SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Computer-Assisted Personalized Sedation System

Device Trade Name: SEDASYS® Computer-Assisted Personalized Sedation System

Device Procode: PDR

Applicant's Name and Address: Ethicon Endo-Surgery (EES), Inc.
4545 Creek Road
Cincinnati, Ohio 45242

Date of Panel Recommendation: May 28, 2009

Premarket Approval Application (PMA) Number: P080009

Date of FDA Notice of Approval: May 3, 2013

Expedited: Granted expedited review status on April 9, 2008 because the SEDASYS System may offer a viable alternative to the current standard of practice for colonoscopy or esophagogastroduodenoscopy (EGD) procedures.

II. INDICATIONS FOR USE

The SEDASYS System is indicated for the intravenous administration of 1% (10 mg/mL) propofol injectable emulsion for the initiation and maintenance of minimal to moderate sedation, as defined by the American Society of Anesthesiologists (ASA) Continuum of Depth of Sedation, in ASA physical status I and II patients ≥ 18 years old undergoing colonoscopy and esophagogastroduodenoscopy (EGD) procedures.

III. CONTRAINDICATIONS

The SEDASYS System is contraindicated in the following:

- Patients with a known hypersensitivity to 1% propofol injectable emulsion or its components.
- Patients with allergies to eggs, egg products, soybeans or soy products.
- Patients with a known hypersensitivity to fentanyl.
- Pregnant or lactating women.
- Delivery of any drug other than 1% propofol injectable emulsion.
- Patients with a full stomach.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SEDASYS System labeling.

V. DEVICE DESCRIPTION

The SEDASYS System is a computer-assisted personalized sedation system that administers propofol for minimal-to-moderate sedation using feedback from monitored patient physiological parameters. The device provides monitoring and alarms for physiological vital signs and other parameters of sedation and limits the depth of sedation.

The SEDASYS Computer-Assisted Personalized Sedation System monitors the following physiologic parameters:

- arterial oxygen saturation
- heart rate
- respiration rate
- blood pressure
- patient responsiveness

The SEDASYS System is divided into four (4) subsystems (or sets of subsystems). These are:

- The Bedside Monitoring Unit (BMU)
- The Procedure Room Unit (PRU)
- Reusable monitors and connectors
- Single patient use devices

Bedside Monitoring Unit (BMU)

The BMU is designed to follow the patient through pre-procedure, procedure, and post-procedure. This device contains the pulse oximeter, blood pressure, electrocardiogram (ECG), and a mechanism to assess patient responsiveness by squeezing a handheld switch in response to an auditory or vibration stimulus. The mechanism to assess patient responsiveness is called the automated responsiveness monitor (ARM). The pulse oximeter, blood pressure, and ECG data are displayed on the BMU when it is not connected to the PRU.

Procedure Room Unit (PRU)

The PRU is designed to remain in the procedure room. It contains a monitor for all physiological parameters and the capnometry device. The control unit houses the infusion pump and the software to deliver the propofol. The PRU contains a battery powered back up that allows for the procedure to be terminated in the event of a power

outage. After the BMU is moved into the procedure room the BMU is connected to the PRU by means of an umbilical cord.

Reusable Monitors and Connectors

The SEDASYS System utilizes five (5) Multiple Patient Use (MPU) items:

1) pulse oximeter probe (and extension cable),
2) ECG lead set (and extension cable),
3) non-invasive blood pressure (NIBP) cuff (and extension tubing),
4) ARM handset
5) oxygen adapter, allowing connection of the BMU directly to an oxygen source.

Each of these is designed to be re-useable. They are for the most part self-explanatory with the exception of the "ARM" device (which will be detailed below) and the oxygen adapter.

Single-Patient Use Devices

The SEDASYS System contains three (3) single-patient use disposable components:

1) The Drug Delivery Cassette is the propofol drug vial/device interface that allows the infusion pump module of the PRU to extract propofol for delivery to the patient.

2) The Oral/Nasal Cannula is the patient/device interface for oxygen delivery and also serves as the collection unit for the capnometer module of the PRU to assess respiratory activity.

3) The Bite Block is used in EGD procedures to enable proper function of the oral/nasal cannula in the presence of a scope or esophageal dilator.

Patient response times are displayed on the PRU monitor, as are the other physiological parameters.

The SEDASYS System uses a drug delivery algorithm and intravenous infusion pump to deliver propofol with a variable rate infusion in order to achieve and maintain a desired sedation effect. It enables the physician-led team to adjust the patient's level of sedation by entering a dose rate that they believe will maintain the desired sedation effect. The System calculates an appropriate loading dose based on the patient's weight, the entered dose rate, and guidelines in propofol labeling which will achieve the sedation effect for the entered dose rate. The loading dose is delivered over 3 minutes; immediately after, the System automatically starts delivering the entered dose rate.

Another feature of the System is the PRN (*pro re nata*) button. The PRN feature is designed to allow the clinician to treat transient episodes of discomfort with a transient

increase in the sedation effect. The PRN dose is 0.25 mg/kg and it is delivered at a pump rate of 450 mL/hour. For lighter patients the PRN dose will be delivered in ~10 seconds, while for heavier patients the dose will be delivered in ~30 seconds. There is also a lockout that prevents another PRN dose for 90 seconds.

System Safeguards

The SEDASYS System integrates patient monitoring with oxygen and propofol delivery in order to provide safeguards.

The SEDASYS System contains dosing restrictions based on propofol pharmacokinetics and data from the patient monitors. These include:

- The initial maintenance rate is limited to a maximum of 75 μg/kg/min.
- A 3-minute lockout between infusion rate increases.
- A 90-second lockout between PRN doses.
- Limits on infusion rate increases are based on ARM responsiveness.

The SEDASYS System contains an automated supplemental oxygen delivery system. The SEDASYS System does not deliver propofol unless oxygen is available. The clinician can set the oxygen administration rate anywhere between 2 and 8 L/min. The default rate for oxygen delivery is 2 L/min. This rate is used for SpO_2 of 96% or greater. When SpO_2 falls below 96% the system will increase the rate to 8 L/min, if not set at this level by the clinician. If the SpO_2 falls to 88% or less, the rate will be increased to 12 L/min.

The SEDASYS System also has alarms to inform the user of possible concerns. These alarms are designated as Red and Yellow.

Red Alarms (or Warning Alarms) alert the clinician, through audible and visual signals, to potential compromised cardiorespiratory conditions, such as hypoxemia, apnea, tachycardia, or hypertension. In response to Red Alarms for apnea and hypoxemia the SEDASYS System stops the delivery of propofol; after the Red Alarm clears, the clinician must manually restart propofol delivery. A PRN dose can be delivered during a Red Alarm, but if the alarm was triggered by apnea or hypoxemia, the System warns the clinician about doing so.

Red alarms triggered by physiological parameters that do not have a high correlation with over-sedation (e.g., low and high heart rate, high respiratory rate, low and high systolic pressure, low and high diastolic pressure, and high $EtCO_2$) do not result in automatic drug action. For example, should a low systolic/diastolic pressure (hypotension) red alarm occur, the etiology of this alarm may be a vasovagal reaction where reducing the drug delivery may not be a clinically appropriate action. Should any of these red alarms occur, the physician should assess the patient to determine the appropriate course of action, including whether it is clinically appropriate to stop drug delivery.

The Yellow Alarms (or Caution Alarms) trigger before physiological conditions requiring a Red Alarm are reached by identifying evolving desaturation and low respiration rate/apnea. For example, the SEDASYS System Yellow Alarm for oxygen saturation is set at 92%. In response to a Yellow Alarm, the SEDASYS System alerts the clinician with distinct audible and visual signals and reduces the propofol infusion rate. The first step in this process is suspending the propofol infusion. When the Yellow Alarm condition clears, the system reinitiates the infusion at a reduced dose rate. A PRN dose can be delivered during a Yellow Alarm, but the System cautions the clinician about doing so.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternatives for the delivery of sedation for colonoscopy and EGD procedures. These alternatives have their own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

The alternative practices include: 1) the current standard of care where a benzodiazepine and opioid are administered by a nurse under the direction of the gastroenterologist and 2) the administration of propofol, with or without fentanyl, by an anesthesiologist or Certified Registered Nurse Anesthetist.

VII. MARKETING HISTORY

The SEDASYS System was granted regulatory approval in both Europe and Canada in May 2010. The SEDASYS System has not been withdrawn from the market.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Deeper than intended level of sedation
- Hypoxia (low oxygen level in the blood)
- Bradycardia (slow heart rate)
- Hypotension (low blood pressure)
- Hypoventilation (slow and/or shallow breathing)
- Upper Airway Obstruction (complete or incomplete closure of the breathing space in patient's throat resulting in diminished air movement)
- Apnea (cessation of breathing)
- Death

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

The following pre-clinical testing was performed on the SEDASYS System and found to be adequate (international standards referenced in the testing provided in parenthesis):

- Sterility (ANSI/AAMI/ISO 11137:2006)
- Biocompatibility (ISO 10993)
- Electromagnetic Compatibility (IEC 60601-1-2)
- Human Factors
- Software

The SEDASYS System claims relevant specifications in accordance to the standards listed below.

A. Laboratory Studies

Reference to Standards

The SEDASYS® Computer-Assisted Personalized Sedation System has been developed and designed in compliance with internationally accepted and FDA-recognized standards. This section discusses the standards that were used as part of development procedures as well as standards that specify safety-critical requirements. The safety standards that apply to the device have been tested for compliance and the SEDASYS System has been found to conform to the applicable clauses of the safety standards listed in this section.

The laboratory testing conducted on the SEDASYS System demonstrated that the device was reasonably safe and effective under the conditions of testing.

Testing was conducted on devices that were, or were equivalent to, the final design. Any changes made to the device after testing was initially conducted were assessed for their impact to the test. Based on these assessments, no tests required repetition. In order to conduct certain tests, special software was developed and released to enable functions for testing that are not normally present in use. For example, special software allows the pump to run without oxygen being delivered, preventing an oxygen-enriched environment. Test devices incorporating this special software are equivalent to the final design.

The ECG module is a 3-wire system. The display sweep speeds are 12.5 and 25 mm/sec with an available gain of 0.2, 0.5, 0.7, 1, 2, 4, or auto. The ECG has defibrillator and electrosurgery interference protection when used with provided ECG cables with <10 second recovery. The ECG module has a heart rate range and accuracy of 30-240 beats/minute (bpm) ± 3 bpm. See Table 1 below for standard conformance.

The Non-Invasive Blood Pressure (NIBP) has a measurement range of 20-260 mmHg. The accuracy is demonstrated per AAMI SP10-1992 Clause 4.4.2: Blood pressure measurements determined with this device are equivalent to those obtained by a trained observer using the cuff/stethoscope auscultation method, within the limits prescribed by "The American National Standard, Electronic or Automated Sphygmomanometers". See Table 1 below for standard conformance.

Accuracy for the pulse oximeter is ±2% SpO_2 over the range of 70-100% with no motion and normal perfusion. The accuracy is ±3% SpO_2 over the range of 70-100% with motion or low perfusion. The SpO_2 resolution is 0.1%. The heart rate resolution is 0.1 beats per minute. See Table 1 below for standard conformance.

The infusion pump infusion range is from 1 to 999 mL/hour with a stated accuracy of < ± 5%. The bolus volume generated after release of an occlusion is 0.18 mL @ 1.2 mL/hour and 0.15 mL @ 25.2 mL/hour with a 1000 mbar occlusion pressure. The volume delivered under a single fault condition is a maximum of 0.5 mL. The air-in-line sensor will detect an air bubble of > 50 mL, with a single bubble of > 250 mL resulting in stopping the infusion or an accumulation of > 1 mL over 15 minutes resulting in stopping the infusion. The occlusion alarm is 800-12000 mbar. See Table 1 below for standard conformance.

The capnometer uses a sidestream measurement method with a measurement range of 0 - 13% CO_2. The accuracy is ± 2.0 mmHg @ < 5% CO_2 ATPS (Ambient Temperature and Pressure, Saturated) and < 10% of reading @ > 5% CO_2 (ATPS). The breath rate range is 2 - 150 breaths per minute. The display sweep speed is 6.25, 12.5, or 25 mm/second. See Table 1 below for standard conformance.

The alarms were tested in several failure modes during single-fault conditions. Both latched and non-latched alarms have been incorporated into the SEDASYS System. This testing was adequate to assure compliance with IEC 60601-1. This standard is recognized by the Center for Devices and Radiological Health (CDRH) and is used for other electrical medical devices such as critical care ventilators. See Tables 1, 4, and 6 below.

Electrical safety has been addressed in this submission. Both the BMU and the PRU were tested to IEC 60601-1. The general requirements are stated as: Equipment when transported, stored, installed, operated in normal use and maintained according to the instructions of the manufacturer, causes no safety hazard which could reasonably be foreseen and which is not connected with its intended application in normal condition (N.C.) and in single fault condition (S.F.C.). The Test Report Form (TRF) originator is Underwriters Laboratories, Inc. The TRF provided detail on the test procedures executed and the pass/acceptance criteria. All tests outlined in the TRF passed. See Tables 1, 4, and 6 below for standard conformance.

Table 1: General Standards

Test	Purpose	Acceptance Criteria	Results
UL 60601-1: 2003	Conformance to General Requirements for Safety	Conformance to applicable clauses within UL 60601-1:2003 must be demonstrated	Passed
IEC60601-2-27: 2005	Conformance to Particular Requirements for Electrocardiographic Monitoring Equipment	Conformance to applicable clauses within IEC 60601-2-27:2005 must be demonstrated	Passed
IEC60601-2-30:1999	Conformance to Particular Requirements for Non-Invasive Blood Pressure Monitoring Equipment	Conformance to applicable clauses within IEC60601-2-30:1999 must be demonstrated	Passed
IEC60825-1:1993	Conformance to Particular Requirements for Laser Products	Conformance to applicable clauses within IEC60825-1:1993 must be demonstrated	Passed
ANSI/AAMI SP10:1992	Conformance to Particular Requirements for Automated Sphygmomanometers	Conformance to applicable clauses within ANSI/AAMI SP10:1992 must be demonstrated	Passed
ISO9919: 2005	Conformance to Particular Requirements for Pulse Oximeter Equipment	Conformance to applicable clauses within ISO9919:2005 must be demonstrated	Passed
IEC60601-2-24: 1998	Conformance to Particular Requirements for Infusion Pumps and Controllers	Conformance to applicable clauses within IEC60601-2-24:1998 must be demonstrated	Passed
EN864: 1996	Conformance to Particular Requirements for Capnometers for Use with Humans	Conformance to applicable clauses EN864: 1996 must be demonstrated	Passed

Sterilization & Shelf-Life

The only part of the SEDASYS System that is provided sterile is the drug delivery cassette. Radiation to establish sterility was administered with a dose of 25 kGy and a SAL of 10^{-6}. ANSI/AAMI/ISO 11137:2006 was used to determine the effective radiation dose. As the drug delivery cassette is considered a non-pyrogenic fluid path, LAL testing was also conducted. The acceptance criterion was not more than 20 EU/unit. Thirty (30) samples of cassettes across three (3) batches were tested. The samples met this criterion. See Table 2 below.

Table 2: Sterility (ANSI/AAMI/ISO 11137:2006)

Test	Purpose	Acceptance Criteria	Results
Sterility of Test as Specified in ANSI/AAMI ISO 11137	Substantiation of 25 kGy as a sterilization dose for the single use cassette.	The average bioburden determination of the batch shall be no greater than 1000 cfu/device.	Passed
Sterility of Test as Specified in ANSI/AAMI ISO 11137	Inhibition/enhancement endpoint concentration for the single use cassette.	Within 2-fold dilution of the label claim sensitivity of the LAL reagent.	Passed
Sterility of Test as Specified in ANSI/AAMI ISO 11137	Bacteriostasis/ fungistasis testing for the single use cassette.	The bacteriostasis / fungistasis (B&F) testing shall exhibit growth within five days for *Bacillus subtilis*, *Candida albican* and *Aspergillus niger* in accordance with USP.	Passed

Expiration dating for the sterile SEDASYS Drug Delivery Cassette and non-sterile Oral/Nasal Cannula has been established and validated at 2 years. Fifty (50) cassettes and sixty (60) cannulas were tested using accelerated aging to demonstrate that the samples met functional requirements at pre-defined sampling intervals.

Biocompatibility

Biocompatibility testing was performed on the patient contacting external communicating components of this device, which included the oral/nasal cannula, bit block, cassette, ECG leads, ECG Extension Cable, Pulse Oximeter Probe, Pulse Oximeter Cable, NIBP Cuffs (small adult, large, plus), NIBP Extension, ARM Handset. This testing was performed in accordance with ISO 10993-1: "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing" and on FDA General Program Memorandum #G95-1: Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing." Extracts of material samples were prepared in accordance with

ISO 10993-12. The extraction ratio for samples was 60 cm^2/ 20 mL. The ten (10) components listed met the performance criteria of ISO 10993. See Table 3 below.

Table 3: Biocompatibility (ISO 10993)

Biocompatibility (ISO 10993)Test	**Purpose**	**Acceptance Criteria**	**Results**
Biocompatibility Test for Oral Nasal Cannula / Bite Block	Surface devices with mucosal tissue contact of less than 24 hours (CC3). Associated risks are cytotoxicity, irritation, and sensitization.	Conformance to applicable clauses within ISO 10993-1:2009, ISO 10993-2:2006, ISO 10993-5:2009, ISO 10993-6:2007, ISO 10993-10:2010, ISO 10993-12:2007, and ISO 10993-18:2005 must be demonstrated	Passed
Biocompatibility Test for Cassette	Externally communicating device with < 24 hours of indirect blood contact (CC9). Associated risks are cytotoxicity, irritation, pyrogenicity, acute system toxicity, hemocompatibility, and sensitization.	Conformance to applicable clauses within ISO 10993-1:2009, ISO 10993-2:2006, ISO 10993-4:2002, including Amd 1:2006 ISO 10993-5:2009, ISO 10993-6:2007, ISO 10993-10:2010, ISO 10993-11:2006, ISO 10993-12:2007, and ISO 10993-18:2005 must be demonstrated	Passed
Biocompatibility Tests for ECG leads, ECG Extension Cable, Pulse Oximeter Probe, Pulse Oximeter Cable, NIBP Cuffs (small, adult, large, plus), NIBP Extension, ARM Handset	Surface devices with skin contact of < 24 hours. Associated risks are cytotoxicity, irritation, and sensitization.	Conformance to applicable clauses within ISO 10993-1:2009, ISO 10993-2:2006, ISO 10993-5:2009, ISO 10993-6:2007, ISO 10993-10:2010, ISO 10993-12:2007, and ISO 10993-18:2005 must be demonstrated	Passed

Electromagnetic Compatibility

Electromagnetic compatibility testing was performed on this device. This testing was done to IEC 60601-1-2. Each criterion listed in Table 4 below was tested on a single System. Detail on the test procedures executed by Green Mountain Electromagnetics, Inc. and the pass/acceptance criteria were provided. All tests passed. See Table 4 below.

Table 4: Electromagnetic Compatibility (EMC) (IEC 60601-1-2)

Test	Purpose	Acceptance Criteria	Results
Radiated Emissions CISPR 11	Emissions	Group 1, Class B	Passed
Conducted Emissions CISPR 11, EN55011	Emissions	Group 1, Class B	Passed
Harmonics IEC 61000-3-2	Emissions	Complies with Standard IEC 61000-3-2	Passed
Flicker IEC 61000-3-3	Emissions	Complies with Standard IEC 61000-3-3	Passed
Electrostatic Discharge IEC 61000-4-2	Immunity	±6kV Contact ±8kV Air	Passed
Radiated RF IEC 61000-4-3	Immunity	80 – 2500 MHz 3V/m	Passed
Electrical Fast Transients IEC 61000-4-4	Immunity	±2kV AC mains ±1kV other	Passed
Surge IEC 61000-4-5	Immunity	±1kV Differential ±2kV Common	Passed
Conducted RF IEC 61000-4-6	Immunity	3Vrms 0.15 – 80 MHz	Passed
Power Frequency (50/60 Hz) Magnetic Field IEC 61000-4-8	Immunity	3A/m	Passed
Voltage Dips and Interrupts IEC 61000-4-11	Immunity	>95%V for 0.5 Cycle 60%V for 5 Cycles 30%V for 25 Cycles >95% for 5 Seconds	Passed

Human Factors

ANSI/AAMI HE48-1993, "Human factors engineering guidelines and preferred practices for the design of medical devices," was used during the design and testing of the SEDASYS System. System, component, and alarm usability testing was performed to test the user-based requirements and key procedure steps. The user-based requirements tested were screen visibility, audible testing, screen interfacing testing, alarm recognition and handling of the different components, including installing and removal of the cassette, umbilical cable, cannula, and associated monitoring cables.

Table 5: Human Factors

Test	Purpose	Acceptance Criteria	Results
System Usability Testing	Test user-based requirements and key procedure steps	Nurse (N=25) operation to demonstrate conformance to user-based requirements.	Passed
Oral/Nasal Cannula and Cassette Usability Testing	Test user-based requirements related to single patient use components.	Gastroenterologist (N=10) and nurse (N=10) to demonstrate conformance to single patient use requirements.	Passed
Patient Interface Human Factors	Test human factors (fit and ability to use ARM handset) for patient interfaces (including ARM handset, oral/nasal cannula, and monitors – NIBP Cuff / SpO_2 Probe / ECG Leads)	The system shall have customized patient interfaces designed to accommodate the 5th percentile to the 95th percentile user as defined by ANSI HE48.	Passed
Connector Human Factors	Test human factors of operator connections	Connectors for custom devices or those designed to combine several connections shall comply with ergonomic standards such that they can be connected and disconnected by 5th through 95th percentile clinicians as defined by ANSI HE48.	Passed

Software

Risk analysis for the system, including software, was performed in accordance with ANSI/AAMI/ISO 14971, Medical devices – Application of risk management activities to medical devices. The software requirements are derived from the SEDASYS System product requirements, human factors studies, and risk management activities. Software testing was performed, starting with unit testing (i.e., module level unit verification), integration testing, and system testing (i.e., software verification/validation). Software was also evaluated as part of the system level testing.

Table 6: Programmable Electrical Medical Systems (IEC 60601-1-4)

Test	Purpose	Acceptance Criteria	Results
IEC60601-1-4: 2000	Conformance to programmable electrical medical system requirements.	Conformance to applicable clauses within IEC60601-1-4: 2000 must be demonstrated.	Passed

The SEDASYS system claims conformance to relevant clauses in the standards listed below:

Table 7: Conformance to Standards

Standard Number	Standard Title
ANSI/AAMI/ISO 11137: 1994	Sterilization of Health Care Products - Validation Routine and Control-Gamma and Electron Beam Radiation Sterilization
EN 552: 1994	Sterilization of Medical Devices - Validation and Routine Control of Sterilization by Irradiation
ISO 10993-1: 2003	Biological evaluation of medical devices - Part 1: Evaluation and testing
ISO 14971: 2000	Medical Devices - Application of Risk Management to Medical Devices
ISO 13485: 2003	Medical Devices - Quality Management Systems
ANSI/AAMI HE48-1993	Human factors engineering guidelines and preferred practices for the design of medical devices
UL 60601-1: 2003	Medical Electrical Equipment - Part 1: General Requirements for Safety
IEC 60601-1-2: 2001, A1: 2005	Medical Electrical Equipment, Part 1: General Requirements for Safety, Section 1.2 Collateral Standard: Electromagnetic Compatibility – Requirements and Tests
IEC 60601-1-4: 1996, A1: 1999	Medical Electrical Equipment Part 1: General Requirements for Safety 4. Collateral Standard Programmable Electrical Medical Systems

Standard Number	Standard Title
IEC 60601-2-27: 2005	Medical Electrical Equipment – Part 2: Particular Requirements for the Safety – Specification for Electrocardiographic Monitoring Equipment
IEC 60601-2-30: 1999	Medical Electrical Equipment – Part 2: Particular Requirements for Safety, Including Essential Performance of Automated Cycling Non-invasive Blood Pressure Monitoring Equipment
IEC 60825-1: 1993, A1: 2001	Safety of Laser Products – Part 1: Equipment Classification, Requirements and User Guide.
ANSI/AAMI SP10: 1992	Electronic or Automated Sphygmomanometers
ISO 9919: 2005	Medical Electrical Equipment - Particular Requirements for the Basic Safety and Essential Performance of Pulse Oximeter Equipment for Medical Use

X. SUMMARY OF PRIMARY CLINICAL STUDY

EES submitted a Request for Designation on February 11, 2002. FDA determined that the SEDASYS System would be regulated as a Class III medical device. EES submitted six (6) Pre-IDE packages of information to FDA between September 2002 and April 2004 (I020308). Six (6) Pre-IDE meetings also occurred on December 4, 2002; March 13, 2003; May 8, 2003; August 28, 2003; January 20, 2004; and July 8, 2004.

EES submitted an Original IDE with a two-stage feasibility study protocol on July 21, 2005 (G050145). The feasibility study was followed by a pivotal trial under the same IDE. P080009 was received on March 25, 2008.

Prior to the pivotal clinical study, the applicant completed two (2) feasibility studies designed to evaluate the feasibility of the SEDASYS System to enable an endoscopist/nurse care team to safely and effectively administer minimal-to-moderate sedation with propofol in patients undergoing a colonoscopy or EGD procedure. An anesthesiologist attended all procedures. The studies were open, single-center studies conducted in the United States (CI-04-0005) and Belgium (CI-05-0002). Each study was conducted in two (2) stages. In Stage 1 an anesthesiologist operated the SEDASYS System to administer propofol sedation to each patient. In stage 2 the physician/nurse care team operated the SEDASYS System to administer propofol sedation to each patient with an anesthesiologist present. The endpoints for the study were AUC_{Desat}. Incidence of hypotension and bradycardia, level of sedation as measured using a Modified Observers Assessment of Alertness/Sedation scale (MOAA/S), gastroenterologist and patient satisfaction with sedation, and propofol dosing.

Ninety-six (96) patients (ASA I-III) were enrolled in the studies (48 patients in each study), with 24 patients (12 colonoscopy and 12 EGD) participating in each stage (Stages 1 and 2) of each study (CI-04-0005 and CI-05-0002). The combined AUC_{Desat} data from both studies in stage 1 was 6 ± 33 (seconds·%) and 12 ± 54 (seconds·%) in stage 2 (p-value = 0.540). In stage 1 there was one (1) patient (2%) that experienced hypotension and one (1) patient (2%) that experienced bradycardia. In stage 2 there were two (2) patients (4%) that experienced bradycardia. The majority of patients experienced minimal-to-moderate sedation throughout the procedure as measured by the MOAA/S scale. One (1) patient (1%) in the feasibility studies was non-responsive to a trapezius squeeze for 2 minutes per the MOAA/S scale. The gastroenterologists were very satisfied with the sedation they were able to administer in the studies, with a mean satisfaction score of 93 ± 9 (out of a possible maximum of 100). Similarly, the patients in the study were very satisfied with the sedation they received, with a mean satisfaction score of 93 ± 10 (out of a possible maximum of 100). The mean propofol maintenance rate used in the studies was 59 ± 15 μg/kg/min, which is consistent with FDA-approved propofol labeling (25 – 75 μg/kg/min). One (1) Serious Adverse Event (SAE) occurred during the feasibility studies (a patient fell off of a ladder resulting in a fractured neck which required hospitalization two (2) days after the procedure). The event was deemed not related to the study procedure, study device, or study drug.

The feasibility studies included an analysis of the Clinician Response Mode of the SEDASYS System. The automated responsiveness monitor (ARM) requires the patient to hear a System generated audible query, feel a handset vibration, and press a button on the handset. The ARM may not work for all patients, due to impairments such as hearing deficits, severe arthritis, and amputation. For these patients the physician-led team can use the Clinician Response Mode. In this mode, the physician-led team responds to a System generated query to assess if the patient is responsive. The System allows similar maintenance rate increases as when using the ARM. The sole difference is that the System will prompt the user to confirm the increase if it is greater than 25 mg/kg/min.

This mode was tested in the feasibility studies in a total of 20 patients as summarized in the Table 8 below:

Table 8: Clinical Response Mode vs. Patient Response Mode

	Clinician Response Mode	Patient Response Mode
Number of Subjects	20	76
Total Propofol Infused (mg) Mean ± SD	52.5 ± 24.0	60.8 ± 44.2
Procedure Time (minutes : seconds) Mean ± SD	6:28 ± 3:55	6:53 ± 5:23
Recovery Time (seconds) Mean ± SD	22 ± 16	20 ± 26

	Clinician Response Mode	Patient Response Mode
Apnea Subjects / Events	10/14	27/59
Oxygen Desaturation Subjects / Events	1/2	4/6
CSSI Mean ± SD Range	94.5 ± 8.1 (79-100)	91.7 ± 11.5 (41-100)
PSSI Mean ± SD Range	97.8 ± 3.7 (92-100)	96.1 ± 7.8 (67-100)

The feasibility study was designed to ensure approximately 25% of subjects were sedated with the Clinician Response Mode, even if they did not have an impairment preventing the use of the ARM. Not all of the 20 subjects above had an impairment. The data above show the safety and efficacy were similar for both the clinician response mode and the patient response mode, so the design of the pivotal did not require a minimum number of subjects sedated with the clinician response mode.

Cumulatively, the two feasibility studies provided sufficient evidence of safety to allow the pivotal trial to be conducted without the presence of an anesthesiologist. A complete list of all clinical studies associated with the SEDASYS System is as follows:

Table 9: List of Clinical Studies

Protocol	Objective	**Study Design**	**Number of Subjects**
Proof-of-Concept/Drug Dosing			
CI-01-0001	Feasibility of prototype	Non-comparative	10
CI-01-0002	Feasibility of prototype	Non-comparative	10
CI-02-0003	Feasibility of opioid pretreatment	Non-comparative	8
CI-02-0005	Determine fentanyl dosing	Non-comparative	32
Evaluate Current Practice of Sedation in GI Suite			
CI-02-0004	Sedation risk Assessment	Comparative: GI team vs Anesthesiologists	300
Lextant	Analysis of nursing tasks	Observational	100
United Biosource	Develop User Satisfaction scales	Validation study	180

Protocol	Objective	Study Design	Number of Subjects
Clinical Functionality Studies			
CI-03-0001	Nasal cannula product comparison	Open	13
CI-03-0004	Evaluate ARM monitor	Open	27
CI-03-0005	Evaluate Capnometer	Open	50
Clinical Accuracy Validation	Evaluate Pulse Oximeter	Open	11
Feasibility Studies			
CI-04-0005	SEDASYS Feasibility	Open	48
CI-04-0002	SEDASYS Feasibility	Open	48
Pivotal Study			
CI-06-0004	Clinical Safety	Open Comparative	1000

Data from the pivotal clinical study were the basis for the PMA approval decision. A summary of the pivotal clinical study is presented below.

A. Study Design

Patients were treated between March 6, 2007 and October 24, 2007. The database for this PMA reflected data collected through October 24, 2007 and included 1,000 patients. The study was a randomized, non-blinded, parallel group active comparator clinical study. There were eight (8) investigational sites.

The stated objective of the pivotal investigation was to: "Demonstrate the SEDASYS System [a.k.a. Sedation Delivery System; SEDASYS] enabled a physician/nurse team to administer propofol sedation in a controlled therapeutic amount to facilitate titration to desired clinical effect and the conduct of colonoscopy or EGD procedures."

The hypothesis was that the SEDASYS System would result in a lower area-under-the-curve of oxygen desaturation (AUC_{Desat}) than a manually administered benzodiazepine-opioid sedation regimen (superiority trial design). The study was designed as a two-armed superiority study with an active comparator ("current standard of care" (CSC) midazolam-opioid moderate sedation). A multi-center, randomized, non-blinded, controlled study was conducted in 1,000 patients, over 7 months, undergoing procedures that were anticipated to require sedation in a gastroenterology suite. Eight (8) centers, including private practice and academic settings, contributed data to the study. Patients were enrolled into one of two treatment arms: 1) sedation delivery via the SEDASYS System or 2) sedation delivery via CSC. In each treatment arm, sedation medication was administered under the direction of a gastroenterologist by a nurse who had not been trained in

general anesthesia. The sedation regimen in the CSC arm was "left to the discretion of the individual centers and practitioners," per each sites standard procedures. The SEDASYS System automatically delivers supplemental oxygen, at 2 L/min, during a procedure. To remove supplemental oxygen delivery as a variable in the study, all sites were required to administer a minimum of 2 L/min supplemental oxygen to all subjects in the CSC group. Sedation was performed for two (2) gastroenterological procedures: colonoscopy and esophagogastroduodenoscopy.

Primary Endpoint

The primary endpoint, intended to evaluate overall safety, was defined as the area under the curve of oxygen desaturation (AUC_{Desat}) (SpO_2 < 90% for > 15 seconds) as determined by pulse oximetry. As stated above, the applicant's hypothesis was that the SEDASYS System would result in a lower AUC_{Desat} of oxygen saturation when compared to CSC (superiority trial design).

Secondary Endpoints

The secondary endpoints were:

- duration of over-sedation
- time to recover from effects of sedation
- physician satisfaction scores
- patient satisfaction scores

Tertiary Endpoints

The additional tertiary endpoints were:

- additional oxygen desaturation measurements
  - number of oxygen desaturation events per patient (SpO_2 < 90 for ≥ 15 sec)
  - mean duration of oxygen desaturation events per patient
  - mean magnitude of oxygen desaturation events per patient
  - minimum oxygen saturation level per patient
- apnea assessments
  - number of events ≥ 30 seconds
  - mean duration of apnea per patient
- bradycardia
  - number of events (< 50 beats/minute or 80% of baseline, lasting ≥ 30 seconds)
  - number of bradycardic events per patient
  - mean duration of bradycardia per patient
  - mean magnitude of bradycardia
- hypotension
  - number of events (≥ two (2) consecutive systolic blood pressure measurements < 80 mm Hg or 80% of screening value)
  - mean magnitude of events per patient
  - mean duration of events per patient
- sedation and analgesic dosing totals per patient

    - sedation included only propofol and midazolam
    - analgesic medication included only fentanyl and meperidine
  - interruptions of the procedure due to under sedation
    - number of events per patient
    - sum duration of events per patient
- rescue interventions, e.g. reversal medications, intubation, bag and mask ventilation
- polyps per patient
- percent change on psychomotor tests, recovery compared with pre-procedure
- nausea, assessed on visual analog scale at pre-procedure and recovery
- adverse events

Statistical Analysis Plan

The primary analysis for colonoscopy and EGD procedures was a between treatment group comparison of mean AUC_{Desat} scores, using an analysis of variance (ANOVA). A linear model including terms for treatment group and study site was used. An F test was conducted at the two-sided, α=0.05 level of significance.

The secondary analyses were conducted at the Tukey multiplicity adjusted α=0.0253 significance level, in order to maintain an overall α=0.05 probability of a Type I error. Between group comparisons for duration of over-sedation, physician satisfaction, and patient satisfaction were conducted using ANOVA methods with an appropriate linear model. Time to recovery from effects of sedation was analyzed using a Cox proportional hazards regression model to determine the treatment effect on recovery time. Graphical displays of survival curves were constructed for the two (2) treatment groups.

Summary statistics were computed for each tertiary endpoint. For categorical measures, the data was summarized using counts and percentages. For continuous measures, summary statistics (mean, median, standard deviation, minima, and maxima) were computed by treatment group.

Adverse events were coded using the current version of the medical dictionary for regulatory activities (MedDRA®) and summarized by treatment for the number of patients reporting the AE and the number of AEs reported. Frequencies of each AE were summarized within group by MedDRA preferred term within system organ class, by severity and by relation to treatment.

A Data Monitoring Committee (DMC) met independently four (4) times during the conduct of the pivotal study to review patient safety data. At no time during the DMC deliberations did they note a major safety concern. After each meeting the DMC recommended that the study continue unchanged.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the pivotal study, CI-06-0004, was limited to patients who met the following inclusion criteria:

Inclusion Criteria:
- Adults ≥ 18 years old;
- Able to comprehend, sign, and date the written informed consent form (ICF);
- English as their primary language;
- Non-emergent EGD or colonoscopy;
- Have taken nothing by mouth [(NPO) except the preparation for colonoscopy] for a minimum of 6 hours prior to the study procedure; and
- ASA [American Society of Anesthesiologists] Physical Class I, II or III as assigned by the endoscopist

Patients were not permitted to enroll in the pivotal study if they met any of the following exclusion criteria:

Exclusion Criteria:
- Allergy or inability to tolerate study medications
- Baseline oxygen saturation < 90% (room air);
- Procedure time anticipated to exceed 45 minutes for anatomical reasons;
- Current use of the fentanyl patch;
- History of diagnosed sleep apnea or gastroparesis;
- Pregnant or nursing females;
- BMI ≥ 35;
- Participation in a clinical trial within the past 30 days.

2. Follow-up Schedule

   Preoperatively, patients were screened according to the above inclusion/exclusion criteria. Postoperatively, the objective parameters measured during the study, as well as adverse events and complications through study exit, were recorded. Patients were exited from the study after 24 to 48 hours post-procedure, upon completing the patient satisfaction survey.

3. Clinical Endpoints

   This study is designed with a primary endpoint intended to inform about safety. Achievement of this endpoint was required for study success. Effectiveness endpoints were secondary and were not intended to determine study success or failure because propofol, in the doses administered, has been established to be safe and efficacious for sedation by the Center for Drug Evaluation and Research (CDER).

   With regards to safety, the study assessed the patient's AUC_{Desat} (the studies primary endpoint). AUC_{Desat} integrates the incidence, duration, and depth of oxygen desaturation events, allowing for a clinically relevant assessment of a patients oxygenation. It allows for an objective assessment of safety of the SEDASYS System, both in the absolute and in comparison to the current standard of care. Other measures of safety, such as the incidence of deeper-than-intended sedation, were also assessed.

With regards to effectiveness, the study assessed patient and physician satisfaction with the sedation, the duration of time patients were over-sedated, and the time to recover from the effects of sedation (the four (4) secondary endpoints). The intent of sedation is to keep the patient calm and comfortable during the endoscopic procedure, therefore, appropriate assessments of the effectiveness of the sedation methodology are physician and patient satisfaction. Measuring the duration of time patients were over-sedated is an appropriate assessment of the effectives of the SEDASYS System to achieve and maintain minimal-to-moderate sedation. Recovery from the effects of sedation assesses how use of the System could impact patient discharge time.

With regard to success/failure criteria, the study would be a successful in achieving its primary endpoint if use of the SEDASYS System resulted in a lower cumulative area-under-the-curve of oxygen desaturation (AUC_{Desat}) when compared to CSC (superiority trial design).

B. Accountability of PMA Cohort

At the time of database lock, of 1,000 patients enrolled in the PMA study, 98% (982) patients were available for analysis at the completion of the study (Table 10). Overall, the number of patients who did not complete the study constituted a small percentage of the patients randomized and therefore did not likely affect interpretation of the study findings.

Table 10: Patient Accountability

Colonoscopy	SEDASYS System (N = 358)	Current Standard of Care (N = 363)	Total (N = 721)
Completed Study	354 (99%)	354 (98%)	708 (98%)
Did Not Complete Study:	4 (1%)	9 (3%)	13 (2%)
Withdrawn for adverse event	0	0	0
Withdrew – noncompliance	0	0	0
Withdrawn for poor prep	0	1 (11%)	1 (8%)
Withdrawn for device failure	1 (25%)	4 (44%)	5 (38%)
Withdrawal of consent	1 (25%)	1 (11%)	2 (15%)
Death	0	0	0
Other, specified as:	2 (50%)	3 (33%)	5 (38%)
Device failure	1	1	2
Data acquisition issue	0	1	1
High tolerance to propofol	1	0	1
History of sleep apnea	0	1	1
EGD	**(N = 138)**	**(N = 141)**	**(N = 279)**
Completed Study	135 (98%)	139 (99%)	274 (98%)
Did Not Complete Study:	3 (2%)	2 (1%)	5 (2%)
Withdrawn for adverse event	0	0	0
Withdrew – noncompliance	1 (33%)	0	1 (20%)
Withdrawn for poor prep	0	0	0
Withdrawn for device failure	0	0	0
Withdrawal of consent	0	1 (50%)	1 (20%)
Death	0	0	0
Other, specified as:	2 (67%)	1 (50%)	3 (60%)
DAQ issue	2	1	3

C. Study Population Demographics and Baseline Parameters

The demographic breakdown of SEDASYS System and CSC study patients was similar in terms of age, gender and race in colonoscopy and EGD groups. The mean age was 55 years (±12 SD) in colonoscopy patients and 50 years (±15 SD) among EGD patients studied. The American Society of Anesthesiologists (ASA) classification of the colonoscopy study population was predominately ASA 1 and 2

with 11 (3%) of the SEDASYS patients and 6 (2%) of the CSC patients classified as ASA 3. The mean body mass index (BMI) in the SEDASYS System treatment group was 26kg/m^2 (± 4 SD) and 27kg/m^2 (± 4 SD) in the CSC treatment group.

EGD patients were also predominately ASA 1 and 2 patients with 7 (5%) of the SEDASYS patients and 4 (3%) of the CSC patients classified as ASA 3. The mean body mass index (BMI) in both treatment groups was 26kg/m^2 (± 4 SD).

The demographic distribution of patients participating in this study appears to be adequately representative of ASA 1 and 2 patients undergoing sedations for gastroenterological procedures.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the intent-to-treat cohort of 982 patients who completed the study. The key safety outcome for this study is presented below in Table 11. Adverse Events are reported in Tables 14 and 15.

The SEDASYS System achieved the primary endpoint among the colonoscopy study patients, but not in the EGD population (See Table 11 below). Among EGD patients there was a trend suggesting improvement in the primary endpoint with the SEDASYS System compared to CSC.

Table 11: Primary Endpoint Findings[a]

Colonoscopy	**SEDASYS System (N=358)**	**Control (N=363)**	**p-value[b]**
AUC_{Desat} (seconds•%) Mean ± std Range	17.8 ± 124.59 [0 – 1741]	98.8 ± 510.32 [0 – 7040]	0.004
EGD	**SEDASYS System (N=138)**	**Control (N=141)**	**p-value**
AUC_{Desat} (seconds•%) Mean ± std Range	38.6 ± 181.87 [0 – 1771]	60.2 ± 179.92 [0 – 996]	0.315

[a.] All data for intent-to-treat population
[b.] Values were analyzed using an ANOVA

Site Effects on Primary Endpoint Analysis:

A marked study site effect was noted in AUC_{Desat} data. Two (2) study sites had a noticeably higher AUC_{Desat} in both study groups when compared to the other sites (See Table 12 below). Additional statistical analysis established that excluding these two (2) sites from the primary endpoint analysis still showed statistical significance for the SEDASYS System in colonoscopy and the EGD trend was still favorable.

Table 12: Primary Endpoint AUC_{Desat} by Center

Colonoscopy						
	SEDASYS System			**CSC**		
Site	N	Mean	SD	N	Mean	SD
0	56	2.9	21.38	56	13.3	46.60
2	30	2.3	12.42	29	40.3	125.40
3	72	1.6	10.63	73	38.9	108.32
4	62	84.9	280.46	64	378.5	1,101.65
5	9	50.3	151.00	9	459.9	757.71
6	13	0.0	0.00	11	0.0	0.00
7	47	0.0	0.00	49	2.8	13.71
8	60	2.6	20.01	59	22.8	99.59
EGD						
	SEDASYS System			**CSC**		
Site	N	Mean	SD	N	Mean	SD
0	15	19.4	61.36	15	4.3	16.78
2	5	0.0	0.00	7	135.7	359.07
3	24	0.0	0.00	25	0.0	0.00
4	33	140.7	346.39	33	186.8	271.12
5	3	0.0	0.00	4	223.3	282.83
6	0	-	-	0	-	-
7	19	10.4	24.75	17	6.6	27.16
8	34	0.0	0.00	35	0.0	0.00

Outlier Analysis:

In order to ensure that the statistically significance reduction in AUC_{Desat}, the study's primary endpoint, seen with the SEDASYS for colonoscopy patients was not due to a few outliers, an outlier analysis was performed. The statistical analysis was rerun with outliers (± 3 Standard Deviations) removed. Statistically the results for the SEDASYS System improved, with the p-value for colonoscopy decreasing from 0.004 to 0.001, and for EGD decreasing from 0.315 to 0.053.

Cardiorespiratory Measures:

Cardiorespiratory measures (See Table 13 below) assessed in the study were:

- Oxygen desaturation (SpO_2 < 90 for > 15 sec)
- Apnea ≥ 30 seconds
- Bradycardia (< 50 beats/minute or 80% of baseline, lasting ≥ 30 seconds)
- Hypotension (≥ two consecutive systolic blood pressure measurements < 80 mm Hg or 80% of screening value)

Table 13: Cardiorespiratory Measures

Cardiorespiratory Measures	Colonoscopy		EGD	
	SEDASYS System (N=358)	**Control (N=363)**	**SEDASYS System (N=138)**	**Control (N=141)**
Oxygen Desaturation				
n (%)	18 (5%)	56 (15%)	17 (12%)	24 (17%)
Magnitude Range (%)	72 – 88	39 – 89	53 – 88	68 – 89
Duration Range (sec)	20 – 133	17 – 335	16 – 97	16 – 199
Apnea				
n (%)	127 (35%)	119 (33%)	52 (38%)	57 (40%)
Duration Range (sec)	30 – 124	30 – 175	30 – 109	30 – 121
Bradycardia				
n (%)	10 (3%)	4 (1%)	2 (1%)	0
Magnitude Range (%)	36 – 47	37 – 45	37 – 43	0
Duration Range (sec)	36 – 143	66 – 253	132 – 144	0
Hypotension				
n (%)	8 (2%)	5 (1%)	0	0
Magnitude Range (%)	55 – 78	65 – 76	0	0
Duration Range (sec)	208 – 678	80 – 335	0	0

The SEDASYS System design does not prevent the occurrence of oxygen desaturation). Some desaturation events occurred despite the System's automatic increase in oxygen delivery.

Adverse effects that occurred in the PMA clinical study:

There were a total of 82 adverse events (AEs) in the pivotal study; 34 in the SEDASYS group and 48 in the current standard of care group (CSC). There were no device-related AEs reported in either group for this study. The AEs reported during the pivotal study possibly related to the study drugs are listed in Table 14 below. The AEs in the study not related to study drugs or device are provided in Table 15 below.

No patients sedated with the SEDASYS System died, were hospitalized, or developed bowel perforation during the study. Therefore, the SEDASYS System was not associated with a Serious Adverse Event (SAE).

Serious Adverse Events
There were no Serious AEs reported in the SEDASYS group, and one (1) Serious AE reported in the Control group (which was neither device- nor drug-related). One (1) CSC patient had a partial small bowel obstruction that resulted in hospitalization.

Severe Adverse Events
There were two (2) Severe AEs reported in the pivotal study. One (1) patient in the CSC group experienced a partial small bowel obstruction (which is the same patient that was also classified as a SAE above), and one (1) patient in the SEDASYS group experienced abdominal pain post-procedure that required drug therapy.

Moderate Adverse Events
There were 41 Moderate AEs reported in the pivotal study. Thirty-six (36) patients in the CSC group experienced a Moderate AE, including oxygen desaturation (one (1) patient required bag-mask ventilation), vomiting, sore throat, nausea, atypical chest pain due to GI complications, hemorrhoid, Crohn's Ileitis, and abdominal pain. Five (5) patients in the SEDASYS group experienced a Moderate AE, including head ache, abdominal pain, vomiting, abdominal cramping, and oxygen desaturation.

Mild Adverse Events
There were 39 Mild AEs reported in the pivotal study. Eleven (11) patients in the CSC group experienced a Mild AE, including flatulence, intravenous (iv) site swelling, vomiting, sore throat, blood with bowel movement, diarrhea, nausea, and oxygen desaturation. Twenty-eight (28) patients in the SEDASYS group experienced a Mild AE, including abdominal bloating, gas, nausea, vomiting, anxiety, dizziness, esophageal pain, apnea, abdominal cramping, hypotension, and hypertension.

Table 14: Causal Adverse Events

	SEDASYS System (N = 496)	**Control** (N = 504)
Body Trembling	3 (0.6%)	0
IV Site Discomfort	2 (0.4%)	0
Oxygen Desaturation	1 (0.2%)	27 (5.4%)
Nausea or Vomiting	1 (0.2%)	2 (0.4%)
Hypertension	1 (0.2%)	0
Apnea	1 (0.2%)	0
Dizziness	1 (0.2%)	0
Rash on Chest/Back	1 (0.2%)	0

Table 15: Non-Causal Adverse Events

	SEDASYS System (N = 496)	**Control** (N = 504)
Nausea or Vomiting	7 (1.4%)	4 (0.8%)
Abdominal Pain/Bloating/Cramping	5 (1.0%)	1 (0.2%)
Esophageal Pain/Hoarse Voice	2 (0.4%)	3 (0.6%)
Flatulence	1 (0.2%)	1 (0.2%)
Hypertension	1 (0.2%)	0
Hypotension	1 (0.2%)	0
Anxiety	1 (0.2%)	0
Fever	1 (0.2%)	0
Headache	1 (0.2%)	0
Sinus Headache	1 (0.2%)	0
Stiff Neck	1 (0.2%)	0
Dizziness	1 (0.2%)	0
Diarrhea	0	2 (0.4%)
IV Site Swelling/Pain	0	2 (0.4%)
Partial Small Bowel Obstruction	0	1 (0.2%)
Oxygen Desaturation	0	1 (0.2%)
GI Related Chest Pain	0	1 (0.2%)
Blood with Bowel Movement	0	1 (0.2%)
Crohn's/Ileitis	0	1 (0.2%)
Hemorrhoid	0	1 (0.2%)

2. Effectiveness Results

The analysis of device effectiveness was based on the intent-to-treat cohort of 982 patients who completed the study. Key effectiveness outcomes (secondary endpoints) are presented in Table 16.

Review of the secondary endpoints was notable for achievement of two (2) secondary endpoints (physician satisfaction and time to recover from sedation) in both colonoscopy and EGD groups (See Table 16 below). The physicians in the pivotal study were more satisfied with the sedation they were able to administer using the SEDASYS System when compared to their current standard for sedation (benzodiazepine and opioid in combination). The patients recovered more rapidly from the effects of sedation when sedated with the SEDASYS System when compared to the current standard of care. Statistical Significance was not achieved for the other two (2) secondary endpoints (patient satisfaction and duration of over-sedation).

Table 16: Secondary Endpoints[a]

Colonoscopy	**SEDASYS System (N=358)**	**Control (N=363)**	**p-value[b]**
Physician Satisfaction			
Mean ± std	92.4 ± 10.32	75.8 ± 17.18	<0.001
Range	27.1 - 100	25.0 - 100	
Patient Satisfaction			
Mean ± std	92.5 ± 12.09	90.5 ± 12.44	0.052
Range	0 - 100	35.4 - 100	
Recovery Time from Sedation (minutes)			
Mean ± std	2.7± 2.37	6.3 ± 6.78	<0.001
Range	0 - 15	0 - 37	
Duration of Deep Sedation and/or Non-Purposeful Response to Trapezius Squeeze (minutes)	0.1 ± 1.16	0.1 ± 1.23	0.573
Mean ± std	0 - 16	0 - 22	
Range			
EGD	**SEDASYS System (N=138)**	**Control (N=141)**	**p-value**
Physician Satisfaction			
Mean ± std	92.1 ± 11.30	77.0 ± 15.84	<0.001
Range	35.4 - 100	42.7 - 100	
Patient Satisfaction			
Mean ± std	91.0 ± 12.68	87.9 ± 12.59	0.067
Range	24.0 - 100	39.6 - 100	
Recovery Time from Sedation (minutes)			
Mean ± std	3.5± 2.53	7.0 ± 7.43	<0.001
Range	0 - 12	0 - 36	
Duration of Deep Sedation and/or Non-Purposeful Response to Trapezius Squeeze (minutes)	0.0± 0.38	0.1 ± 0.85	0.731
Mean ± std	0 - 4	0 - 10	
Range			

[a] All data for the intent-to-treat population

[b] Values were analyzed using an ANOVA except Recovery Time which used a Cox Proportional Hazards Regression Analysis

The SEDASYS System was associated with deeper-than-intended sedation, including non-responsiveness to a painful trapezius squeeze. There were a total of 17 patients in the study out of 1,000 randomized (1.7%) who had at least one (1) episode of deeper-

than-intended sedation. Of these, 12 were sedated using the device (2.4% (12/496) of SEDASYS patients) and 5 were CSC patients (1.0% (5/504) of CSC patients).

Efficacy findings were consistent with labeled information regarding propofol as a sedation product. Depth of sedation was evaluated using the applicant's customized version of the Modified Observers Assessment of Alertness and Sedation Scale (MOAA/S). A MOAA/S score of 5 was interpreted as minimal sedation, scores of 4-2 as moderate sedation, and scores of 1 or 0 as comparable to deep sedation or general anesthesia, respectively. The mean MOAA/S score among colonoscopy patients was 4.3 (± 0.6 SD) managed with the SEDASYS System and 4.2 (± 0.6 SD) among patients in the CSC group. Among patients undergoing EGD procedures, the mean sedation scale score was 4.5 (± 0.5 SD) and 4.4 (± 0.6 SD) in the SEDASYS group and CSC group, respectively.

3. Subgroup Analyses

The following characteristics were evaluated for potential association with outcomes:

* Demographic subgroup analysis: An analysis of demographic subgroups revealed that the primary endpoint was not affected by gender, race, age, or ASA classification.

* Dosing of midazolam among colonoscopy patients in the CSC group: Dosing of sedation products was not controlled in the CSC group. The sedative administered in the CSC group was midazolam. The midazolam label recommends that not more than 2.5 mg be administered as a single dose. In the CSC group, 71 of 354 CSC patients (20%) undergoing colonoscopy received midazolam doses of three (3) or four (4) mg. The statistical analysis of the primary endpoint excluding these patients also demonstrated study success.

* PRN dosing among colonoscopy patients in the SEDASYS System arm: Healthcare providers administered at least one bolus dose of propofol (0.25 mg/kg) in 267 out of 347 procedures (77%). Of the total dose of propofol administered to patients, 27% (27.8 mg/104.7 mg) was via bolus doses. A noteworthy feature of the SEDASYS System is that the only condition that prevented delivery of a bolus dose at the discretion of the healthcare provider is enforcement of a 90 second lockout since the last bolus dose. Specifically, the presence of hypoxemia, apnea, and ARM-unresponsiveness did not preclude supplemental bolus dosing of propofol at the discretion of the healthcare provider.

* Site Effects on Primary Efficacy Analysis: This analysis can be found above under Section D.1.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included eight (8) investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on May 28, 2009, the Anesthesiology and Respiratory Therapy Devices Panel voted (8-2) in favor of an "Approvable with Conditions" decision on the application. Five (5) conditions were recommended, and four (4) of these were accepted prior to voting on the approvable with conditions decision:

Condition 1: The Indications for Use should be revised to exclude EGD. There was no motion to second this condition, therefore, this was not actually a Condition recommended by the Panel.

Condition 2: The Indications for Use should be revised to limit the use of the device on adult patients aged 70 or less. The Panel voted (6-4) to accept this condition. The FDA and EES agreed that the age restriction would not be a condition of approval. Specifically, the FDA and EES agreed that the use of the device would be limited based on the ASA Physical Status Classification.

Condition 3: The device should be operated by a three (3) person team under the direction of a physician where one (1) person, with at least the training of a nurse, is only responsible for monitoring the device and managing the patient airway. The Panel voted (10-0) to accept this condition. FDA determined that the intent of this panel recommendation was that the healthcare provider managing sedation and monitoring the patient was to be dedicated to this task, and have no other responsibilities during the procedure. The number of nurses present in the procedure room was therefore irrelevant to the conduct of sedation, provided that the healthcare provider identified as administering sedation was solely occupied with sedation management.

Condition 4: The device should require training for operation including advanced airway management, pharmacology of propofol and opiates, monitoring aspects of the device including capnometry, device setup, and patient selection. This training should be conducted in a facility that has been accredited to provide this type of training by persons who are credentialed by the facility to provide this type of training

to health care providers. Continuing competency training and evaluation of this training may be conducted in this type of facility or in an accredited facility with validated clinical simulators. The Panel voted (9-1) to accept this condition.

Condition 5: A post-market study and a controlled launch of the device should be mandated. The Panel voted (9-0) with one (1) abstention to accept this condition. The Panel believed that the device raises the standard of care by providing additional patient monitoring to ensure the safe administration of propofol. They also believed the delivery of oxygen by the device is a beneficial feature of the device. However, there were concerns regarding safety due to over sedation, and the study design due to the heterogeneity (lack of standardization) of the control group, small number of sites, and the use of a surrogate endpoint.

The Panel Meeting Summary can be found at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/AnesthesiologyandRespiratoryTherapyDevicesPanel/ucm163851.htm.

B. FDA's Post-Panel Action

Following an extensive review, and taking into account the recommendations of the May 28, 2009 advisory panel meeting, CDRH had three (3) outstanding concerns regarding the safety of the device under the conditions of use prescribed, recommended, or suggested in the proposed labeling. First, CDRH determined that the incidents of deeper-than-intended sedation during the conduct of the pivotal study raised a safety issue that did not support departing from the currently approved drug label for propofol by expanding the population of healthcare professionals who administer the drug. Second, CDRH found that a targeted training program proposed by the applicant to instruct the proposed expanded population of healthcare professionals in the management of deeper-than-intended sedation was inadequate because an outcome-based clinical study to enable evaluation of such a program had not been proposed or conducted. Third, CDRH determined that an advanced airway program to augment the skills of mild-to-moderate sedation providers was not adequate to ensure the safe administration of propofol by healthcare professionals not trained in the management of general anesthesia. Further, as with the targeted training program described above, the advanced airway management program was not evaluated by an outcome-based study appropriate to the proposed setting of use.

After additional interaction with the applicant and subsequent review, the Agency determined that the risk associated with deeper-than-intended sedation was mitigated by (1) the development of an clinical training program by an independent third party intended to instruct users in the safe administration of propofol for minimal-to-moderate sedation and (2) a restriction for use stating that the use of the proposed device is limited to environments where a trained anesthesia provider is immediately available to the SEDASYS System user as needed for assistance or consultation.

The final device labeling includes a statement indicating that the SEDASYS System must only be used in hospitals and/or healthcare facilities where an anesthesia provider is immediately available for assistance of consultation as needed. The final device labeling also includes a warning statement that notes that the SEDASYS System is associated with non-sustained, unintended episodes of deep sedation and/or complete unresponsiveness or non-purposeful response to painful stimulation. The warning statement further notes that the System should be used by a physician-led team trained in administering moderate sedation and in the management of under and over sedation and that the identified team member responsible for monitoring the patient and managing sedation should not be involved in the conduct of the procedure.

With regards to training, the final device labeling specifies that at a minimum, the member of the physician-led team who is administering sedation must have training in the management of the cardiorespiratory effects of propofol when administered using computer-assisted personalized sedation systems. The training must include instruction covering (1) pharmacology of propofol, (2) identification of high risk patients, recognition of progression of levels of sedation, and actions necessary to return a patient to intended levels of sedation, (4) use of capnometry and the determination of adequate ventilation, and (5) management of airway obstruction and hypoventilation.

The applicant has submitted the contents of a training program developed by an independent third party with expertise in the practice of sedation and airway management. This training program is designed to provide users of the SEDASYS System the training specified in the device labeling. The training program submitted consists of an online didactic program intended to convey the knowledge base considered necessary to safely administer propofol for moderate sedation (e.g., pharmacology of propofol, recognition of progression of levels of sedation) and simulation-based rescue skillset training that incorporates five (5) scenarios that are intended to communicate appropriate responses to risk factors associated with the use of propofol.

In addition, the applicant has submitted two (2) post-approval studies cumulatively intended to demonstrate that the SEDASYS System is safe for use in clinical practice by users that have been instructed in the safe administration of propofol for minimal-to-moderate sedation using the independent third-party training program. These studies may enable the future removal of the restriction requiring that a professional trained in the administration of anesthesia is immediately available. See Section XIII below for a description of the post-approval studies.

Cumulatively, this information addresses the recommendations of the Panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Effectiveness findings were consistent with labeled information regarding propofol as a sedation product. The effectiveness endpoints studied were all secondary endpoints because propofol has been found to be safe and efficacious for sedation by CDER. Physicians were significantly more satisfied with the sedation they were able to administer with the SEDASYS System compared to the control. Patients sedated with the System recovered from the effects of sedation significantly faster when compared to the control. Patients were satisfied with the sedation they received, but not significantly more satisfied than the sedation administered in the CSC group.

The physician-led teams were able to achieve and maintain minimal-to-moderate sedation. Depth of sedation was evaluated using a customized version Modified Observers Assessment of Alertness and Sedation (MOAA/S) scale. A score of 5 was defined as minimal sedation, scores of 4-2 were defined as moderate sedation, and scores of 1 or 0 were defined as comparable to deep sedation or general anesthesia, respectively. The mean MOAA/S score among colonoscopy patients was 4.3 ($\pm$ 0.6 SD) managed with the SEDASYS System and 4.2 ($\pm$ 0.6 SD) among patients in the CSC group. The mean MOAA/S score among EGD patients was 4.5 ($\pm$ 0.5 SD) and 4.4 ($\pm$ 0.6 SD) in the SEDASYS group and CSC group, respectively.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory data as well as data collected in a clinical study conducted to support PMA approval as described above. The primary endpoint, intended to evaluate overall safety, was area under the curve of oxygen desaturation (AUC_{Desat}) ($SpO_2 < 90\%$ for > 15 seconds) as determined by pulse oximetry. The SEDASYS System achieved the primary endpoint among the colonoscopy patients in the study. Among EGD patients there was a trend suggesting improvement in the primary endpoint with the SEDASYS System compared to CSC.

FDA's findings of safety and effectiveness were primarily based on colonoscopy patients because the duration of sedation in colonoscopy was longer than with EGD patients. Therefore sedation in colonoscopy was expected to be more revealing of sedation-related adverse events.

In colonoscopy patients, a marked study site effect was noted . FDA's review established that even with a reanalysis of the data that excluded the two (2) study sites where AUC_{Desat} was noticeably higher, the SEDASYS System still achieved the primary endpoint for colonoscopy.

In the pivotal trial, administration of propofol using the SEDASYS System was associated with non-sustained, unintended episodes of deep sedation and/or complete unresponsiveness or non-purposeful response to painful stimulation. The pivotal

study results and outstanding safety concerns necessitated an adequate training program structured to address episodes of deeper-than-intended sedation during the pivotal study as outlined in the approvable letter dated February 29, 2012.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

Benefits:

- Findings from the pivotal study that demonstrate a statistically-significant decrease in area under the curve (AUC_{Desat}) of hypoxemia (deficient oxygenation of arterial blood) in colonoscopy patients compared to similar patients sedated using the "Current Standard of Care" (CSC) – benzodiazepines and opioids – during gastroenterological procedures. In EGD patients there was a trend suggesting improvement in the primary endpoint with the SEDASYS System compared to patients sedated using benzodiazepines.

Risks:

- The SEDASYS System was associated with greater incidences of deeper-than-intended sedation.

Safe use of the SEDASYS System may only be reasonably assured by imparting additional training to the intended users by those with expertise in training anesthesiologists. Evaluation of this training can only be completed by review of clinical data. Until this training has been thoroughly evaluated, a person trained in administration of general anesthesia must be immediately available.

The simulation-based moderate sedation training program developed by the International Society of Anaesthetic Pharmacologists is expected to aid in preventing and mitigating the risks of over-sedation by expert instruction in the pharmacology of propofol and airway management. Additionally, without additional data, a restriction for use requiring immediate availability of an anesthesia provider will provide assurance of patient safety. The two (2) post-approval studies are to evaluate whether this restriction can be removed.

In conclusion, given the available information above, the data support that for the intravenous administration of 1% (10 mg/mL) propofol injectable emulsion for the initiation and maintenance of minimal to moderate sedation, as defined by the American Society of Anesthesiologists (ASA) Continuum of Depth of Sedation, in ASA physical status I and II patients ≥18 years old undergoing colonoscopy and esophagogastroduodenoscopy (EGD) procedures the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the intended use provided that (1) users are instructed in the management of the cardiorespiratory effects of propofol when administered using computer-assisted personalized sedation systems and (2) the use of the device is restricted to environments where a trained anesthesia provider is immediately available to the SEDASYS System user as needed for assistance or consultation.

The approval of this submission is primarily based on findings from the pivotal study that demonstrate a statistically-significant decrease in area under the curve (AUC_{Desat}) of hypoxemia (deficient oxygenation of arterial blood) in colonoscopy patients compared to similar patients sedated using the "Current Standard of Care" (CSC) – benzodiazepines and opioids – during gastroenterological procedures. Incidence, duration, and depth of oxygen desaturation are all components of AUC_{Desat}. With a higher incidence of oxygen desaturation, and longer and deeper desaturation events, patients receiving CSC had a larger AUC_{Desat} than patients receiving sedation with the SEDASYS System. In EGD patients there was a trend suggesting improvement in the primary endpoint with the SEDASYS System compared to patients sedated using benzodiazepines.

The approval of the SEDASYS System carries a number of public health implications:

1. The SEDASYS System is the first device that will expand the group of healthcare providers who may administer propofol during colonoscopy and EGD procedures. As described above, the use of the device is limited to healthcare providers who will have completed clinically-directed training in sedation management taught by experts credentialed in anesthesiology. Along these lines, a moderate sedation training program has been developed for non-anesthesia professionals. This training program will be expected to impart the skillset required in order to provide reasonable assurance that SEDASYS System users are able to administer propofol using the device without preventable, sedation-related adverse events. It should be noted that this program is not intended specifically for the SEDASYS System, but instead may be used with any future computer-assisted personalized sedation systems that are developed to administer propofol. The knowledge base imparted by the program may also be helpful to any healthcare provider that is seeking credentialing to administer sedation. As designed, the training program exceeds the level of sedation training typically received by gastroenterology teams and may thereby improve overall safety outcomes associated with sedation during colonoscopy and EGD procedures.

   The approved propofol drug label states that the use of the drug is limited to those with training in the administration of general anesthesia. The training program is expected to convey the requisite skills required to safely

administer propofol for moderate sedation consistent with the propofol labeling. The post-approval studies are intended to provide clinical validation of the training program. Until the training program has been adequately validated in the intended clinical settings, the device will be restricted for use in environments where a conventionally-trained anesthesia professional is immediately available.

2. The introduction of a simulation-based training program in moderate sedation means that SEDASYS System users will be trained differently from anesthesiologists and nurse anesthetists. The content and methodology of the training program has substantial support from independent experts (e.g. independent professional medical society, anesthesia department chairs) in the training of anesthesia providers and addresses several of the risk factors for propofol defined in the approved drug label for propofol. However, it remains to be seen if this type of training is an adequate substitute in the context of computer-assisted personalized sedation for the hands-on experience required of anesthesia residents and nurse anesthetists. Accordingly, safety may only be reasonably assured in settings where an anesthesia provider is immediately available. While initial approval is thus restricted to these settings, the clinical safety profile of the device demonstrated in post-approval studies will determine whether the SEDASYS System can be safely and effectively used without the need for the immediate availability of an individual trained in the administration of general anesthesia.

3. The approval of the SEDASYS System represents a notable advancement in the field of semi-autonomous control of drug administration in medicine. The device utilizes negative feedback from specialized physiological monitors to assess and limit drug dosing and thereby control the depth of sedation. The principle of negative feedback control may be applicable to a variety of drugs and clinical scenarios different from those associated with sedation management. Accordingly, the approval of the SEDASYS System may promote the development of innovative technologies for both the anesthesia field and for other specialties of medicine.

For the above reasons, the review team has determined that the information provided for review is sufficient to establish a reasonable assurance of safety and effectiveness of the SEDASYS System for the specified intended use in settings where an anesthesia provider is immediately available.

XIII. CDRH DECISION

CDRH issued an approval order on May 3, 2013. The final restrictions of use and condition of approval cited in the approval order are described below.

Restrictions of Use

1. The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. Specifically, the device labeling must include the requirement that the member of the physician-led team who is administering sedation must have training in the management of the cardiorespiratory effects of propofol when administered using computer-assisted personalized sedation systems. The device labeling must also state that the training must include: (1) pharmacology of propofol, (2) identification of high risk patients, (3) recognition of progression of levels of sedation, and actions necessary to return a patient to intended levels of sedation, (4) use of capnometry and the determination of adequate ventilation and (5) management of airway obstruction and hypoventilation.

2. In addition, the use of the device is restricted to settings where a practitioner trained in the administration of general anesthesia is immediately available to the user for assistance or consultation as needed. Immediate availability in this context means that an anesthesia professional will be available on site to respond to an emergency situation. In order to ensure that the use of the SEDASYS System is restricted to the practitioners and settings defined above, FDA expects that Ethicon Endo-Surgery, Inc. (EES) will include the requirement to have an anesthesia provider's immediate availability be stated within the contract with each of the accredited facilities carrying the device. In addition, the device labeling will specifically state that the SEDASYS System must only be used in hospitals and/or healthcare facilities where an anesthesia professional is immediately available for assistance or consultation as needed.

FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Conditions of Approval

1. Post-Approval Study of the SEDASYS System User Response to System Alarms: This study will be conducted as per study protocol version CI-13-000X, dated March 26, 2013 (e-mailed). The study will evaluate if the SEDASYS System can be used safely in routine clinical practice, by measuring the trained users' responses to

System alarms. In addition, data from this study will be used to determine if the Restriction of Use that limits use of the SEDASYS System to settings where an anesthesia professional is immediately available can be removed. This is a single arm, non-randomized, non-blinded, multi-center, prospective, study of sedation during colonoscopy and EGD, performed in routine clinical practice.

Accounting for a 3% patient dropout a total of 866 subjects will be enrolled. The primary endpoint will be the percentage of documented responses to alarms. The secondary endpoint will be sufficiency of response and all hands-on airway rescue interventions by anesthesia professionals. Subject data will be collected prior to and during use of SEDASYS System through discharge. Subjects will be followed for one day after the procedure. Severe Adverse Events will be followed to resolution. Data collection will include complete real-time documentation of all episodes in the entire enrolled population where $SpO_2 \leq 92\%$ (yellow alarm) and/or $SpO_2 \leq 85\%$ (red alarm) occurs and clinical responses to these events. An acceptable clinical response will be considered to be both an emergent patient assessment for a yellow alarm and a therapeutically appropriate intervention for a red alarm. A Data Safety Monitoring Board (DSMB) is required in order to capture and assess any adverse events in a timely fashion. The DSMB should be comprised of independent physicians; and regular meetings should be scheduled to monitor early events. The response rate to alarms is expected to be 100%. Confirmation of a non-response will be determined by the Endpoint Adjudication Committee (EAC). If there is a single confirmed failure to respond to an alarm, the aforementioned Restriction of Use may not be removed. Confirmed non-responses will be sent to the Agency within 15 days of the EAC notifying the sponsor.

Data collection will include complete real-time documentation of all interventions needed to assist or maintain spontaneous ventilation, including routine maneuvers (e.g., chin lift, repositioning of the head). All interventions where an anesthesia professional had to perform a hands-on airway rescue intervention due to over-sedation, following inability of the gastroenterologist-led team to successfully manage the patient's airway/respiration, will be captured and details of these cases will be collected.

Documentation of response will be summarized with counts and percentages. Descriptive statistics will be provided for all failures leading to injury, adverse events and severe adverse events. The true proportion of sufficiency of response will be estimated with 95% confidence intervals using exact Binomial methods. Additional endpoints will be summarized with descriptive statistics as appropriate for continuous or categorical measures.

2. Post-Approval Study of the SEDASYS System in Routine Clinical Practice: This study will be conducted per protocol version CI-13-000Y, dated March 19, 2013 (e-mail). The study will provide additional assurance that the SEDASYS System can be used safely in routine clinical practice. The primary endpoint assesses the total number of anesthesia professional rescue interventions. The secondary endpoint

assesses the total number of patients sedated with the SEDASYS System requiring bag-mask ventilations (BMV) and/or artificial airway interventions (AAI). All adverse events (AEs) and serious adverse events (SAEs) will be reported and classified as unrelated or related to SEDASYS System sedation. Data from this study will be used to determine if the Restriction of Use, which limits initial use of the SEDASYS System to settings where an anesthesia provider is immediately available, can be removed.

A total of 7,430 subjects will be initially enrolled and will provide 99% confidence that the actual proportion of anesthesia professional rescue interventions does not exceed 1/1,000. The secondary endpoint will be assessed using a one-sided exact binomial test for a proportion and a 0.025 level of significance will be used. In the event a case involves an anesthesia professional rescue intervention, a root cause analysis will be conducted by the sponsor and reviewed by FDA. If the first intervention was determined to be a result of a deficiency related to the training program, the primary endpoint has failed; therefore the aforementioned Restriction of Use may not be removed. If the first anesthesia professional rescue intervention was determined to be required irrespective of the training program, the study can continue. However, if two or more interventions by an anesthesia professional occur, the primary endpoint has failed and the Restriction of Use may not be removed. The sales of the SEDASYS System will be limited to facilities that have an anesthesia professional immediately available.

All interventions where an anesthesia professional had to perform a hands-on airway rescue intervention due to over-sedation, following inability of the gastroenterologist-led team to successfully manage the patient's airway/respiration, will be captured and details of these cases will be collected.

The proportion of subjects sedated with the SEDASYS System requiring BMV and/or AAI will be estimated with 95% confidence interval. The hypothesis will be tested using a one-sided exact binomial test for a proportion and a 0.025 level of significance. Descriptive statistics will be provided for adverse events, and narratives will be provided for the events.

The root cause analysis will be performed for all anesthesia professional rescue interventions and serious adverse events. The outcome of this analysis will be shared with the Agency within 15 days of the event. All adverse event case report forms will be consolidated into listings and/or tables for submission to the FDA by EES in a status report every six (6) months from the first subject enrolled until the last subject completed.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.