; 3 = "Moderate charring, browning and few black spots"; 4 = "Severe charring, confluent black spots".

‡ The SSS population consisted of the same ordinal data point at low power setting; a statistical hypothesis could not be used, and therefore, the distribution of populations was represented on an interval plot.

REFERENCES

1. 21 CFR Part 807, Subpart E, Premarket Notification Procedures.
2. Draft Guidance for Industry and Food and Drug Administration Staff, Premarket Notification [510(k)] Submissions for Bipolar Electrosurgical Vessel Sealers for General Surgery, Issued March 24, 2014
3. FDA 510(k) Clearance: K150538 (Reprocessed LigaSure Impact Vessel Sealer/Divider (LF4318)).
4. Report on file. ENG-70734-14, Functional Performance Validation of the Reprocessed Covidien™ LigaSure Impact™ Curved, Large Jaw, Open Sealer/Divider (LF4318)
5. Reports on file. (APS HWP003-IS17; HWP006-IS17)
6. Reports on file. (SSS ENG-70728-14; ENG-70729-14)

AUTHORS (SSS)

Jennifer Canteo, MSBE, BSChE
Product Manager, Marketing

Heidi Cole, MSBE, BSIE
Principal Engineer, Research & Development

Ashley Twitty, BSBME, CSSGB
Sr. Engineer, Advanced Quality Assurance

TESTING FACILITY & CLINICAL STAFF

American Preclinical Services (APS)
8945 Evergreen Blvd.
Minneapolis, MN 55433

Liisa Carter, SRS, CVT, ALAT
Associate Scientist, Assistant Surgeon

Christina Gross, BA, SRS
Scientist/Senior Surgeon

Joe Vislisel, DVM
Research Veterinarian

Kevin Catalano, MBA
Director of Quality Systems

Sheree Beam, DVM, MS, DACVP
Preclinical Pathology Consulting Service, LLC
Comparative Veterinary Pathologist/Chief Manager