DE NOVO CLASSIFICATION REQUEST FOR HEMOSPRAY® ENDOSCOPIC HEMOSTAT

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Hemostatic device for intraluminal gastrointestinal use: A hemostatic device for intraluminal gastrointestinal use is a prescription device that is endoscopically applied to the upper and/or lower gastrointestinal tract and is intended to produce hemostasis via absorption of fluid or by other physical means.

NEW REGULATION NUMBER: 21 CFR 878.4456

CLASSIFICATION: Class II

PRODUCT CODE: QAU

BACKGROUND

DEVICE NAME: Hemospray® Endoscopic Hemostat

SUBMISSION NUMBER: DEN170015

DATE OF DE NOVO: March 9, 2017

CONTACT: Wilson-Cook Medical, Inc.
4900 Bethania Station Road
Winston-Salem, NC 27105

INDICATIONS FOR USE

The COOK Hemospray® Endoscopic Hemostat is used for hemostasis of non-variceal gastrointestinal bleeding.

LIMITATIONS

The sale, distribution, and use of the Hemospray® Endoscopic Hemostat is restricted to prescription use in accordance with 21 CFR 801.109. Please refer to the labeling of the device for a complete list of warnings, precautions, and contraindications. Limitations on device use include the following statements in the Instructions for Use:

Contraindication for gastrointestinal endoscopy should also be a contraindication for the use of Hemospray®.

Hemospray® Endoscopic Hemostat is also contraindicated in patients who have

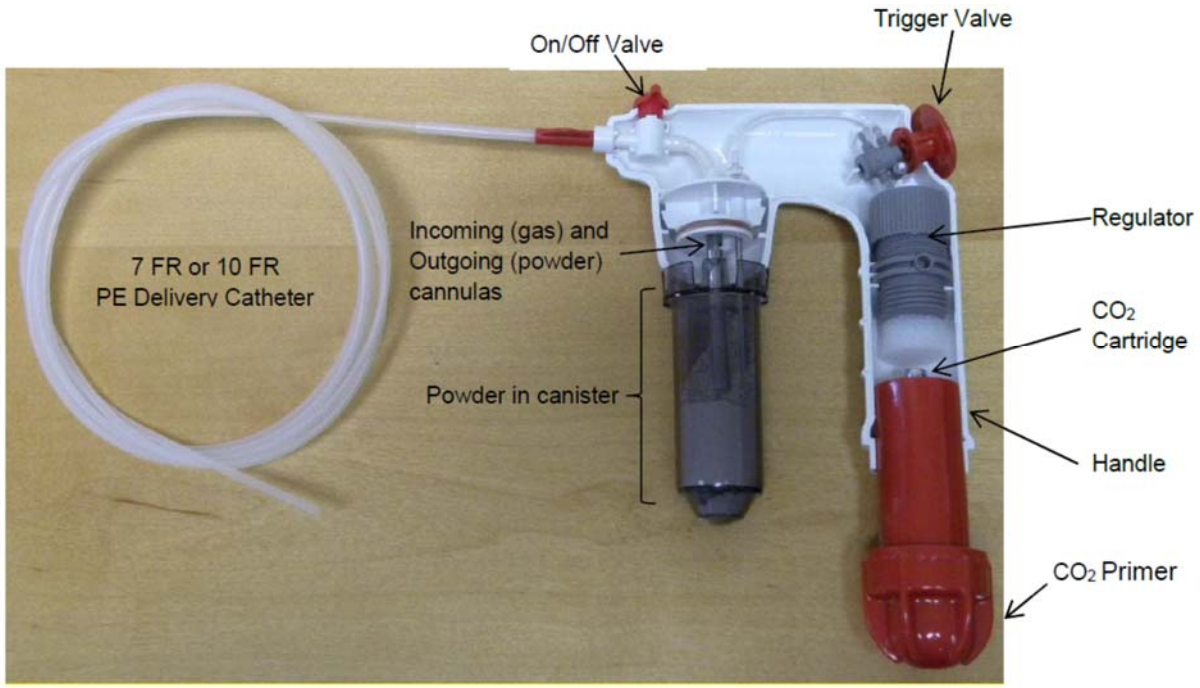
gastrointestinal fistulas, are suspected of having a gastrointestinal perforation, or are at high risk of gastrointestinal perforation during endoscopic treatment.

DEVICE DESCRIPTION

The Hemospray® Endoscopic Hemostat is a prescription use device consisting of a hemostatic agent and a delivery system. The hemostatic agent is (b) (4) bentonite powder, a naturally-sourced aluminum phyllosilicate clay. The delivery system is an endoscopic accessory used for spraying the powder onto the bleeding surface. The delivery device consists of a 220cm polyethylene application catheter, a handle with a pressurized CO_2 cartridge, and a powder chamber containing approximately 20g of the Hemospray® material. The material is propelled through the application catheter by release of CO_2 from the cartridge located in the device handle. A trigger valve with an activation button allows the physician to control the amount of powder delivered to the affected area. Each actuation of Hemospray® delivers (b) (4) cc of CO_2 and (b) (4) gram of (b) (4) bentonite. Use of the complete 20-gram canister can produce a volume increase within the lumen of the bowel of 3 liters. In the presence of blood, the (b) (4) bentonite may swell 10-15% in volume.

(b)

The delivery system is offered in two configurations (*i.e.*, two different outer diameters of the powder delivery catheter). The HEMO-7 version is used with a 2.8mm endoscope accessory channel, and the HEMO-10 version is used in a 3.7mm endoscope accessory channel.



SUMMARY OF NONCLINICAL/BENCH STUDIES

The sponsor conducted a series of non-clinical performance tests to demonstrate that the Hemospray® Endoscopic Hemostat would perform as anticipated for its intended use population.

BIOCOMPATIBILITY

The patient-contacting materials of the Hemospray® Endoscopic Hemostat include the (b) (4) bentonite powder and the polyethylene delivery catheter. Hemospray® powder is classified as an implant with prolonged tissue contact and indirect contact with blood. The following biocompatibility testing was completed on the Hemospray® powder in accordance with FDA's guidance document entitled "*Use of ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*": cytotoxicity, irritation, sensitization, acute systemic toxicity, materials mediated pyrogenicity and hemolysis testing. The subchronic toxicity and implantation endpoints were evaluated in a clinically relevant porcine gastric bleeding animal study. Genotoxicity was evaluated through chemical characterization, toxicological risk assessment and establishment of heavy metal purity specifications. All studies were conducted in compliance with GLP requirements and testing was completed on the final sterilized device. All tests met the acceptance criteria and were supportive of the overall biocompatibility conclusion that the Hemospray® product is expected to be biocompatible when used as indicated. A summary of the biocompatibility testing completed can be found below in Table 1.

The delivery catheter is classified as an externally communicating device with less than 24-hours tissue contact. The following biocompatibility testing was completed on the delivery catheter: cytotoxicity, irritation and sensitization. A summary of the biocompatibility testing completed on the delivery catheter can be found below in Table 2.

Table 1. Biocompatibility Testing/Assessment Completed on Hemospray® Powder

Biocompatibility Endpoint	***Method and Purpose***	***Result***
Cytotoxicity	ISO 10993-5: MEM Elution Study used to evaluate device extracts for cytotoxicity risks.	Non-cytotoxic
Sensitization	ISO 10993-10: Guinea Pig Maximization Sensitization Test used to evaluate device extracts for dermal sensitization risks.	Non-sensitizer
Irritation	ISO 10993-10: Intracutaneous Irritation Test used to evaluate device extracts for irritation risks.	Non-irritant
Acute Systemic Toxicity	ISO 10993-11: Acute systemic toxicity study used to evaluate device extracts for systemic toxicity risks.	No acute systemic toxicity
Material mediated pyrogenicity	USP <151>: Rabbit pyrogen test used to evaluate device extracts for pyrogenicity risks.	Non-pyrogenic
Hemolysis	ASTM: F756: Hemolytic study used to evaluate device extracts for hemocompatibility risks.	Non-hemolytic

Genotoxicity	Genotoxicity risks were evaluated through chemical characterization, toxicological risk assessment and establishment of heavy metal purity specifications.	Genotoxicity risks mitigated
Subchronic Toxicity and implantation (Animal study)	GLP porcine gastric bleeding model used to evaluate the Hemospray® product of local and systemic toxicity risks in a clinically relevant animal model.	No local or systemic toxicity

Table 2. Biocompatibility Testing/Assessment completed on Hemospray® Delivery Device

Biocompatibility Endpoint	*Method and Purpose*	*Result*
Cytotoxicity	ISO 10993-5: MEM Elution Study used to evaluate device extracts for cytotoxicity risks.	Non-cytotoxic
Sensitization	ISO 10993-10: Guinea Pig Maximization Sensitization Test used to evaluate device extracts for dermal sensitization risks.	Non-sensitizer
Irritation	ISO 10993-10: Intracutaneous Irritation Test used to evaluate device extracts for irritation risks.	Non-irritant

SHELF LIFE/STERILITY

Sterilization validation, packaging validation, and shelf life testing completed for the device can be found below in Table 3.

Table 3. Sterilization Validation, Packaging Validation, and Shelf Life Testing Overview for Hemospray® Endoscopic Hemostat

Test	*Purpose*	*Result*
Sterilization Validation ISO 11137:2006/AAMI TIR 33:2005	Verify product sterility (gamma irradiation)	Passed
Packaging Validation Visual Inspection	Visual assessment of product packaging to ensure no defects	Passed
Packaging Validation Dye Leak Test (ASTM F 1929 (R2012), (R2015))	Demonstrate that the packaging is not compromised	Passed
Packaging Validation Burst Testing (ASTM F 1140-07, R 2012)	Assess the strength of the packaging seal	Passed
Shelf Life – Device Stability Visual Inspection	Visual assessment of product to ensure that it is not compromised	Passed
Shelf Life – Device Stability Functional Testing	Evaluate the ability of the device to meet functional requirements after aging	Passed

MAGNETIC RESONANCE (MR) COMPATIBILITY

Hemospray® has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating, migration, or image artifact in the MR environment.

Hemospray® powder is composed of naturally occurring bentonite clay, which may contain elements containing metals. The safety of Hemospray® in the MR environment is unknown. Scanning a patient who has this device may result in patient injury or image artifact. No MR safety, device-related adverse effects have been observed in clinical use.

PERFORMANCE TESTING – BENCH

A summary of the performance bench testing completed on the Hemospray® Endoscopic Hemostat can be found below in Table 4.

Table 4. Performance Bench Testing Overview of Hemospray® Endoscopic Hemostat

Test	*Purpose*	*Result*
Output pressure	Demonstrate that the output pressure at the catheter tip and at the recommended use distance is below the specified threshold and therefore mitigates the risk of powder entering the bloodstream	Passed
Functional testing	Demonstrate that the user can set up the device for use, insert and remove the device from a compatible endoscope, adjust the system to reach the targeted site, detach and reattach catheters during use, press the delivery button, and deploy powder to the targeted site with the Hemospray® device	Passed
Rupture Testing	Demonstrate that the Hemospray® handle will not rupture at or below working pressures	Passed
Human Factors Testing	Demonstrate that the Hemospray® device has an acceptable torque to detach/reattach catheters, torque to open/close valve and force to press button	Passed
Powder Density	Demonstrate that the Hemospray® device can deliver powder to the desired location, that the catheter will not clog, and that powder will not be delivered intermittently	Passed
Cartridge Integrity	Demonstrate that the Hemospray® introducer component meets functional requirements after simulated shipping test	Passed
***Ex vivo* tissue trauma**	Evaluate local effects of Hemospray® when delivery catheter is positioned at recommended use distance	No significant pathological alterations were observed. Hemospray® did not penetrate the mucosal layer.

MATERIALS CHARACTERIZATION

A summary of the materials characterization completed on the Hemospray® Endoscopic Hemostat can be found below in Table 5.

Table 5. Materials Characterization Overview of Hemospray® Endoscopic Hemostat

Test	*Purpose*	*Result*
Mineral phase identification and quantification by x-ray diffraction (XRD) on a per-lot basis	Establish the compositional identity and purity of Hemospray® powder. Measurements will ensure the compositional identity and purity of each lot is within specifications.	Compositional identity and purity were established and allowed lot-to-lot acceptance criteria to be set.
Free Swell Test and Moisture Content	Establish that Hemospray® powder's extent of water absorption and moisture content meet specifications. Measurements will ensure the swelling characteristics and moisture content of each lot are within specifications.	Passed
Extraction in simulated gastric fluid for lead and arsenic on a per lot basis	Demonstrate that bioavailable lead and arsenic levels are within safe limits for each lot per limits identified in the USP monograph for Bentonite.	Passed
Particle Size Characterization	Characterize the particle size distribution of Hemospray® powder to ensure that each lot can be adequately sprayed.	Results demonstrate consistent particle size distribution across lots.

PERFORMANCE TESTING – ANIMAL

The safety and effectiveness of Hemospray® Endoscopic Hemostat was evaluated in a GLP porcine gastric bleeding model. The study is summarized below:

Table 6. Performance Animal Testing Overview of Hemospray® Endoscopic Hemostat

Test	*Purpose*	*Method*	*Results*
GLP Porcine Study	Assess hemostatic ability (effectiveness) and safety of the device	**Design:** Gastric bleeding model. Animals: 6 Hemospray® treated, 3 sham control. Duration: 10-day follow-up followed by termination	Acute hemostasis was achieved in all animals in the treatment group (6/6). One control animal (1/3) and two (2/6) treatment group animals showed re-bleeding 8 to 10 days post-operatively. The re-bleeding observed were most likely associated with limitations of the chosen surgical procedure. Histopathological evaluation of the device application site did not reveal any important histological differences between treatment group and control group animals. No evidence of Hemospray® powder was

		Endpoints: gross and histologic assessment of regional and systemic effects of powder/treatment	observed in any local or regional tissue sections of the gastric surgical site or the regional lymph nodes. No Hemospray® powder particles were observed to have been embedded in any tissue layers in any of the three histological sections collected at and around the treatment site.

Results of the animal study suggest that the Hemospray® Endoscopic Hemostat is effective at achieving initial hemostasis in a worst-case gastric bleeding model (Forrest 1a and 1b peptic ulcer type bleeding). This study does not demonstrate safety/effectiveness in large area low-pressure bleeding where the probability of embolization may be more likely nor did it assess the potential rate of delayed re-bleeding.

SUMMARY OF CLINICAL INFORMATION

Wilson-Cook Medical, Inc. has sponsored a pre-market pilot study, a survey and 2 postmarket clinical studies of Hemospray® to date, all performed outside the United States (OUS). The pilot study was a "first-in-human" feasibility study to determine performance and safety issues associated with the endoscopic use of Hemospray® powder as a hemostatic material to treat bleeding peptic ulcers. This study was conducted in Hong Kong, China from 2009 to 2010.

The Survey to Evaluate the Application of Hemospray® in the Luminal Tract (SEAL), was conducted in Canada, Denmark, England, France, Germany, Italy and Holland.

The first post-market study, Hemostasis of Active GI Luminal Tract Bleeding (HALT) trial, was conducted in the European Union (EU). It was intended to study the safety and effectiveness of Hemospray® in treating upper gastrointestinal bleeds (UGIB), specifically Forrest 1a and 1b actively bleeding ulcers. Peptic ulcers are the most common cause of UGIB and are usually classified as spurting/pulsatile (1a) or oozing (1b) according to the Forrest scale. They account for up to 50% of peptic ulcer bleeds. The study began in 2011 with an intent to enroll 80 patients; 64 patients have been enrolled to date. The HALT study continues to enroll patients in the EU and Canada.

Finally, the second post-market study, APPROACH (A Prospective Observational Cohort Study of Hemospray® for Lower Gastrointestinal Hemorrhage), was conducted in Canada and designed to collect safety and performance data on non-variceal lower gastrointestinal bleeding (NVLGIB). APPROACH has recently completed enrolling its entire complement of 50 patients at 4 Canadian sites. The results of all the studies are presented below.

PILOT STUDY

This pilot clinical trial was designed as a single-center, early feasibility study of Hemospray® powder for the treatment of bleeding peptic ulcers. The aim of the study was to investigate the safety and effectiveness of Hemospray® in achieving acute hemostasis in peptic ulcer bleeding in subjects diagnosed with Forrest 1a or 1b bleeding peptic ulcers. The protocol for this prospective trial was approved by the ethics committee of the faculty of medicine of the Chinese University

of Hong Kong, China and conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practices, and other regulations in force in Hong Kong. Written informed consent was obtained from all patients. All patients were to undergo upper GI endoscopy within approximately 24 hours of hospital admission. Each patient was allowed up to 2 applications of Hemospray® (potentially using multiple canisters during each application) during the index procedure, not exceeding a total of 150 g. Recurrent bleeding was monitored post-procedure and at a second-look endoscopy (72 hours post-treatment) was conducted on all patients. Patients were contacted by phone at 30 days to monitor the occurrence of any serious adverse events and mortality.

The safety and performance outcome measures of this study were:

Primary safety endpoint:

- The incidence of procedural and treatment-related serious adverse events for subjects treated with Hemospray®.

Primary effectiveness endpoint:

- Proportion of subjects with acute (procedural) hemostasis.
- Rate of recurrent bleeding within 72 hours of the application of Hemospray®.

Secondary Outcome Measures

- Severe adverse events and mortality within 30 days of the study procedure
- Surgery required for failure to achieve hemostasis within 72 hours

Rate of hemostasis, rate of recurrent bleeding, need for surgical intervention, treatment-related and procedure-related serious adverse events and major adverse events (*e.g.*, arterial embolization, allergic reaction, bowel obstruction) were also assessed.

Twenty patients were enrolled in the study. An interim analysis was conducted on data collected from the first 10 patients. Since no major adverse events related to the Hemospray® powder or delivery catheters were reported, 10 additional patients were enrolled. The study consisted of 18 males and 2 females. Mean age was 60.2 years (range 37-85 y). The first patient was enrolled in the study on November 17, 2009 and the last patient was enrolled on August 27, 2010. The final follow-up visit was on September 27, 2010.

All 20 patients included in this study presented with melena at hospital admission, 7 of whom also had concurrent hematemesis. Nineteen patients were diagnosed with a Forrest 1b ulcer and 1 patient had Forrest 1a bleeding. Most ulcers were in the duodenum 14 (70%) and the remaining 6 (30%) were in the stomach. A single application of Hemospray® was used in 17 (85%) patients, and two applications were used in 3 (15%) patients. The number of syringes of Hemospray® used for each patient ranged between 1 and 7, with most patients (13/20, 65%) receiving only 1 syringe (20g). Of the remaining 7 patients, 5 received 2 syringes, one patient received 4 syringes, and one patient received 7 syringes.

Results:
Endoscopic application of Hemospray® onto the ulcer bleeding site was successfully performed in all patients. Acute hemostasis was achieved in 19 of 20 patients (95%). There were no treatment-related or procedure-related serious adverse events. All patients were stable after the procedure and recovered uneventfully. The one patient in which acute hemostasis was not achieved was treated with 7 syringes of Hemospray® or 140 grams in one application. This patient was then treated according to institutional standard of care (endoscopic epinephrine injection and hemostasis clips) in 3 additional unsuccessful attempts to achieve endoscopic hemostasis and was referred for angiography during which a pseudoaneurysm was identified in the artery feeding the ulcer site. Ultimately, TAE (trans-arterial embolization) of the feeding artery was required to stop bleeding in this patient. The patient was contacted at 30 days and reported no serious adverse events.

Of the 19 patients in which acute hemostasis was achieved, sustained hemostasis as defined by the study was observed in 17 (89.5%) patients through 72 hours. Two patients met the study definition of recurrent bleeding or re-bleeding within 72 hours. However, in both patients, no active bleeding was observed at the treated lesion sites at the planned second-look endoscopy. Both patients reported no adverse event or serious adverse event at 30-day follow-up.

Safety outcome:
The Hemospray® powder was found to have been eliminated from the stomach and duodenum in all patients at the second-look endoscopy, conducted on Day 2 for one patient and Day 3 for all others. None of the patients, including the patient who received 140 grams or 7 syringes reported any adverse issues with passage of the powder through the gastrointestinal tract (*e.g.*, no bowel obstruction). All patients were stable after the procedure and discharged uneventfully. There was no mortality reported during the 30-day follow-up. No treatment-related or procedure-related serious adverse events and no major adverse events (*e.g.*, embolization, bowel obstruction, or allergic reaction) were reported. While there were no reports of serious adverse events related to either the treatment or the procedure, 5 cases of non-device related serious adverse events were reported. These included 4 cases of prolonged hospitalization: 2 due to upper respiratory tract infection, 1 due to altered liver function and psychotic depression, and 1 patient who required more time to recover and regain stable blood values. The fifth event was the diagnosis of adenocarcinoma that was initially diagnosed as a gastric ulcer during the Hemospray® treatment procedure. In this last patient, a large gastric ulcer oozing from the base was found during endoscopy. There were some features suggestive of malignancy and biopsy was performed. The bleeding was successfully controlled by Hemospray®, and no Hemospray® powder was observed at the 72-hour endoscopy at the treatment site. Histology subsequently confirmed malignancy, and this patient was referred to a medical oncologist for further management. The only observations of relevance were clogging of the Hemospray® application catheter, but in each case a new catheter was used and the procedure completed.

SURVEY TO EVALUATE THE APPLICATION OF HEMOSPRAY IN THE LUMINAL TRACT (SEAL)

Wilson-Cook Medical, Inc. initiated the post-market Survey to Evaluate the Application of Hemospray® in the Luminal Tract (SEAL) to collect limited, non-protected health information

and data on the Wilson-Cook Medical, Inc. Hemospray® Endoscopic Hemostat as part of a limited marketing release OUS. The information was used to develop educational materials for physicians new to this technology. Hemospray® used endoscopically by gastroenterologists provided effective acute hemostasis in the most common types of gastrointestinal (GI) bleeding, including Forrest 1a and 1b bleeding peptic ulcers.

As a requirement of participation in the SEAL registry, all physician participants were trained on the use of the Hemospray® kit by Wilson-Cook Medical, Inc. personnel. Training included discussion of hemostasis techniques, appropriate intended use and product labeling in the countries where the evaluation took place, and hands-on experience with the Hemospray® device. Each participating physician group was assigned a unique sign-on to access an electronic data capture form hosted on a secure internet portal. All cases entered into the database were numbered sequentially in the order of entry. No queries or audits to identify and correct missing data were performed. Summaries generated from the collected information were, therefore, constrained by the scope of the information collected, and are limited to counts of cases, common location of bleeding sites, severity of the bleeding treated, and other methods to achieve hemostasis if used in conjunction with Hemospray®. Complaints and adverse events were to be reported directly to the manufacturer. Ninety-two patients treated in Canada, Denmark, England, France, Germany, Italy and Holland were registered in this survey. Two patients had no data entered in the electronic database by the site other than age and sex. In a third patient, the CO_2 cartridge in the Hemospray® delivery system was found to be defective so the device was not used and the patient was not treated with Hemospray®. These 3 patients were excluded from analysis. Therefore, evaluable data from 89 patients were available for analysis.

Eight-four percent (84%) of patients were over the age of 50 (n = 75), and 71% (n = 63) were male. Acute hemostasis was achieved in all (100%) cases. Approximately 98% of the bleeding sites were in the upper GI tract and were identified in the duodenum (n = 38), stomach (n = 29), and esophagus (n = 20). Peptic ulcers constituted most cause of GI bleeding treated with Hemospray® (n = 40; 45%). Of the 40 patients with peptic ulcers, 16 were Forrest 1a bleeds (spurting or pulsatile), 19 were Forrest Class 1b (oozing), 3 were Forrest 2b (adherent clot), and 2 patients were unclassified. In one Forrest 2b case, a procedural video confirmed the clot was removed prior to treatment with Hemospray®. It is not known if the other 2 cases were treated in a similar fashion. Other conditions treated with Hemospray® included: bleeding after endoscopic mucosal resection or dissection (n = 9; 10%); diffuse bleeding from gastric malignancy (n = 8; 9%); Mallory-Weiss tears (n = 6; 7%); and upper GI post-polypectomy bleeding (n = 5; 6%); Hemospray® was used successfully in the colon for acute hemostasis in 2 cases.

Fifty-one (51) patients (57%) were successfully treated with Hemospray® alone, and the remaining 38 patients (43%) were successfully treated with Hemospray® as an adjunct to other standard of care methods. Hemospray® was identified as the final hemostasis treatment in 24 of 38 cases where more than one other method was used. In 5 patients, Hemospray® was used as the initial treatment and was followed by alternate methods including epinephrine injection, argon-plasma coagulation, bi-polar electrocautery, and hemoclips. In 9 patients, the order of use was unclear. Hemospray® was used as a single modality in 51 patients. Of the 51 patients treated with Hemospray® alone, 11 were diagnosed with Forrest 1a bleeds, 38 with Forrest 1b, and 2 with Forrest 2b. Acute hemostasis was achieved with Hemospray® alone in all 51 of

these patients. The remaining 38 patients were treated with Hemospray® and at least one other modality; 16 of these with Forrest 1a, 19 with Forrest 1b, 1 with Forrest 2b, and 2 were unclassified. Acute hemostasis was achieved in all 38. There were no unanticipated adverse events or serious adverse events attributed to the Hemospray® Endoscopic Hemostat. Holster I.L, *et. al*., published a study of patients in the SEAL survey with upper gastrointestinal bleeding who were on antithrombotic therapy which included mostly patients on antiplatelet agents and a few on anticoagulation therapy. Patients had 63% initial hemostasis with a 38% rebleeding rate following Hemospray® treatment.

HEMOSTASIS OF ACTIVE GI LUMINAL TRACT BLEEDING (HALT) STUDY

The HALT trial was designed to study the safety and effectiveness of Hemospray® in treating upper GI bleeds (UGIB), specifically Forrest 1a and 1b actively bleeding ulcers.
The HALT trial continues to enroll patients in Canada and Europe with a final goal of 80 enrollments. An interim report of the study findings at 64 enrollments is presented as part of this submission. The data lock was instituted on August 24, 2016. The HALT study was initiated with Version 1 of the Hemospray® device (55 psi CO_2 canisters), but all sites were converted to the Version 2 device (37 psi CO_2 canisters) effective January 2013. There are 10 enrollment sites.

Table 7: Patient Comorbidities

	%(n/N)
Hypertension	47.6% (30/63[a])
Diabetes	27.0% (17/63[a])
Patient already hospitalized for another illness when GI bleeding occurred	10.9% (7[b]/64)
Previous treatment(s) for peptic ulcer bleeding[c]	22.2% (14/63[a])
Hemostasis clips	35.7% (5/14)
Injection	42.9% (6/14)
Thermal probe	28.6% (4/14)
Upper GI surgery	0.0% (0/14)
Other Endoscopic/surgical treatment	7.1% (1/14)
Transfusion	64.3% (9/14)
IV administration of PPI	64.3% (9/14)
Oral administration of PPI	21.4% (3/14)
Other Medical treatment	0.0% (0/14)
Current symptoms of peptic ulcer bleeding[d]	98.4% (62/63[a])
Hematemesis	22.6% (14/62)
Hematochezia	12.9% (8/62)
Melena	91.9% (57/62)

[a] Data were outstanding at time of data lock for one patient.

[b] Prior hospitalization for chest, abdominal, and loin pain (1); fall(s) (2); syncope related to GI bleed (1); low hemoglobin, chest pain, shortness of breath (1); prior GI bleed (1); loose stools and generally unwell (1).
[c] Patients may have more than one treatment on prior admissions for peptic ulcer bleeding.
[d] Patients may have more than one current symptom of peptic ulcer bleeding.

Table 8. Baseline Bleed Site Characteristics

Lesion size (diameter)[a,b]	
< 1 cm	32.3% (20/62)
1-2 cm	54.8% (34/62)
> 2 cm	12.9% (8/62)
Lesion location[b]	
Stomach	25.4% (16/63)
Duodenum	74.6% (47/63)
Forrest classification[b]	
1a (spurting)	15.9% (10/63)
1b (oozing)	84.1% (53/63)

[a] One patient did not have an ulcer diameter measurement.
[b] Data were outstanding at time of data lock for one patient.

Primary Endpoint

The primary effectiveness endpoint is the proportion of patients with further bleeds within 72 hours of the index procedure. Further bleed within 72 hours is defined as persistent bleeding (bleeding at the conclusion of the index endoscopy; 7 patients did not achieve initial hemostasis with Hemospray®) or recurrent bleeding (visualization of bleeding at the treated study lesion [assessed only in patients with successful initial hemostasis]) within 72 hours.

Table 9. Primary Endpoint

	% (n/N)
Patients with further bleeds within 72 hours	17.2% (11/63[a])
Persistent bleeding after Hemospray application(s)	11.1% (7/63[a])
Endoscopically-confirmed recurrent bleed within 72 hours	7.1% (4/56[b])

[a] Data were outstanding at time of data lock for one patient.
[b] Recurrent bleed was only assessed in patients with successful initial hemostasis (*i.e.*, patients without persistent bleeding).

To further investigate if demographics or baseline characteristics affected the primary endpoint, persistent bleeding, or early recurrent bleed, a stepwise logistic regression was performed using sex, ulcer location, ulcer diameter, Forrest score, and hypertension as variables (criterion was $p<0.3$ for inclusion in the model; criterion for removal was $p>0.35$). No variables were found to significantly affect the primary endpoint of persistent bleeding; however, stepwise logistical regression indicated that patients with Forrest 1a bleeds are more likely to have an early recurrent bleed than patients with Forrest 1b bleeds. Further, patients with Forrest 1a bleeds are

more likely to have any recurrent bleed (early or late) than patients with Forrest 1b bleeds based on stepwise logistical regression.

Secondary Endpoints

Secondary endpoints include: proportion of patients with hemostasis at the conclusion of the index procedure (*i.e.*, initial hemostasis), clinical success (*i.e.*, initial hemostasis and no SAE within 72 hours of the index procedure), early recurrent bleed (*i.e.*, recurrent bleeding within 72 hours of the application of Hemospray®), late recurrent bleed (*i.e.*, recurrent bleed occurring 72 hours-30 days), incidence of serious adverse GI events within 30 days of the application of Hemospray®, incidence of serious adverse events within 30 days of the application of Hemospray® and incidence of mortality at 30 days.

Table 10. HALT Study Secondary Endpoints

	Number	**Percent**
Patients achieving hemostasis during index endoscopy	61	96.8
Successful hemostasis achieved after Hemospray® application	56	88.9
Re-bleeding within 72 hours after successful initial hemostasis	4	7.1[b]
30-day all-cause mortality	2[a]	3.2
Patients with device-related Serious Adverse Events within 30 days of index procedure	0	0.0

[a]First patient cause of death was liver failure. Second patient cause of death was pneumonia.
[b] Re-bleeding was only assessed in patients with successful initial hemostasis (n=56).

Of the twelve patients with serious adverse events, one patient had an intra-operative perforation reported. This patient died two days post-procedure due to liver failure. Ten patients had clinical signs and symptoms of re-bleeds (seven with confirmed recurrent bleeding at the study lesion site, one which endoscopically confirmed that the initial study lesion was not involved, and two which were not considered to be a recurrent bleed at the study lesion site by the physician and therefore did not have repeat endoscopy performed). Of note, clinical signs and symptoms of re-bleed are a common adverse event in patients recently treated for peptic ulcer bleeds. One patient had no signs of re-bleeding, however, developed pneumonia that resulted in death.

Table 11. Adverse Events by Organ System

Organ System	**0-3 Days (n)**	**4-7 Days (n)**	**8-30 Days (n)**
Gastrointestinal	15	5	5
Cardiovascular	0	0	1
Pulmonary	0	0	0
Miscellaneous	4	2	4

Table 12. Gastrointestinal Events

Event	**0-3 Days (n)**	**4-7 Days (n)**	**8-30 Days (n)**

Clinical signs and symptoms of re-bleed	11	5	4
Other	2	0	1
Perforation	2	0	0

Specifically, 11 events of clinical signs and symptoms of re-bleeding in 10 patients and 2 perforations were considered serious adverse events. Of the reports of re-bleeding, two were not considered recurrent bleeds because hemostasis had not been achieved with Hemospray® during the initial procedure. No treatment or repeat endoscopy was performed for either patient and neither patient had further reports of clinical signs and symptoms of re-bleeding throughout the follow-up period. In three additional cases that were not considered recurrent bleeds, correspondence between Wilson-Cook Medical, Inc. and the study physician indicated that the clinical signs and symptoms of re-bleeding were attributable to the original bleed, rather than recurrent bleeding; therefore, additional endoscopy was not performed. None of the signs or symptoms were treated (although one patient was instructed to take an iron supplement), and no further reports of clinical signs or symptoms of re-bleeding were submitted throughout the remainder of the study follow-up. In one case that was not considered recurrent bleeding, it was reported that re-bleed from the treated site was not suspected. One individual with hypotension and melena after normalization of stool color was not re-scoped as the study site reported that the patient was not well enough to undergo repeat endoscopy and the patient's melena had resolved on the same day. The remaining patient with clinical signs and symptoms of re-bleeding did have recurrent bleed with endoscopic confirmation of study lesion involvement, which was treated with epinephrine injection, hemostasis clips, and transfusion.

Initial hemostasis was achieved using Hemospray® as a single-modality treatment method in 88.9% (56/63) of cases. Initial hemostasis was defined as patients with hemostasis at the conclusion of the index procedure, where 'index procedure' is considered to be the application of Hemospray® and a 5-minute observation period. Patients that did not achieve initial hemostasis with Hemospray® were treated with hemostasis clips (1 patient), injection (with epinephrine) and hemostasis clips (2 patients), injection and argon beam therapy (1 patient), injection and thermal probe (1 patient), conversion to surgical repair (1 patient is described further in Table 10, HALT Summary Study Data), and proton pump inhibitor (PPI) therapy (1 patient). Subsequent events of perforation and death were reported for 1 patient.

Fifty-five patients completed their 30-day follow-up; eight patients exited the study prior to completion of 30-day follow-up. Of these eight, one patient died 2 days after the procedure, and one patient died 18 days after the procedure. Both deaths occurred after surgical intervention, one for bowel perforation and one for re-bleeding, resulting in death from postoperative liver failure and pneumonia, respectively. Six other patients were lost to follow up prior to completing the study follow-up schedule.

A PROSPECTIVE OBSERVATIONAL COHORT STUDY OF HEMOSPRAY™ FOR LOWER GASTROINTESTINAL HEMORRHAGE (APPROACH)

The second study is the APPROACH study in Canada. APPROACH is designed to collect safety and performance data on NVLGIB. Although the rate of occurrence and mortality in LGIB is lower than UGIB, bleeding in the lower GI tract can become clinically significant and/or

exacerbate existing co-morbidities. This prospective, single-arm, post-market study collected data on the safety and performance of the Hemospray® device when used as a treatment to achieve hemostasis of non-variceal lower GI bleeding. The study enrolled 50 patients at 4 clinical sites in Canada. Patient enrollment and data collection were completed in October and November 2016, respectively. The final site monitoring visit was completed in February 2017. Results are presented below.

Table 13. APPROACH Study Summary Data

	Number	Percent
Number of sites	4	na
Patients enrolled	50	na
Patients achieving hemostasis during index endoscopy	50	100.0
Successful hemostasis achieved using Hemospray®	49[a]	98.0
Patients with recurrent bleed as defined by the study protocol	5	10.0
30-day all-cause mortality	1[b]	2.0
Patients with device-related adverse events within 30 days of the index procedure	0	0.0

[a] In one patient, hemostasis was not achieved with the initial, single modality use of Hemospray®. Hemostasis clips were used also in order to achieve hemostasis.

[b] Includes 1 patient who died within 30 days. Cause of death: gastrointestinal bleeding (site unclear) secondary to pre-existing idiopathic thrombocytopenia.

Table 14. Patient Demographics

Demographic Characteristic	Reported (n=50)
Age (years) Mean ± SD (number of patients, age range)	64.6 ± 12.5 (50, 37 - 85)
Sex Male Female	 72.0% (36/50) 28.0% (14/50)

Table 15. Pre-procedure Co-Morbid Conditions

Co-morbid Conditions	Percent of Patients (n/N)
Patient already hospitalized for another illness when lower GI bleeding occurred	8.0% (4/50)
Previous episodes of GI bleeding	56.0% (28/50)
Current symptoms of lower GI bleeding	52.0% (26/50) [a]
Hematochezia	24.0% (12/50)
Melena	8.0% (4/50)

Chronic anemia	6.0% (3/50)
Acute anemia	6.0% (3/50)
Positive fecal occult blood test	18% (9/50)

[a] Patients may have more than one current symptom of lower GI bleeding.

Table 16. Hemospray® Use during Study Procedure

Hemospray® Use		**Percent of Patients (n/N)**
Number of bleed sites treated per patient	1	96.0% (48/50)
	2	4.0% (2/50)
Index procedural use of Hemospray®	Initial intervention (Hemospray® as monotherapy)	26.0% (13/50)
	Supplemental intervention (Hemospray® in conjunction with another intervention)	40.0% (20/50)
	Rescue intervention (Hemospray® after failure of prior intervention)	34.0% (17/50)
Was Hemospray® applied to bleed site as intended?	Yes	100% (50/50)

The Primary Endpoint is Hemospray®-related adverse events occurring within 30 days of the index procedure. Hemospray®-related adverse events include, but are not limited to, powder impaction in colon or embolization.

Table 17. Primary Endpoint

Hemospray® Related Adverse Events within 30 Days of the Index Procedure	**Percent of Patients (n/N)**
Yes	0.0% (0/50)
No	100% (50/50)

Secondary Endpoints:

- Hemostasis following application of Hemospray®
- Recurrent bleeding within 30 days of the index procedure
- Mortality within 30 days of the index procedure

Table 18. Secondary Endpoints

Endpoints		Percent of Patients (n/N)
Hemostasis following application of Hemospray®	Yes	98.0% (49/50)
	No	2.0% (1/50)
Recurrent Bleeding Within 30 Days of Index Procedure	Yes	10.0% (5/50)
	No	90.0% (45/50)
Mortality Within 30 Days of Index Procedure	Yes	2.0% (1/50)
	No	98.0% (49/50)

Hemostasis was achieved after the index procedural use of Hemospray® as an initial, supplemental, or rescue intervention treatment method in 97.3% of cases. Hemostasis, defined as the absence of persistent bleeding at the conclusion of the index colonoscopy, was achieved in all but one patient who had a visibly oozing or spurting bleed.

Table 19. Clinical Follow-up Data

		Percent of Data Available	Endpoint Since Previous Time Period			
Period	Patients Eligible for Follow-Up[a]	Telephone Follow-up	Death	Lost to Follow-up	Withdrawal	Not Eligible for Next Follow-up Visit
Procedure	50	N/A	0	1	0	0
14-day	49	98.0% (48/49)	0	0	0	0
30-day	49	98.0% (48/49)	1	N/A	N/A	N/A

[a] Number of patients eligible = previous number eligible – (death + LTF + withdrawal + not eligible for next follow-up visit).

Table 20. Comparison of APPROACH Study Results with American Society of Gastrointestinal Endoscopy (ASGE) Standard of Care

Endpoint	APPROACH Study Results	Standard of Care per ASGE
30-day Mortality Rate	2.0%	2.0-4.0%
Hemostasis Achieved During Index Endoscopy	100.0%	50-100.0%

Re-bleeding Rate	10.0%	18-22.0%

Serious Adverse Events

Of the six patients with serious adverse events, one patient died from gastrointestinal bleeding secondary to pre-existing chronic idiopathic thrombocytopenia 27 days after the procedure. Five cases of clinical signs and symptoms of lower GI bleeding were reported in four patients. Two of these cases were confirmed to have a recurrent bleed at the study lesion site, one case was conservatively assumed to be a recurrent bleed at the study lesion site as visual confirmation was not attained, and three cases were considered not to be recurrent bleeds. Two additional post-operative serious adverse events were reported in which clinical signs and symptoms of lower GI bleeding were not noted.

Table 21. Patient Morbidity

Category	0-14 Days (N)	15-30 Days (N)
Gastrointestinal	10	1
Pulmonary		0
Cardiovascular	0	0
Miscellaneous	4	1

0

Forty-eight patients completed their final follow-up. One patient exited the study prior to completion of the 14-day and 30-day follow-ups. One patient died 27 days after the procedure, as noted above. No other patients were lost to follow up prior to completing the study follow-up schedule.

Literature Summary of Recent Clinical Hemospray® Use

An extensive search was performed to identify the existing clinical literature on the recent use of Hemospray®. The search terms “Hemospray” or “TC-325” were used in PubMed and Google Scholar. Only publications in clinical journals were included in the analysis. Non-clinical studies, review articles, conference abstracts, and publications not in English were excluded. Publications that appeared to have overlapping patients with another study were excluded. Treatments of contraindicated bleeding types (*e.g.*, varices or fistulas) were excluded from the analysis. Thirty (30) relevant studies were identified comprising the treatment of 522 patients with Hemospray®. Overall, the hemostasis rate after the use of Hemospray® was 96% and the endoscopically achieved hemostasis rate was 97%. The 30-day gastrointestinal bleeding-related mortality rate was 3%. Four potential device-related adverse events (0.8%) were identified in the literature (2 reports of perforation and 2 reports of aspiration pneumonia); however, none of these events were reported to be directly attributed to the use of Hemospray® in the publications.

Table 22. Hemospray® Clinical Literature Summary

	Number	Percent
Number of studies	30	n/a
Patients treated	522	n/a
Hemospray® procedures	532	n/a
Successful hemostasis achieved using Hemospray®	509	96%
Patients achieving hemostasis during index endoscopy	518	97%
Re-bleeding within 7 days after successful initial hemostasis	97	19%
Re-bleeding 8-30 days after successful initial hemostasis	20	4%
30-day all-cause mortality	80	11%
30-day gastrointestinal bleeding mortality	23	3%
Potential device-related adverse events[a]	4	0.8%

[a] Potential device-related adverse events were 2 perforations and 2 cases of aspiration pneumonia. None of these adverse events could be directly attributed to the use of Hemospray®.

The literature reports consisted of the following levels of evidence:

- Level II: 12 Registry Derived Studies
- Level IV: The remainder of the studies consist of level IV evidence single arm retrospective or prospective studies, case series and case reports.

For a total of 30 studies in which there were 532 Hemospray® applications, resulting in 96% hemostasis rate and an overall re-bleeding rate of 23%. There were 2 instances of bowel perforation which may have been attributed to the use of Hemospray® and 2 aspiration pneumonias which could not be conclusively attributed to Hemospray®. There were no reports of bowel powder impaction or thromboembolic events.

Table 23. Summary of Clinical Literature on the use of Hemospray®

Study	Patients (n)	Hemospray Applications	Hemostasis after Hemospray Application	Endoscopic Hemostasis	Hemospray Hemostasis Rate	Endoscopic Hemostasis Rate	Rebleeding at risk patients	Rebleeding Events (7d)	Rebleeding Rate (7d)	Rebleeding Events (8-30d)	Rebleeding Rate (8-30d)
Sung 2011	19	20	19	19	95%	95%	19	2	11%	0	0%
Chen 2012	5	6	5	5	83%	83%	5	1	20%	0	0%
Granata 2013	1	1	1	1	100%	100%	1	0	0%	0	0%
Holster 2013	15	15	12	14	80%	93%	15	5	33%	0	0%
Leblanc 2013	12	12	12	12	100%	100%	12	0	0%	0	0%
Smith 2013	4	4	4	4	100%	100%	4	0	0%	0	0%
Smith 2013 (SEAL)	62	63	56	61	89%	97%	61	8	13%	0	0%
Soulellis 2013	4	4	4	4	100%	100%	4	0	0%	0	0%
Appleby 2014	1	1	1	1	100%	100%	1	0	0%	0	0%
Chen 2014	67	67	66	67	99%	100%	63	6	10%	9	14%
Curcio 2014		1	1	1	100%	100%	1	0	0%	0	0%
Dietrich 2014		2	2	2	100%	100%	2	1	50%	0	0%
Holster 2014	9	9	9	9	100%	100%	9	2	22%	0	0%
Kratt Endoscopy 2014	1	2	2	2	100%	100%	2	0	0%	0	0%
Masci 2014	13	13	13	13	100%	100%	13	2	15%	0	0%
Selvapatt 2014	1	1	1	1	100%	100%	1	0	0%	0	0%
Sulz 2014	15	15	14	15	93%	100%	14	2	14%	0	0%
Tarantino 2014	1	1	1	1	100%	100%	1	0	0%	0	0%
Yau 2014	19	19	18	18	95%	95%	18	7	39%	0	0%
Zimmer 2014	1	1	1	1	100%	100%	1	0	0%	0	0%
Chen Endoscopy 2015	1	1	1	1	100%	100%	1	0	0%	0	0%
Granata Int J Colorectal 2015	4	5	5	5	100%	100%	5	1	20%	0	0%
Granata Endoscopy 2015	1	1	1	1	100%	100%	1	0	0%	0	0%
Ivekovic 2015	1	1	1	1	100%	100%	1	0	0%	0	0%
Giles 2016	36	36	36	36	100%	100%	36	4	11%	0	0%
Gubler 2016	5	7	7	7	100%	100%	7	2	29%	0	0%
Haddara 2016	202	202	195	195	97%	97%	191	51	27%	11	6%
Sinha 2016	20	20	19	19	95%	95%	19	3	16%	0	0%
Venezia 2016	1	1	1	1	100%	100%	1	0	0%	0	0%
Xavier 2016	1	1	1	1	100%	100%	1	0	0%	0	0%
Total	**522**	**532**	**509**	**518**	**96%**	**97%**	**510**	**97**	**19%**	**20**	**4%**

Successful hemostasis defined as hemostasis achieved during procedure where Hemospray was used. Could be monotherapy, rescue, or initial followed by additional modalities.

Table 24. Summary of Clinical Literature on the use of Hemospray® (Continued)

Study	Adverse Events (n)	Upper GI	Lower GI	Lesion Types (See Table # for identifiers)	30-day All-cause mortality (n)	30-day GI bleeding mortality (n)	Primary Therapy (n)	Secondary Therapy (n)
Sung 2011	0	20	0	PU (20)	0	0	20	0
Chen 2012	0	5	0	Tumor (5)	1	1	5	0
Granata 2013	0	0	1	OU (1)	0	0	0	1
Holster 2013	0	15	0	PU (9), Tumor (2), Div (1), DL (1), TR (1)	0	0	6	11
Leblanc 2013	0	12	0	TR (11), post-EBS (1)	0	0	8	4
Smith 2013	P	3	1	PH (4)	1	1	3	1
Smith 2013 (SEAL)	P, AP	62	0	PU (30), TR (9), Tumor (6), DL (1), Post-EBS (1), Div (1), Other (5)	4	0	55	8
Soulellis 2013	0	0	4	TR (2), DL (1), RP (1)	0	0	0	4
Appleby 2014	0	1	0	post-EBS (1)	0	0	1	0
Chen 2014	0	50	17	PU (13), OU (4), Tumor (21), DL (2), RP (1), AVM (3)	4	1		
Curcio 2014	0	0	1	TR (1)	0	0	1	0
Dietrich 2014	0	1	0	Div	0	0	1	1
Holster 2014	0	0	9	OU (3), Div (1), Tumor (1), RP (1), TR (4)	0	0	6	3
Kratt Endoscopy 2014	0	0	2	OU (2)	0	0	2	0
Masci 2014	0	13	0	PU (13)	0	0	7	6
Selvapatt 2014	0	1	0	Tumor (1)	0	0	1	0
Sulz 2014	0	14	1	PU (3), OU (3), post-EBS (2), TR (1), PH (1), DL (1), Tumor (2), Other (2)	0	0	2	13
Tarantino 2014	0	1	0	Other (1)	0	0	0	1
Yau 2014	0	19	0	PU (13), AVM (1), TR (1), DL (1), Other (2)	4	1	3	16
Zimmer 2014	0	1	0	PU (1)	0	0	1	0
Chen Endoscopy 2015	0	1	0	Tumor (1)	0	0	1	0
Granata Int J Colorectal 2015	0	0	5	OU (5)	0	0	0	5
Granata Endoscopy 2015	0	1	0	Other (1)	0	0	0	1
Ivekovic 2015	0	0	1	TR (1)	0	0	0	1
Giles 2016	0	36	0	PU (25), TR (6), Tumor (2), DL (1), PH (1), Other (1)	9	5	9	27
Gubler 2016	0	1	4	OU (5)	0	0	6	1
Haddara 2016	0	202	0	PU (72), Tumor (61), TR (25), post-EBS (7), DL (3), PH (7), OU (1), Other (64)	30	7	94	108
Sinha 2016	AP	20	0	PU (20)	3	1	0	20
Venezia 2016	0	1	0	Tumor (1)	0	0	0	1
Xavier 2016	0	1	0	Tumor (1)	0	0	0	1
Total	**4**	**481**	**46**		**56 (11%)**	**17 (3.0%)**	**232**	**234**

Potential Adverse Events reviewed for are: perforation (P), aspiration pneumonia (AP), embolization, and bowel impaction.

Primary Therapy = Monotherapy or first-line as Hemospray followed by additional modalities.

Secondary Therapy = Adjunct therapy or Rescue therapy, including from previous treatment of same lesion during prior procedure.

Lesion Identifier	Description
PU	Peptic Ulcer
Tumor	Tumor
TR	Tissue Resection (e.g. endoscopic mucosal resection, endoscopic submucosal dissection, polypectomy, and ampullary resection)
post-EBS	Endoscopic biliary sphincterotomy (aka ERCP)
DL	Dieulafoy's lesion
OU	other Ulcer (e.g. anastomotic ulcer, ulcerative colitis, post-polypectomy ulcer, post-EMR ulcer, post-Barrett's Ablation Ulcer, post-banding)
PH	portal hypertensive gastropathy
RP	radiation proctitis
Div	Diverticulum
AVM	arteriovenous malformation (includes angiodysplasia)
Other	Includes Esophagitis, Gastritis, Mallory-Weiss tear, Gastric antral vascular ectasia, pseudocyst, infection, ischemic colitis, unknown causes

Wilson-Cook Medical, Inc. has sponsored 3 clinical studies and 1 survey of the use of Hemospray® to date, and has also conducted a literature search of relevant studies comprising the treatment of 522 patients with Hemospray®. The first and only premarket study was a pilot "first-in-human" feasibility study completed on 20 patients in Hong Kong, China who presented with upper gastrointestinal bleeding. The other two clinical studies and the survey were also

conducted outside the U.S. as post-market studies. Wilson-Cook Medical, Inc. initiated the post-market Survey to Evaluate the Application of Hemospray® in the Luminal Tract (SEAL) to collect limited, non-protected health information and data on the Wilson-Cook Medical, Inc. Hemospray® Endoscopic Hemostat as part of a limited marketing release. The survey was conducted in Canada, Denmark, England, France, Germany, Italy and Holland and currently stores data on over 100 patients, primarily with upper gastrointestinal bleeding. The post-market studies include the Hemostasis of Active GI Luminal Tract Bleeding (HALT) study, which was a European and Canadian single-arm study recruiting only patients with upper gastrointestinal bleeding, and A Prospective Observational Cohort Study of Hemospray® for Lower Gastrointestinal Hemorrhage (APPROACH) study, a Canadian single-arm study evaluating the use of Hemospray® in lower gastrointestinal bleeding. Published clinical literature information was cited for use as historical control data for evaluation of each of these single-armed studies.

Acute (procedural) hemostasis was achieved in 19 of 20 patients (95%) in the pilot study. There were no treatment-related or procedure-related serious adverse events. The HALT study continues to enroll patients in Europe and Canada, and the APPROACH study reports on 50 patients, demonstrating 100% initial hemostasis with use of Hemospray® in this group of patients with diverse lower gastrointestinal etiologies of bleeding. This endoscopic hemostat is approved for use in upper gastrointestinal nonvariceal bleeding in Europe and both upper and lower gastrointestinal nonvariceal bleeding in Canada. The post-market experience reported in medical literature from Europe, Canada, and Asia all report favorable results with the use of Hemospray® in the treatment of nonvariceal gastrointestinal bleeding. 92% of the literature reports are on the treatment of upper gastrointestinal bleeding with Hemospray®, while 8% of the reports include only lower gastrointestinal bleeding cases.

Finally, the sponsor reports on 5 cases of Hemospray® application under humanitarian device exemption emergency use in critically ill patients who were very high-risk surgical patients. These were patients from one center in the United States. Hemospray® was used after all other modalities of endoscopic treatment failed. Hemospray® stopped the upper gastrointestinal bleeding in all these patients; none died of recurrent bleeding and only one died from progression of lymphoma during the time interval reported.

The clinical data are summarized in the following table:

Table 25: Summary of Hemospray® Clinical Data

Study	*N*	*Hemostasis on Index Endoscopy (%)*	*Re-bleed Rate (%)*	*30-day Mortality (%)*	*Bowel Perforation (%)*	*Powder Impaction (%)*	*Thromboembolic Event (%)*
Pilot Study	20	95	10	0	0	0	0
SEAL Registry	89	100	19	5.6	3.4	0	0
HALT Study	64	97	20	3.2	3.1	0	0
APPROACH Study	50	100	10	2	0	0	0
Literature Hemospray® Studies	522	97.4	22	10.7	0.4	0	0
Emergency Use	5	100	0	20	0	0	0
Total	**750**	**97.8**	**20.2**	**11.6**	**0.9**	**0**	**0**

The emergency pre-market use of Hemospray® was accomplished in the treatment of 5 patients, all with intractable upper gastrointestinal bleeding requiring multiple transfusions and very high-risk, precluding other interventions, including surgery. All these patients attained successful hemostasis with Hemospray®; one died from the progression of their underlying malignancy.

Holster I.L, *et. al*., published a study which reported on patients with upper gastrointestinal bleeding and antithrombotic therapy and demonstrated 63% initial hemostasis with a 38% re-bleeding rate. These results are similar or better than those of traditional endoscopic modalities of treating gastrointestinal bleeding in this subgroup of patients.

The sponsor also reports on outside the United States Complaint Data: 280 total reports for over 50,000 units sold. Only 10% of these complaints required medical intervention. There were 4 deaths reported in the complaint data. Two deaths were related to patient co-morbidities and 2 may have been related to the device – one perforation, sepsis, and death, possibly from bowel over-inflation, and one death from exsanguination due to device malfunction. The latter resulted in change in device design to mitigate for the risk of malfunction. The table below summarizes the complaint data, stratified by Risk Severity Score (RSS)[a]:

Table 26: Risk Severity Score

RSS Value:	2	3	4	5	6	7	10
Number of Complaint Reports	1	246	3	16	4	6	4
Description of Harm	Label damage	Low impact, loss of all or part of device function; nuisance to patient or end user	Negligible harm; harm not requiring medical intervention	Minor harm; harm requiring medical intervention	Moderate harm; harm requiring medical intervention	Significant harm; harm resulting in hospitalization, major	Critical harm; death.

[a] Risk Severity Score (RSS)
RSS 10: 4 deaths – 2 comorbidities, 1 perforation sepsis, 1 device malfunction resulting in exsanguination
RSS 7: 5 re-bleed, 1 perforation requiring surgery
RSS 6: less significant re-bleed, 1 requiring surgery
RSS 5: re-bleed, stricture, failed hemostasis

Conclusions:

- Hemospray® has been used as primary treatment of non-variceal gastrointestinal bleeding, rescue therapy, adjunctive therapy, bridging therapy, and, in some cases, prophylactic therapy after polyp excision or mucosectomy. Both upper gastrointestinal and lower gastrointestinal non-variceal bleeding have been treated with Hemospray® outside the United States for the last seven years with few reports of device-related adverse events and possible device-related adverse events. In all these clinical applications of Hemospray®, initial hemostasis was achieved in over 90% of patients.
- The HALT and APPROACH studies were prospective, post-market, single-armed studies that demonstrated the effectiveness of Hemospray® in treating both upper and lower gastrointestinal bleeding.
- Complaint data resulted in label warnings and device manufacturing changes to limit the risk of bowel perforation and device malfunction.
- In Patients on antithrombotic therapy (ATT), Hemospray® rivaled standard of care (SOC) with 63% initial hemostasis and 38% re-bleed rate.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

Labeling provided for the Hemospray® Endoscopic Hemostat includes Instructions for Use and packaging labels. The labeling satisfies the requirements of 21 CFR § 801.109 Prescription devices, and includes information regarding specifications, instructions for use, contraindications, warnings, and precautions, as well as a prescription statement.

Important components of the labeling include:

- Contraindications, warnings, cautions, or limitations needed for safe use of the device, including
  - Contraindications specific to the primary endoscopic procedure to be performed in gaining access to desired target site
  - Specific contraindication for patients who have gastrointestinal fistulas, are suspected of having a gastrointestinal perforation, or are at high risk of gastrointestinal perforation during endoscopic treatment.
  - A caution that patients with gastrointestinal bleeding that are on antithrombotic medication may be at an increased risk of re-bleeding
  - A caution that use of more than (3) Hemospray® devices per patient may result in impaction in colon and is not recommended
  - A caution that use of Hemospray® in the presence of bowel obstruction and/or an anastomosis may pose a risk of injury due to over-distention.
  - A caution that Hemospray® may occlude ducts and orifices which communicate with the main bowel lumen. Use caution when using Hemospray® in the vicinity of these orifices.
  - A warning that although not seen in clinical practice, there is a risk of aspiration of Hemospray® powder resulting in respiratory complications. It is prudent to restrict the use of Hemospray® to 5 cm below the upper esophageal sphincter (UES).
  - A statement that use of an end-viewing endoscope is recommended
- Information on how the device operates and directions for use
- A shelf life
- A prescription statement as required by 21 CFR 801.109
- Information regarding magnetic resonance compatibility.

RISKS TO HEALTH

Table 27 identifies the risks to health that may be associated with use of a hemostatic device for intra-luminal gastrointestinal internal use and the measures necessary to mitigate these risks.

Table 27: Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Bleeding - Inability to achieve hemostasis - Recurrence of bleeding	*In vivo* performance testing Non-clinical performance testing Labeling
Infection	Sterilization validation Shelf life testing Labeling
Adverse tissue reaction	*In vivo* performance testing Non-clinical performance testing Biocompatibility evaluation Labeling
Obstruction of GI tract	*In vivo* performance testing Labeling
GI distension or perforation	*In vivo* performance testing Labeling
Vascular obstruction - Ischemia - Emboli formation	*In vivo* performance testing Non-clinical performance testing Labeling
Tissue trauma	*In vivo* performance testing Non-clinical performance testing Labeling
Improper device use	*In vivo* performance testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the hemostatic device for intraluminal gastrointestinal internal use is subject to the following special controls:

1. The device must be demonstrated to be biocompatible.

2. Performance data must support the sterility and pyrogenicity of the device.

3. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

4. *In vivo* performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The testing must evaluate the following:

    a) The ability to deliver the hemostatic material to the bleeding site;

b) The ability to achieve hemostasis in a clinically relevant model of gastrointestinal bleeding; and
c) Safety endpoints, including thromboembolic events, local and systemic toxicity, tissue trauma, gastrointestinal tract obstruction, and bowel distension and perforation.

5. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be evaluated:

    a) Materials characterization of all components must demonstrate the device meets established specifications, which must include compositional identity and purity, characterization of impurities, physical characteristics, and reactivity with fluids.
    b) Performance testing must demonstrate the mechanical integrity and functionality of the system used to deliver the device and demonstrate the device meets established specifications, including output pressure for propellant-based systems.

6. Labeling must include:

    a) Information identifying and explaining how to use the device and its components; and
    b) A shelf life.

BENEFIT/RISK DETERMINATION

The benefits and risks of the device are based on the data collected in clinical studies as well as on the outside U.S. post-market complaint data. These benefits and risks are summarized below:

Benefits

1. Ease of application; no need for direct targeting, direct pressure or *en face* positioning of the endoscope to the bleeding site or touching of tissue. The device can be applied tangentially or at any angle with good effect. It may be less injurious to a bleeding fresh bowel anastomosis and can be applied in areas that are difficult to reach anatomically. Such areas include the proximal lesser curvature of the stomach and the back wall of the duodenum. Hemospray® can be effective where bleeding is originating at an ulcer base that is fibrotic and on which a clip cannot be easily applied.

2. Rapid application with minimal need for anaesthesia that is easily repeatable.

3. Can be applied to a wide area to cover diffuse or multifocal bleeding.

4. Can be applied by gastroenterologists and general surgeons in smaller hospitals to control initial bleeding as a bridge to more definitive treatment in tertiary care hospitals with greater clinical resources

5. Can be used as a novel non-contact rescue therapy when other traditional therapies have failed in a patient who would otherwise require a high-risk operation.

6. Can be used therapeutically as well as prophylactically to treat recently active bleeding lesions of the GI tract or after procedures with high risk of delayed bleeding, such as endoscopic submucosal dissection or endoscopic mucosal resection.

7. Can be used in coagulopathic patients who are bleeding from a GI lesion where the coagulopathy cannot be easily reversed since Hemospray® powder, which is both cohesive and adhesive when exposed to blood, provides a mechanical barrier to bleeding.

Risks

1. Literature-supported risks of Hemospray®: Re-bleeding 20%, bowel perforation and continued bleeding requiring surgical intervention 1%, 30-day mortality 20%.

2. Hemospray® can cause bowel obstruction or obstruction of ducts and GI structures emptying into the main GI tract. Anatomic and physiologic gastrointestinal abnormalities can contribute to this problem.

3. Over-inflation of bowel may result in perforation. Patients with gastrointestinal fistulas or compromised bowel may be at greatest risk. Each canister of Hemospray® could potentially add over 3 litres of additional volume to the GI tract comprised primarily of CO_2 and to a lesser extent Hemospray® powder.

4. Embolization of CO_2 gas or Hemospray® to distant sites, resulting in adverse cardiopulmonary events or migration of (b) (4) bentonite into nearby feeding vessels causing more diffuse or uncontrolled thrombosis and local ischemic events.

5. Local toxicity to endothelial cells or macrophages causing thrombosis of blood vessels and affect healing.

6. Allergic reaction, systemic toxicity from leached components of the device.

7. The device is an ion exchange resin and a bulk laxative which may affect absorption of electrolytes, drugs, vitamins, and nutrients from the GI Tract.

8. When used for proximal esophageal bleeding, the risk of patient aspiration of the (b) (4) bentonite may be present especially in an unprotected airway.

9. Mechanical malfunction of the CO_2 delivery mechanism resulting from obstruction of the endoscopic channel or catheter or CO_2 canister malfunction may result in delayed treatment of uncontrolled gastrointestinal bleeding. The resulting risk of explosion with harm to patient or health personnel is unknown.

10. Hemospray® cannot be easily applied through a side viewing duodenoscope and may require exchange to a forward viewing gastroscope. The resulting treatment delay may be detrimental to the patient.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

Traditional endoscopic treatment of gastrointestinal bleeding includes: injection of vasoconstrictors, directed by endoscopic ultrasound, thermos-probe or bipolar cautery, argon plasma coagulator (APC), Over the Scope Clip (OTSC), endo-suturing, bands, detachable snares, covered stents, radiation therapy, angiography with angio-embolization and surgery. Blood vessels feeding the gastrointestinal bleeding site can now be identified with endoscopic ultrasound and directly occluded with cyanoacrylic glues (off-label) and coils. These modalities are effective in greater than 80% of cases, with a re-bleed rate in up to 10% of cases. However, they require specific targeting of the bleeding lesion, specialized expertise and, in some cases, are invasive. All these modalities require touching of the tissue with potential collateral injury. This disadvantage may be most appreciated in the patient with a fresh gastrointestinal anastomosis who can least afford injury to that surgical site during an effort to achieve hemostasis. Many of these treatment modalities are time consuming and difficult to accomplish further compromising a hemodynamically unstable patient. Hemospray® offers a less technically demanding, more rapid means of achieving hemostasis. The risks of bowel obstruction, allergic reaction, and embolization were not realized in all the clinical evidence submitted. There were episodes of device malfunction that resulted in delayed treatment as well as bowel over-distension, which resulted in pain and in some cases bowel perforation. The perforation rates in all cases did not exceed that of traditional endoscopic treatment of gastrointestinal bleeding. The early and late re-bleeding rates, especially for malignant and large friable lesions, were significantly less than that noted with traditional treatment. The lesions that are more likely to re-bleed or continue bleeding may still benefit from the application of Hemospray® to stop the bleeding acutely, allowing for patient stabilization and bridging to more definitive therapy.

Given the available information summarized above, the data support the conclusion that Hemospray® is an endoscopic hemostat with a very low risk profile compared to traditional endoscopic hemostatic procedures, with a greater than 95% immediate hemostasis in most cases of upper and lower non-variceal gastrointestinal bleeding. While Hemospray® has a similar early and late re-bleeding rate when compared to many traditional techniques of endoscopic hemostasis, it has been shown to decrease the need for salvage surgical intervention and angiographic embolization. Because direct targeting and specialized skill are not necessary with the use of Hemospray®, it is especially useful in controlling gastrointestinal bleeding in difficult-to-reach anatomic locations and for controlling diffuse bleeding in large lesions, such as tumors, and large ulcers. The most significant advantage of Hemospray® is its ability to convert a bleeding, hemodynamically unstable patient to one in which bleeding is controlled, the patient resuscitated and bridged to a more elective definitive treatment of the target bleeding site. The literature and studies provided on Hemospray® use in Europe, Asia, and Canada report no episodes of embolization of the device components, major thrombosis outside the target bleeding site, bowel obstruction, or allergic reaction. There have been reports of transient episodes of pain and rare perforation events, both attributed to over-distension of bowel with application of Hemospray®. This problem may be mitigated with labeling and instruction to partially de-

sufflate the bowel prior to device application. Additionally, if CO_2 is used as the insufflating gas rather than air, the more rapid absorption of CO_2 may mitigate the risk of persistent bowel distension.

The device provides benefits, and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the Hemospray® Endoscopic Hemostat is granted and the device is classified under the following:

Product Code: QAU
Device Type: Hemostatic device for intraluminal gastrointestinal use
Class: II
Regulation: 21 CFR 878.4456

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