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FDA Executive Summary

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P080009

Ethicon Endo-Surgery, Inc.

The SEDASYS System® Computer-Assisted Personalized Sedation System

Anesthesiology and Respiratory Therapy Devices Panel

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1 Introduction

Ethicon Endo-Surgery, Inc. has proposed for consideration a first-of-a-kind device, the SEDASYS ® Computer Assisted Personalized Sedation System (SEDASYS). The SEDASYS System is intended to enable health care providers without training in general anesthesia to administer propofol to patients having colonoscopy or esophagogastroduodenoscopy (EGD) procedures. Propofol is a sedative hypnotic drug only approved for use by health care providers who are trained to administer general anesthetics.

The SEDASYS System consists of four components. The first component of the SEDASYS System is a Bedside Monitoring Unit (BMU) designed to be transported with the patient from the period immediately before the gastroenterological procedure through the procedure and through the post-procedure recovery period. The BMU contains a port to deliver oxygen by nasal cannula and an adapter for an oxygen source. The second component of the SEDASYS System is the Procedure Room Unit (PRU), a patient monitor screen for peripheral hemoglobin oxygen saturation, heart rate, respiration rate, capnometry, blood pressure, and patient responsiveness. The control unit in the PRU houses the propofol infusion pump and a automated responsiveness monitor (ARM) that enables propofol to be infused if the patient responds to an auditory or vibration request by activating a hand held switch. The third component consists of reusable monitors and connectors. The final component consists of disposable devices for single patient use. This component includes a cassette with a spike which the operator will insert into the standard off-the-shelf 10 mg/mL infusion vial of propofol.

The safety mechanisms of the SEDASYS System designed to prevent over-sedation are device-based dosing restrictions, increased oxygen delivery when peripheral oxygen saturation of hemoglobin declines, physiology alarms, and internal subsystem status advisories.

The SEDASYS System is intended to enable a maintenance infusion of propofol to be administered at $\leq$ 75 mcg/kg/min with a 3 minute lockout between increases in the maintenance dose, provided that the patient complies with the device's periodic request for a response. The health care provider can also administer bolus doses of propofol at 0.25 mg/kg with a lock-out interval of 90 seconds. The maximum maintenance dose of propofol allowed by the device is 200 mcg/kg/min.

The report for one pivotal study of 1000 patients was submitted to support the evaluation of safety and effectiveness. The pivotal study was a multi-institutional, randomized, non-blinded, parallel group active comparator design conducted in patients undergoing elective colonoscopy or EGD. The study entry criteria were designed to enroll patients who would not normally be referred to an anesthesiologist for management of their sedation. Among colonoscopy patients, the mean age was 54 years ($\pm$ 12 SD), the mean body mass index was 27 ($\pm$ 4 SD) and 98% of the patients were classified according to

the American Society of Anesthesologists (ASA) physical classification 1 or 2. The control arm utilized sedation with opioids and benzodiazepines administered according to the investigator's local practice, termed current standard of care (CSC). CSC regimens were allowed to vary between investigators and institutions. The hypothesis was that the SEDASYS System would be superior to the primary endpoint defined as the area-under-the-curve (AUC) of peripheral oxygen saturation of hemoglobin monitored on a pulse oximeter. Patients having colonoscopy or EGD were analyzed separately. The study's primary endpoint was achieved for patients having colonoscopy, but not EGD.

Efficacy findings were consistent regarding 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. The applicant interpreted a score of 5 as fully alert and scores of 1 or 0 on their scale as comparable to deep sedation and general anesthesia respectively. The mean sedation scale 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 treatment arm. Among patients having colonoscopy with the SEDASYS System, 2 (1%) patients did not complete the study because of device failure. Among patients having EGD with the SEDASYS System, 1 (1%) patients did not complete the study because of inability to comply with the study requirements. Although the SEDASYS System achieved the primary endpoint among the colonoscopy study patient population, a marked study site effect was noted. FDA's analysis of this effect indicated that patient hypoxia did not always result in an increase in oxygen delivery at two study sites in the CSC arm. Therefore, in this non-blinded study, investigator behavior rather than product performance may have favored the SEDASYS System compared to CSC in achieving the primary endpoint.

The focus of the ongoing FDA review is evaluation of the clinical safety of sedation conducted by health care providers who are not trained in general anesthesia and utilized the SEDASYS System according to the proposed indication. Sedation with the SEDASYS System resulted in periods of patient unresponsiveness assessed on the applicant's custom sedation scale. Ten colonoscopy patients (3%) having sedation with the SEDASYS System experienced deep sedation or general anesthesia at some point during their procedure. The mean duration of general anesthesia in colonoscopy patients who experienced general anesthesia while being sedated with propofol using the SEDASYS System was 5 minutes ($\pm$ 4.8 min SD) and the maximum duration of deep sedation/general anesthesia was 16 minutes. Hypoxemia indicated by pulse oximeter measurements ($SpO_2 < 90\%$ for > 15 seconds) occurred in 21 colonoscopy patients (6%) managed with the SEDASYS System. Although the incidence was not reported, one hundred and twenty seven apneic events among the 358 colonoscopy patients sedated in the SEDASYS System arm. The only airway intervention reported among the patients managed with the SEDASYS System was described as manipulation of the patient's airway using a tongue depressor to restore ventilation; that patient underwent an EGD. Ten patients (3%) undergoing colonoscopy developed bradycardia (< 50 beats/minute or 80% of baseline and lasting > 30 seconds, whichever was lower) and/or eight patients (2%) developed hypotension (two consecutive systolic pressure measurements < 80 mm Hg or 80% of baseline, whichever was less) while being managed with the SEDASYS

System. There were no patient deaths, hospitalizations or bowel perforations during the conduct of this study.

It should be noted that the Agency's assessment of this submission is ongoing, and is reflected in the content of this briefing document.

We request that the panel address whether the applicant has presented adequate data to support the safety of propofol when administered by health care providers using the SEDASYS System, but who do not have training in general anesthesia. Factors that may be considered are the patient population, the procedures that were studied, and how the SEDASYS System would be used in clinical practice.

The panel is asked to consider the issues in its deliberations regarding the need for additional information about this product, including any potential safety concerns that may arise were the product to be approved for marketing.

2 Rationale for Presentation to Panel

This PMA application for Ethicon Endo-Surgery, Inc. the SEDASYS System™ Computer Assisted Personalized Sedation System (the SEDASYS System) is a first of its kind device for the administration of 1% (10 mg/mL) propofol injectable emulsion for the initiation and maintenance of minimal to moderate sedation for patients undergoing colonoscopy and/or esophagogastroduodenoscopy (EGD) procedures and the monitoring of these patients.

FDA is seeking input from the panel regarding the safety of the product. An important consideration is the longstanding history of risk management of the drug propofol based on the warnings in the propofol label. This warning indicates that propofol should only be administered by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. The fundamental reason for this warning is the potential for patients to become completely unresponsive to stimulation and lose their inherent capacity to maintain adequate respiratory gas exchange through a patent airway. Also, endogenous reflexes that protect the respiratory tract from aspiration are lost as patients become deeply sedated. A small increment in propofol dose can transition a patient from being capable of self sustaining their vital signs to a state of general anesthesia where vital signs must be vigilantly monitored and managed. There is no pharmacological reversal agent for an overdose of propofol. Therefore patients who become unresponsive and also lose respiratory integrity require immediate mechanical intervention to prevent a serious adverse event or death of the patient.

The SEDASYS System device purports to allow safe management of propofol sedation in certain kinds of patients without supervision by a health care provider trained in general anesthesia.

This panel is asked to interpret the applicant's data to determine whether administration of propofol by health care providers using the SEDASYS System will result in cases of unintended general anesthesia.

3 Background Information

3.1 Indications for Use

The indication proposed by the applicant for the SEDASYS System™ Computer-Assisted Personalized Sedation System is:

"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 Continuum of Depth of Sedation, in adult patients (American Society of Anesthesiologists physical status I and II) undergoing colonoscopy and esophagogastroduodenoscopy (EGD) procedures."

3.2 Regulatory History

The applicant, Ethicon Endo-Surgery, Inc (EES) submitted a Request for Designation by FDA on February 8, 2002 and received FDA's response on April 11, 2002 indicating the SEDASYS System System will be regulated as a device with CDRH having lead responsibility for premarket review and regulation. FDA noted the SEDASYS System will be considered a Class III device subject to review and regulation under the PMA requirements of 21 CFR Part 814. FDA also indicated FDA would conduct its review with consultation from CDER review staff due to the propofol drug component.

EES submitted six Pre-IDE packages of information to FDA between September 2002 and April 2004 (I020308). Six Pre-IDE meetings also took place after receipt of the Designation Letter on December 4, 2002; March 13, 2003; May 8, 2003; August 28, 2003; January 20, 2004; and July 8, 2004.

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

3.3 Device Description

This device is designed to administer propofol to a patient undergoing colonoscopy and/or esophagogastroduodenoscopy (EGD) procedures. Propofol is a hypnotic and sedative drug labeled with an explicit warning that it is to be administered by persons trained in general anesthesia. The applicant states that the pharmacokinetic profile of propofol – rapid onset of action, short half-life – makes it a drug for which titration to sedation is achieved easily. They also state that low incidences of nausea and vomiting along with prompt recovery make propofol particularly well suited for ambulatory procedures.

The applicant stated that in 2005 anesthesia professionals were involved in 25% of all endoscopies. The applicant believes that the SEDASYS System will provide a safe means for a nurse/physician team who have not been trained to administer general

anesthesia to administer propofol for sedation of patients undergoing non-emergent EGD and colonoscopy.

The SEDASYS System monitors the physiologic parameters recommended by the American Society of Anesthesiologists (ASA) for sedation by non-anesthesiologists. These are:

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

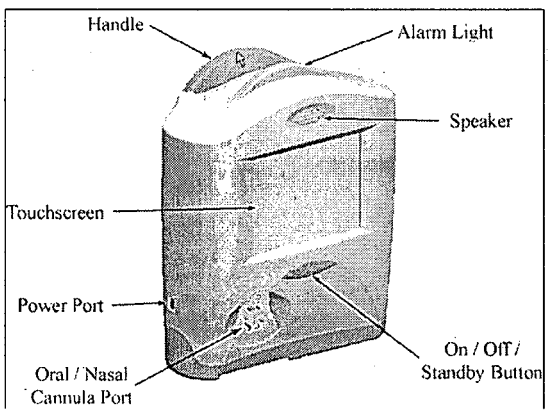
The SEDASYS System device is divided into four subsystems (or sets of subsystems). These are:

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

Exploded diagrams of all the major components have been provided. Details of each of the four subsystems are also provided below.

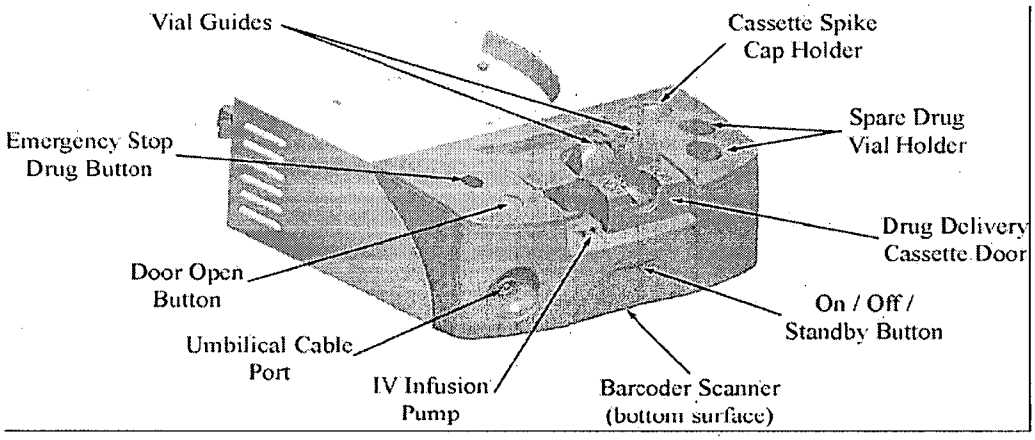
The BMU is designed to follow the patient through pre-procedure, procedure and post-procedure. This device contains the pulse oximeter, blood pressure, ECG and a mechanism to assess patient responsiveness by squeezing a handheld switch in response to an auditory or vibration stimulus. The mechanism to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

Figure 1 BMU



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.

Figure 2 The Control Unit



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.

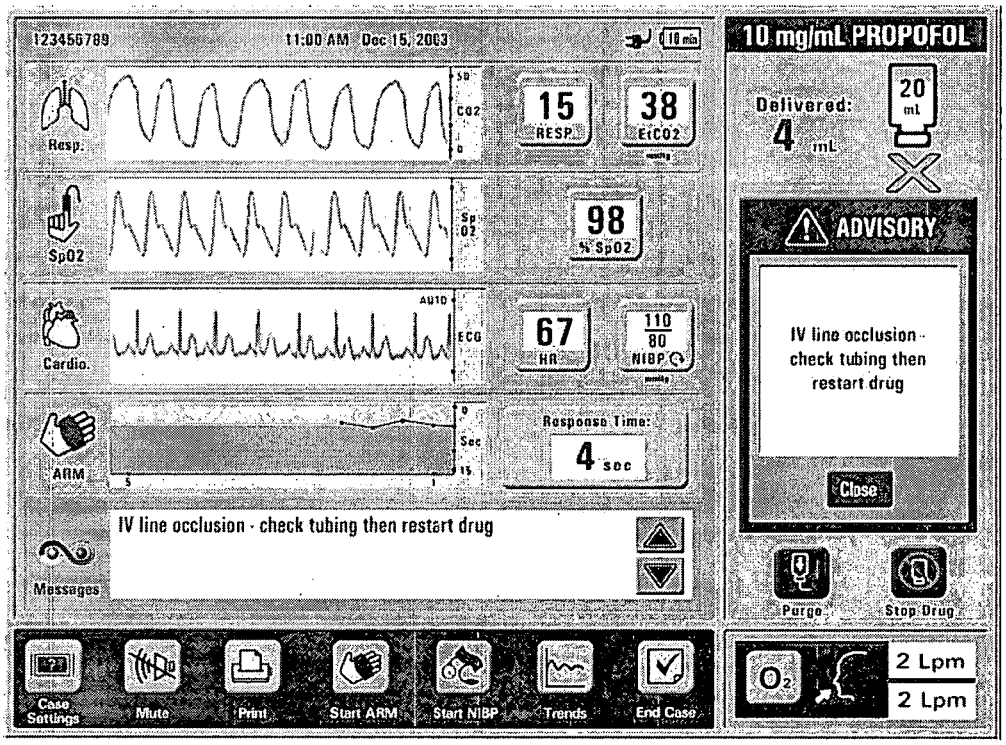
The SEDASYS System utilizes five Multiple Patient Use (MPU) items:

1) pulse oximeter probe (and extension cable),
2) ECG lead set (and extension cable),
3) NIBP cuff (and extension tubing),
4) ARM Handset
5) oxygen Adaptor, 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.

Patient response times are displayed on the PRU monitor, as are the other physiological parameters (Figure 3, in this example displaying an advisory)

Figure 3



The SEDASYS System also contains an automated supplemental oxygen delivery system. The SEDASYS System does not deliver propofol unless oxygen is available. The clinician can set the rate anywhere between 2 and 8 L/min. The default rate for oxygen delivery is 2 L/min. This rate is used for SpO2 of 96% or greater. When SpO2 falls below 96% the system will increase the rate to 8 L/min, if not already set there by the clinician. If the SpO2 falls to 88% or less, the rate will be increased to 12 L/min.

Another feature of the device is the PRN 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.

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

The Yellow Alarm (or Caution Alarm) is to prevent, or guard against, adverse changes in physiology. It is designed to trigger an alarm when the system's monitors detect that the patient's condition could become compromised if additional action is not taken. It should

be noted that these alarms are only designed for events with a high correlation with over-sedation: desaturation and low respiration rate / apnea.

In response to these alarms, the SEDASYS System reduces the maintenance rate and alerts the clinician of the patient's compromised condition. The first step in this process is interrupting the 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.

Because Yellow Alarms aim to prevent adverse clinical events, the default thresholds are more conservative than typical patient monitors. For example, most stand-alone pulse oximeters are set to alarm at SpO2 < 90%; signaling an adverse condition. The SEDASYS System Yellow Alarm default threshold is 92% to prevent the saturation from falling below 90%.

Should the response to a Yellow Alarm not prevent monitored signs of clinical deterioration, a Red Alarm will trigger. Again, it should be noted that these are only designed for events highly correlated to over-sedation: desaturation and low respiration rate / apnea. In response to these Red Alarms, the system automatically stops the delivery of propofol and alerts the clinician of the patient's compromised condition. Unlike a Yellow Alarm, the propofol maintenance rate cannot be re-initiated during a Red Alarm. After the Red Alarm clears, the clinician must manually restart propofol delivery. Again, the clinician, not the SEDASYS System System, is ultimately responsible for the care of the patient. If the patient's condition was poor enough to trigger a Red Alarm, it is the clinician who should decide when to re-start propofol delivery. A PRN dose can be delivered during a Red Alarm.

3.4 Propofol Description:

Propofol Injectable Emulsion is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. Intravenous injection of a therapeutic dose of propofol produces hypnosis rapidly with minimal excitation, usually within 40 seconds from the start of an injection (the time for one arm-brain circulation). As with other rapidly acting intravenous anesthetic agents, the half-time of the blood-brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia. The labeling for propofol contains the following warning:

WARNINGS

For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Sedated patients should be continuously monitored, and facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation

must be immediately available. Patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation…

4 Clinical Studies

4.1 Preliminary Clinical Studies

A complete list of clinical studies is found in the Appendix (7.4).
Prior to the pivotal clinical study, the applicant completed two feasibility studies, each enrolling 48 gastroenterology patients. An anesthesiologist attended all procedures. These studies were not reviewed here, but provided sufficient evidence of safety to allow the pivotal trial to be conducted.

4.2 Pivotal Study (CI-06-0004)

4.2.1 Objective

The stated objective of the pivotal investigation was to: "Demonstrate the SEDASYS System [a.k.a. Sedation Delivery System; the SEDASYS System] 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."

4.2.2 Synopsis

One multi-center, randomized non-blinded, controlled study was conducted in 1000 patients undergoing procedures that were anticipated to require sedation in a gastroenterology suite. Eight centers, including private practice and academic settings, contributed data to the study. Patients were enrolled into one of two treatment arms: sedation delivery via the SEDASYS System or sedation delivery via "current standard of care" (CSC). In each treatment arm, sedation medication was administered under the direction of a gastroenterologist by a nurse who had not been training in general anesthesia. The sedation regimen in the CSC arm was "left to the discretion of the individual centers and practitioners." For the CSC group, opioids and benzodiazepines were administered per each site's CSC. 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 2 liters per minute supplemental oxygen to all subjects in the CSC group. Sedation was performed for two gastroenterological procedures: colonoscopy and esophagogastroduodenoscopy. Outcomes for these procedures were analyzed separately.

The <u>primary endpoint</u>, intended to evaluated overall safety, was area under the curve (AUC) for oxygen saturation (< 90% for > 15 seconds) as determined by pulse oximetry; S_pO_2. No attempt was made to weight these desaturations, e.g., a desaturation to 50% for 1 min produced the same AUC as a desaturation to 70% for 2 min. The applicant's hypothesis was that the SEDASYS System would result in a lower AUC of oxygen saturation than CSC (superiority trial design).

<u>Secondary outcome variables</u> included:

- duration of sedation scale scores of 0 or 1

- recovery time (minutes from endoscope removal to first of two consecutive sedation scores of 5),
- physician satisfaction scores
- patient satisfaction scores.

Additional outcome variables 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, whichever was lower)
  - number of bradycardic events per patient
  - mean duration of bradycardia per patient
  - mean magnitude of bradycardia
- hypotension
  - number of events (≥ two 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 preprocedure
- nausea, assessed on visual analog scale at recovery
- adverse events

Inclusion criteria:

- Adults ≥ 18 years old;
- Able to comprehend, sign, and date the written informed consent form (ICF);
- Understand 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.

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 sleep apnea or gastroparesis diagnosed independently;
- Pregnant or nursing females;
- BMI ≥ 35;
- Participation in a clinical trial within the past 30 days.

In addition to the following entry criteria the applicant's protocol stipulated: "The SEDASYS System is not targeted for the 26% of cases where anesthesia professionals administer propofol sedation. It is targeted for the 74% of cases where propofol is not currently being used." Therefore, the intended application for the SEDASYS System is gastrenterologists who prefer their patients to be sedated with propofol, but also prefer to direct sedation themselves.

After screening, CSC patients were sedated with opioids and benzodiazepines according to the investigator's practice and administered 2 liters of oxygen by nasal cannula. The flow of oxygen was to be increased manually if clinically indicated. the SEDASYS System patients were to receive 50 - 100 mcg of fentanyl for healthy patients aged ≤ 64 years or 25 – 50 mcg for patients ≥ 65 or if they were "frail or debilitated". Three minutes after administration of fentanyl, the SEDASYS System patients were to receive propofol at 5 - 75 mcg/kg/min maintenance as determined by the physician. The physician was also to direct further administration of propofol as needed during the procedure by adjustments of the maintenance rate of administration or by administration of supplemental bolus doses of propofol with a 90 second lock out period. Supplemental bolus doses of propofol (0.25 mg/kg) were able to be administered at the discretion of the health care provider regardless of patient responsiveness and device oximetric and capnometric limits to prevent propofol infusion.

Sedation effect was evaluated at two minute intervals using the applicant's custom modification of the Modified Observers Assessment of Awareness and Sedation Scale. This custom scale was modified by the applicant to include the term "purposeful" at sedation level 2. The protocol did not stipulate how patients who responded with a non-purposeful response to mild prodding or mild shaking would be classified. However, the applicant has indicated that these patients would have been classified as sedation level 1. The applicant also interpreted their scale using ASA terminology for sedation and general anesthesia.

Table 1. Applicant's Sedation Scale

MOAA/S Score	Description	ASA Continuum
5	Responds readily to name spoken in normal tone (awake)	Minimal Sedation
4	Lethargic response to name spoken in normal tone	Moderate Sedation
3	Responds after name called loudly or repeatedly	Moderate Sedation
2	Purposeful response to mild prodding or mild shaking	Moderate Sedation
1	Responds to trapezius squeeze (includes purposeful and reflexive withdrawal)	Deep Sedation
0	No response to painful stimulus (trapezius squeeze)	General Anesthesia

From Applicant's Table 11 page 69 of their briefing document.

4.2.3 Results

Of 1000 patients randomized, 496 patients (50%) were randomized to the SEDASYS System arm and 504 patients (50%) were randomized to CSC. Of 721 patients who underwent colonoscopy, 358 (50%) were randomized to the SEDASYS System and 363 (50%) were randomized to CSC. Four SEDASYS System patients and 9 CSC patients undergoing colonoscopy did not complete the study. Of the 279 patients who underwent esophagogastroduodenoscopy (EDG), 138 patients (49%) were randomized to the SEDASYS System and 141 (51%) were randomized to CSC. Three SEDASYS System patients and 2 CSC patients undergoing EGD did not complete the study. No discontinuation was reported by the applicant to result from an adverse event.

The demographic breakdown of the 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 study population was predominately ASA 1 and 2 with few (the SEDASYS System 11, 3%, CSC 6, 2%) colonoscopy 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 System patients and 4 (3%) of the CSC patients classified as ASA 3. The mean body mass index (BMI) in both treatment groups was 26 kg/m^2 ($\pm$ 4 SD).

4.2.3.1 Effectiveness

The mean sedation scale 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 treatment arm. Among patients having colonoscopy with the SEDASYS System, 3 (1%) patients did not complete the study because of device failure. Among patients having EGD with the SEDASYS System, 3 (2%) patients did not complete the study because of device failure or inability to comply with the requirements of the study. These findings are consistent with labeled information regarding efficacy of propofol as a sedative product.

4.2.3.2 Clinical Safety

Preliminary review of safety was notable for achievement of the primary endpoint in colonoscopy patients, but not EGD patients. Considering that EGD patients sedated with the SEDASYS System failed to achieve the primary endpoint, the Agency review concentrated on findings from the colonoscopy patients. While we acknowledge the similarities between sedation of patients having colonoscopy and EGD, in terms of the skill set of the health care provider team performing the procedure and managing sedation, we also recognize that colonoscopy is typically longer in duration and a more stimulating procedure than EGD so that there may be a greater potential for unintended deep sedation/general anesthesia and hypoxia. Therefore, the FDA preliminary review has concentrated on evaluation of safety among the study's colonoscopy patients.

There was marked variability in the mean AUC among colonoscopy patients at study sites that was also associated with events of patient unresponsiveness and hypoxia.

1. The applicant's primary endpoint was achieved for patients having colonoscopy.

Table 2. Applicant's Primary Endpoint Findings for Colonoscopy Patients

Parameter	Sedation Delivery System (SDS) (N = 358)	Current Standard of Care (CSC) (N = 363)
n[a]	349	350
AUC (%*seconds)[b] ± SD	17.8 ± 124.59	98.8 ± 510.32
Range (%*seconds)	0 – 1741	0 – 7040

The table was abstracted from the applicant's study report. The review statistician calculated a p-value of 0.004.

2. Study site center specific effects on data:

A marked study site center-effect is apparent in these data from colonoscopy patients, with two sites (4 and 5) reporting larger mean AUC values than the remaining sites (42-fold and 21-fold greater for the SEDASYS System and CSC subjects, respectively. Analysis of the center effect is presented in the Statistical Analysis section 4.2.3.4 below.

3. Supplemental bolus dosing of propofol by health care providers:

Health care providers administered bolus doses of propofol (0.25 mg/kg) actuated at least once in 77% of procedures. Of the total dose of propofol administered to patients, 27% 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 health care provider is enforcement of a 90-s 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 health care provider.

4. Deep sedation/general anesthesia

Patient unresponsiveness, reported as 0 or 1 on the applicant's sedation scale, was also considered by the applicant as general anesthesia or deep sedation, respectively. Review of these data focused on the incidence of events and the maximum duration of events because inadvertent deep sedation/general anesthesia with the attendant risks of an unresponsive patient is an established property of propofol. Among patients having colonoscopy with the SEDASYS System, the maximum duration of deep sedation/general anesthesia was a total of 16 minutes. Ten colonoscopy patients (3%) having sedation with the SEDASYS System experienced deep sedation or general anesthesia at some point during their procedure.

A lower incidence of deep sedation/general anesthesia occurred when colonoscopy patients were sedated with CSC (4 patients, 1%). The maximum duration of deep sedation/general anesthesia in colonoscopy patients having CSC was 22 minutes.

5. Hypoxia

Hypoxic events were reviewed for incidence and severity. Among colonoscopy patients managed with the SEDASYS System, 21 patients (6%) experienced oxygen desaturation of hemoglobin.

Fifty-nine patients (17%) experienced hemoglobin desaturation among colonoscopy patients managed with CSC. Sixteen patients, 80% of the colonoscopy patients managed with CSC who experienced hemoglobin desaturation were from a single study site (#4). This indicates that the clinical population or that the sedation management was different than the other study sites. One patient at the study site with the highest incidence of patients with hemoglobin desaturation experienced repeated events including an hypoxemic episode that lasted 335 seconds. This episode was treated by increasing

oxygen flow from 4 to 8 L/min. Another patient required manual ventilation with a bag and mask.

6. Apnea and hypoventilation:

The incidence of apneic events (> 30 seconds) among colonoscopy patients was 143 (41%) for SEDASYS system and 141 (40%) for CSC. . The mean duration of apneic events was similar among colonoscopy patients managed with the SEDASYS System and CSC.

Table 4. Duration Of The Longest Period Of Apnea Among Colonoscopy Patients Who Had Apnea.

Parameter		Sedation Delivery System (SDS) (N=127)	Current Standard of Care (CSC) (N=119)
Duration of events (seconds) (range)	mean ± SD	49.5 ± 14.96 (30 – 124)	50.6 ± 23.14 (30 – 175)

From applicant's Table 27 of the study report.

The number of elevated capnography assessments was similar between the SEDASYS System (n = 6) and CSC (n = 5). Capnographic measurements are not quantitative measures of alveolar carbon dioxide concentration because the trachea is not intubated and therefore do not accurately indicate pCO_2. However, elevated measurements of expired carbon dioxide do indicate that there is ongoing hypoventilation. The applicant reported that similar mean durations of hypercarbia, indicated capnographically as ≥ 50 mm Hg for ≥ 30 seconds between the SEDASYS System 49 sec (± 27 SD) and CSC 56 sec (± 32 SD).

7. Airway and respiratory interventions:
Airway interventions are a sign of respiratory inadequacy even when patients do not become hypoxic because treatments of early signs of hypoventilation prevent clinically significant events. These treatments include physical maneuvers to open airway such as repositioning the head, chin lifts and jaw thrusts. At the recommendation of the applicant's Data Monitoring Committee, the applicant instructed their study sites to document these types of actions if they were required for at least 30 seconds. However the protocol was already finalized prior to this recommendation. Therefore, the sites were instructed via a note-to-file to record chin lifts or jaw thrusts lasting > 30 seconds. The applicant reported that approximately 4 subjects were studied prior to this note-to-file. The applicant reported that one patient treated with the SEDASYS System undergoing EGD required manipulation of the airway with a tongue depressor to restore ventilation. In addition, one CSC patient undergoing colonoscopy required manual ventilation with a bag and face mask.

8. Hemodynamic events (bradycardia and hypotension)
Review of the incidence of bradycardia and of hypotension among colonoscopy patients was conducted by the FDA statistical review team.

Table 3. Incidence of Hemodynamic Events Among Colonoscopy Patients

Event	The SEDASYS System; n = 358 n (%)	CSC; n = 363 n (%)
bradycardia	13 (4%)	7(2%)
hypotension	8 (2%)	7 (2%)

Abstracted from the applicant's study report.

This analysis indicates a higher incidence of bradycardia and hypotension among patients managed with the SEDASYS System than CSC.

The applicant reported one case of bradycardia among the 12 combined EGD and colonoscopy patients managed with the SEDASYS System who achieved sedation scores of 0 or 1.

10. Adverse events

No patients died, were hospitalized or developed bowel perforation during the study. Therefore, the applicant has indicated that the SEDASYS System was not associated with serious adverse events. It was also noted by the FDA review team that the SEDASYS System did not prevent hypoxemia as indicated by peripheral desaturation of hemoglobin and that some of the desaturation events were profound despite an autonomous increase in the oxygen flow to the patient by the SEDASYS System.

4.2.3.3 Device Failures

Twenty three device failures occurred during the study. These failures occurred either before the start of a procedure or after the completion of a procedure. There were no reported device failures during a procedure. These failures can be grouped into seven categories. The failures will be described, followed by the root cause (if known). Finally the corrective action (if any) was described:

1. The high-pressure relief valve failed in the PRU oxygen manifold. The identified cause was that the pressure regulator on the oxygen tank was opened to the maximum pressure, exceeding the system's input specification. There was no post-study modification of the device due to this failure. The labeling now includes detailed instructions that describe the proper method of connecting the system to an oxygen source.

2. Two failures of the pulse oximeter module were reported. These occurred at the start of the day. These failures were caused by an "invalid" value coming from the pulse oximeter board during the power on test. While the system was failed the BMU would not allow the entry of a new case. The applicant could not reproduce this failure and no post-study modifications were made due to this failure.

3. One failure of the PRU display monitor module was reported. This failure was caused by a damaged power control chip in the PRU display power circuit. This failure was obvious to the user: the display remained blank. A circuit was modified to limit current surges during connection of the BMU to the PRU.

4. Three reported failures of the BMU wireless pointer were reported. These failures were caused by a conflict between the printer and the facility's wireless network. Because the BMU configures the wireless network during power-up procedures, this failure could only occur at that time. The wireless LAN driver has been updated to correct this issue.

5. One failure of data transfer between the BMU and PRU was reported. This failure occurred due to a large amount of data overwhelming the fixed buffer allocated for storing this information. The software has been modified to replace the fixed memory partition with a dynamic allocation.

6. Six failures of the BMU power management subsystem were reported. These failures were caused by a power surge in the power input circuit resulting in the blowing of an internal fuse. Five of these failures occurred prior to the start of a procedure, and one occurred after the completion of a procedure. The BMU battery charger circuit has been modified to prevent fuse damage while continuing to provide short circuit protection.

7. Nine failures of the nasal cannula were reported. These failures occurred prior to initiating sedation. These failures were caused by the misalignment of a gasket when the oral/nasal cannula is connected to the BMU resulting in the inability of the system to detect respiration rate. The applicant has modified the sampling interface component to assure that rigid sampling pins engage the BMU receiving unit, especially during off axis connection.

4.2.3.4 Statistical Analysis

A marked center-effect is apparent in AUC hypoxia data, with two sites (4 and 5) reporting a larger mean AUC values than the remaining sites (42-fold and 21-fold greater for the SEDASYS System and CSC subjects, respectively):

Table 4. Mean AUC, Findings by Study Site

	Sedation Delivery System (SDS) Group			Current Standard of Care (CSC) Group		
	N	Mean	(95% CI)	n	Mean	(95% CI)
Site 0	56	2.9	(-2.9, 8.6)	56	13.3	(0.8, 25.8)
Site 2	30	2.3	(-2.4, 6.9)	29	40.3	(-7.4, 88.0)
Site 3	72	1.6	(-0.9, 4.1)	73	38.9	(13.6, 64.2)
Site 4	62	84.9	(13.7, 156.1)	64	378.5	(103.3, 653.7)
Site 5	9	50.3	(-65.7, 166.4)	9	459.9	(-122.5, 1042.3)
Site 6	13	0.0		11	0.0	
Site 7	47	0.0		49	2.8	(-1.1, 6.7)
Site 8	60	2.6	(-2.6, 7.8)	59	22.8	(-3.1, 48.8)

The table was reproduced from the applicant's study report.

FDA conducted a multivariate model analysis to assess the between center difference. The result showed that the differences between centers were statistically significant in both the magnitude and the variability of observed treatment effects.

In response to the prominent heterogeneity observed in the mean AUC across different centers and the disparate clinical practice of the Sites 4 and 5 in terms of the prevention and treatment of hypoxemic episodes, FDA stratified the statistical analysis into two groups: centers with low or high desaturation level. The observed mean AUC reduction in the SEDASYS System group is much smaller in centers with low desaturation level than those in high desaturation level. The mean AUC between the SEDASYS System and CSC by desaturation level was as follows:

Center Group	Mean $AUC_{CSC} - AUC_{\text{the SEDASYS System}}$
Low level	20.5 (p=0.0001)
High level	313.7 (p=0.016)

The applicant adopted a different strategy to address the heterogeneous AUC issue. The marginal mean regression model analysis submitted by the applicant differed from the pre-specified ANOVA model in the following ways: instead of modeling the *difference* $AUC_{CSC} - AUC_{\text{the SEDASYS System}}$ between the SEDASYS System and CSC group, the analysis assessed the logarithm of the *ratio* of $AUC_{\text{the SEDASYS System}} / AUC_{CSC}$ between the SEDASYS System and CSC group. Moreover, it does not require the assumption of equal variance because the model focused on modeling the mean rather than the variance. However, for the 2 centers that reported all desaturation level being zero, the logarithm of the AUC ratio was undefined. The applicant used a technique called penalized estimation to overcome this. The average AUC ratio ($AUC_{\text{the SEDASYS System}} / AUC_{CSC}$) of the SEDASYS System to the CSC group was 0.18 (95% C.I. = 0.068 – 0.42).

Because of the categorical difference in clinical practice between the low and high level centers, the FDA statistical review team determined that these two center groups should be assessed by two separate models. Therefore, the applicant's proposed marginal mean regression model is not critical in assessing the treatment effects. Although it is valid and

acceptable, their analysis included all the highly heterogenous centers in one model and also, it changed the scale of the treatment effect from AUC difference to AUC ratio.

4.3 Summary

Sedation findings for colonoscopy and EGD patients were analyzed separately regarding the primary endpoint, (AUC_{Desat} for $SpO_2 < 90$) because EGD is a briefer procedure than colonoscopy so there is less opportunity for titration of sedation medications.

- Management of EGD patients with the SEDASYS System was not superior to CSC in the primary endpoint analysis. Because sedation for colonoscopy was expected to provide more information regarding safety and failure of the study objective in EGD patients, the FDA review has focused on findings from sedation of colonoscopy patients.

- Management of colonoscopy patients with the SEDASYS System did meet its primary endpoint. AUC_{Desat} was lower for the SEDASYS System (experimental) group in comparison to the CSC (control) group. Relative to CSC patients, the SEDASYS System patients had fewer and shorter hypoxemic events, although the magnitude of these events was similar.

A finding of safety based upon the primary endpoint in colonoscopy patients was confounded because CSC patients did not receive as much oxygen as the SEDASYS System patients at certain study sites despite similar levels of CNS depression (as reflected by sedation scores, capnography, and apnea events).

- In 38% of clinically significant hypoxemic events ($S_pO_2 < 90\%$ [$P_aO_2 < 60$ mm Hg] for > 15 sec) in CSC patients, oxygen flow remained at 2 L/min throughout the event (the comparable value for the SEDASYS System subjects is 0%).

- In only 17% of CSC subjects was oxygen administered above 2 L/min at some time during their procedure (the comparable value for the SEDASYS System subjects is 89%).

- Due to large differences between study sites with respect to AUC_{Desat}, FDA analyzed the data combined from all study sites and by study site. Hypoxemia detected by oximetry criteria (< 90%) was not always treated by increasing oxygen delivery to the patient in the CSC treatment arm.

Therefore differences in oxygen administration between treatment arms of this non-blinded study may have contributed to superiority of the SEDASYS System in the primary endpoint compared with CSC in minimizing AUC_{Desat} (< 90%).

Patients managed with the SEDASYS System exhibited deep sedation/general anesthesia and experienced hypoxemia .

- In the SEDASYS System patients having colonoscopy, 4 of 358 (1%) subjects reached a sedation depth characterized by the applicant as general anesthesia, and an additional 6 (2%) reached deep sedation. In CSC patients having colonoscopy, 0 of 363 reached general anesthesia, and 4 (1%) reached deep sedation.

- In the SEDASYS System patients, the majority (54%) of incipient hypoxemic events (S_pO_2 <92% for > 15 s) progressed to clinically significant hypoxemia, i.e., the product did not prevent these significant events.

  Severe hypoxemic events ($S_pO_2 \leq 75\%$ [$P_aO_2 \leq 40$ mm Hg]) occurred in three the SEDASYS System subjects.

The SEDASYS System "bolus button" was used in 77% of the procedures, and 27% of the total drug administered was through bolus doses. The only condition that prevented delivery of a bolus dose (other than equipment failure) is enforcement of a 90 second lockout from a prior bolus dose.

5 Preclinical Study Information

The following pre-clinical testing was performed on the SEDASYS System device 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

There were no animal studies reported in this PMA.

6 Post-Approval Studies

FDA's inclusion of a section/discussion on a Post-approval study in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether or not to approve a device must be based on the pre-market data. The pre-market data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding a potential post-approval study should the panel find the device approvable following its discussions and deliberations of the pre-market data.

The FDA review team identified several postmarket concerns about the Sedasys System. Should FDA approve this PMA, these concerns, might be addressed in an appropriate post-approval study (PAS).

1. The role of gender in the safety and effectiveness of the device is unclear.

   For colonoscopy patients in the IDE study the gender distribution was significantly different in the Sedation Delivery System (SDS) compared to Current Standard of Care (CSC) patients. As Table 1 shows, there was a statistically significant difference for gender (p = 0.015).

Table 1: Gender Characteristics for Colonoscopy Patients[1]			
Parameter	SDS Group	CSC Group	p-value
Male	198 (55%)	168 (46%)	
Female	160 (45%)	195 (54%)	0.015

   The applicant asserts that there are no gender differences in pharmacokinetics for propofol. However, the literature indicates that gender differences exist for propofol. This effect could impact on both the effect of anesthesia and patient satisfaction. Haensch et al (2009), Kodaka et al (2006) and Hoymork & Raeder (2005)[2,3,4] evaluated the gender differences in the effect of propofol and have found that women wake up faster compared to men. This difference would have an effect on recovery time and may also affect responsiveness to the anesthesia.

2. The impact of the learning curve with the device on the overall safety remains unclear.

[1] Ethicon Endo-Surgery, Inc. CI-06-0004 SDS Final Report March 14, 2008, p. 69.

[2] Kodaka M, Suzuki T, Maeyama A, Koyama K, Miyao H. Gender differences between predicted and measured propofol C(P50) for loss of consciousness. J Clin Anesth. 2006 Nov;18(7):486-9.

[3] Hoymork SC, Raeder J. Why do women wake up faster than men from propofol anaesthesia? Br J Anaesth. 2005 Nov;95(5):627-33. Epub 2005 Sep 16.

[4] Haensch K, Schults A, Krauß T,Grouven U, Schultz B. Biomed Tech (Berl) 2009 Apr; 54(2): 76-82.

The device requires advanced clinical assessment and management skills that should include a training program. Whether the safety profile will vary depending on the experience of the operator and the training plan provided by the applicant is unknown. If the device is approved, a long-term study of the effectiveness of a training program should be considered.

3. The risk of hypoxic encephalopathy as a consequence of oxygen desaturation is unknown and is a serious concern.

   During the study 17 (2.4%) of subjects in the study (2 SDS and 15 CSC) experienced oxygen desaturation events lasted over 75 seconds (maximum of 133 seconds in SDS and 335 seconds in CSC) and reached minimum SpO_2 of 72% in the study group and 39% in the control group respectively. The consequence of these findings is unknown and one stated purpose of the SEDASYS System is to respond to changes in clinical status by increasing oxygen administration. Additionally, the protocol stated that in the control group oxygen administration would be adjusted based on clinical status and it is unclear whether this happened in these cases.

4. The safety of the bolus-dosing feature of the device in the real world setting is unknown.

   During the study, 77% of procedures included at least one actuation of the bolus dose feature and of the total dose of propofol administered to patients during the study 27% was administered via bolus doses.

5. The generalizability of these safety and effectiveness results to the real world setting, where the device may be used by operators and centers that have a lower volume of surgeries and less experience is unknown.

FDA has discussed these concerns with the applicant and the applicant agreed to conduct a post-approval study to address both clinical and training concerns. The applicant submitted an outline of their proposed study.

Synopsis of the Proposed Post-Marketing Study

The applicant proposes to conduct a single arm, non randomized, non-blinded, multi-center, prospective, safety study of colonoscopy, and EGD, performed in routine clinical practice. Adult male and female patients scheduled for non-emergent endoscopy procedures during the study timeframe will be invited to participate in the study. Up to 20 sites will be recruited into the study. Additional facilities that have had no prior training or experience using the SEDASYS System will be invited to participate in training evaluations at specified time points over the course of 1-year.

The study will evaluate safety and training effectiveness.

The primary endpoints are:

1. Rescue interventions
2. Pre- and post-training testing (up to 1 year post-training)

The secondary endpoints are:

1. Pharmacologic interventions for hemodynamic events
2. Oxygen saturation every 5 minutes
3. Level of sedation
4. All AEs and SAEs, classified by device-relatedness
5. Product malfunctions

The study will enroll a total of 1511 patients and include 496 patients who were enrolled under the pivotal trial for a total of 2000 patients.

FDA continues to work interactively with the applicant to develop the post-approval study protocol.

During the panel meeting, FDA will ask the panel to comment on the following:

1. The need to design the post-approval study to evaluate the role of gender in the safety and effectiveness of the device.
2. The significance of the findings that 23 (3.2%) of subjects in the study (3 SDS and 20 CSC) experienced oxygen desaturation events that lasted over 30 seconds (maximum of 133 seconds in SDS and 335 seconds in CSC) and reached minimum SpO_2 of 72% in the study group and 39% in the control group respectively.
3. The expected level and duration of oxygen desaturation for the evaluation of safety
4. The adequacy of the applicant's proposed post-approval study plan
5. The safety of the bolus-dosing feature in real world use.
6. The need to include clinical sites and operators that vary by type, surgical volume or other characteristics.
7. Any other short and long-term safety concerns that the panel thinks should be addressed.

7 Appendix

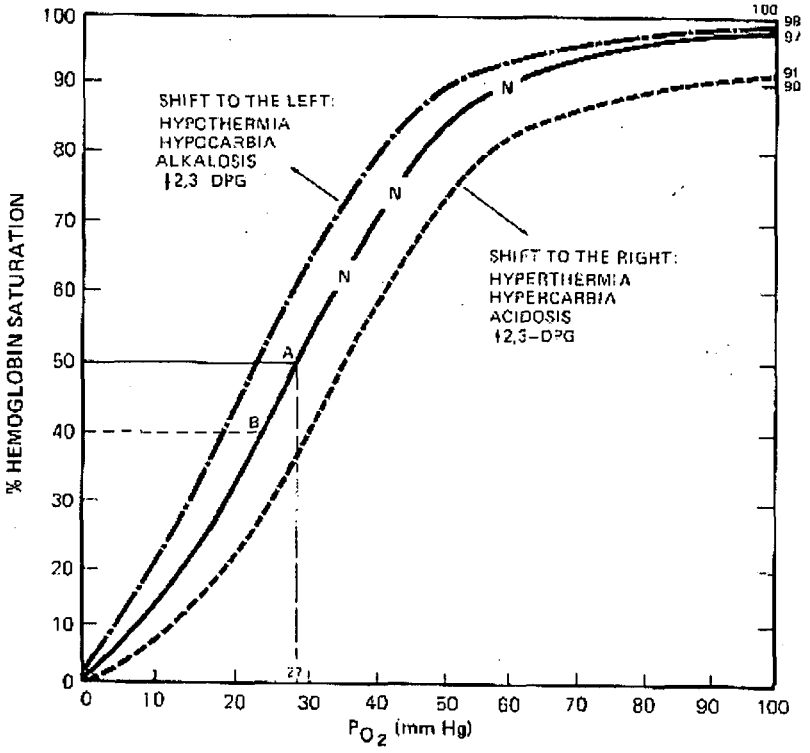
7.1 References

American Society of Anesthesiologists 2002 Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists: An Updated Report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Anesthesiology 96(4): 1004-17.

7.2 Propofol Label

Included under separate cover

7.3 Hemoglobin Saturation Relationship to Arterial Oxygen Tension



7.4 List of Clinical Studies

Protocol/Year Completed	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	Non-comparative	8

	opioid pretreament		
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
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 sensor hardware	Open	11
Feasibility Studies			
CI-04-0005	the SEDASYS System Feasibility	Open	48
CI-04-0002	the SEDASYS System Feasibility	Open	48
Pivotal Study			
CI-06-0004	Clinical Safety	Open Comparative	1000

7.5 Abbreviations

ANOVA Analysis Of Variance

ARM Automated Responsiveness Monitor

ASA American Society of Anesthesiologists

AUC Area Under the Curve

BMU	Bedside Monitoring Unit
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CSC	Current Standard of Care
EES	Ethicon Endo-Surgery
EGD	Esophagogastroduodenoscopy
IDE	Investigational Device Exemption
NIBP	Non-Invasive Blood Pressure
PMA	Premarket Approval
PRN	Pro Re Nata (Latin) ~ as needed
PRU	Procedure Room Unit