

## SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

### I. GENERAL INFORMATION

Device Generic Name: Diaphragmatic Pacing System

Device Trade Name: NeuRx DPS™, RA/4 Respiratory Stimulation System

Applicant's Name and Address: Synapse Biomedical Inc.  
300 Artino Street  
Oberlin, OH 44074

Humanitarian Device Exemption (HDE) Number: H070003

Humanitarian Use Device (HUD) Designation Number: 06-0165

Date of Humanitarian Use Device (HUD) Designation: March 14, 2006

Date(s) of Panel Recommendation: None

Date of Good Manufacturing Practice Inspection: November 27, 2007 and April 23, 2008

Date of Notice of Approval to Applicant: June 17, 2008

### II. INDICATIONS FOR USE

*The NeuRx™ RA/4 is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. For use only in patients 18 years of age or older.*

### III. CONTRAINDICATIONS

None known

### IV. WARNINGS AND PRECAUTIONS

See labeling for warnings and precautions

### V. DEVICE DESCRIPTION

The NeuRx DPS™, RA/4 is an intramuscular, percutaneous, motor point diaphragm stimulation system. It is implanted using standard laparoscopic surgical techniques in an outpatient procedure. The implanted intramuscular diaphragm electrodes are connected to a four channel external stimulator at a percutaneous exit site. The stimulator provides a capacitively coupled, charge balanced, biphasic stimulation to each electrode with a common indifferent electrode

that is placed subcutaneously. The stimulator controls the charge delivered through clinician programmed parameters of pulse amplitude, pulse duration, pulse frequency, pulse ramp, inspiration time, and respiratory rate. The clinician uses a clinical station to characterize electrode response to stimulation and program the external stimulator with the patient specific parameters. The user connects the stimulator and turns it on for use; no other controls are available or necessary for operation.

## VI. ALTERNATIVE PRACTICES OR PROCEDURES

The standard therapy for high spinal cord injured (SCI) patients is mechanical ventilation via a trachostomy. These devices periodically force air directly into a patient's airway to inflate the lungs.

An alternative to positive pressure mechanical ventilation, for a subset of patients, is the Avery Laboratories Mark IV device. The Avery device was approved through a PMA submission in 1987 (P860026). The Avery device is indicated for use in persons who require chronic ventilatory support because of upper motor neuron respiratory muscle paralysis (RMP) or because of central alveolar hypoventilation (CAH) and whose remaining phrenic nerve, lung and diaphragm function are sufficient to accommodate electrical stimulation.

The Avery device is composed of four principal components: a radio frequency (RF) transmitter, a transmitter antenna coil, an RF receiver with a built-in coil and a nerve electrode with insulated lead wires to connect the receiver to the electrode. The electrode is cuffed directly to the phrenic nerve in either the neck or thorax using an open thoracic procedure. This is different from the Synapse device where the electrodes are implanted directly into the diaphragm. The pacer operates on the principle of RF induction of energy and control through the intact skin. The transmitter and transmitting antenna are external to the body. The Synapse device is designed with a direct connection through a wire to the control mechanism. The Avery device uses an implanted RF receiver where none is required with the Synapse device.

Other alternatives to positive pressure mechanical ventilation consist of various forms of non-invasive ventilation. Non-invasive positive pressure ventilation (NPPV) may be used for limited ventilatory support in some patients with spinal cord injury to provide periods of time off mechanical ventilation. NPPV is delivered either as continuous positive pressure ventilation (CPAP) or bilevel positive pressure ventilation (BiPAP) via a mask, nasal occlusion device, or tracheostomy adapter. Other forms of non-invasive ventilation include the pneumobelt and rocking bed. The pneumobelt inflates and deflates a bladder wrapped around the patient's abdomen and lower chest. Inflation of the bladder forces the abdominal contents to rise, compressing the lung allowing expiration of gas; deflation of the bladder allows the abdominal contents to move downward and the lung to expand. This device is used in the sitting position. Rocker beds are used in the supine position and rely on the shifting of abdominal contents by positional changes in the patient.

## VII. MARKETING HISTORY

NeuRx DPST™, RA/4 Respiratory Stimulation System has been CE Marked since November 20, 2007, has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device. . Synapse Biomedical Inc. intends to begin actively marketing the device in the EU.

VIII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In a clinical study using the subject device, the following adverse events were observed:

	Adverse Event	# Events	# Affected Patients	% of Patients (n=50)
*	Capnothorax	21	21	42%
	<b>Equipment Failures</b>			
*	Broken External Wire	10	7	14%
*	Broken Anode	3	3	6%
*	External Equipment Failure	2	2	4%
	<b>Infectious Diseases</b>			
	UTI	10	6	12%
	Pneumonia	6	3	6%
	Upper Respiratory Infection	8	3	6%
*	Localized Infection	2	2	4%
*	Spasms	5	5	10%
*	Pain/Discomfort with stimulation	5	3	6%
	<b>Airway Compromise</b>			
*	Aspiration	11	3	6%
*	Increased Secretions	3	3	6%
*	Airway Obstruction	3	3	6%
*	Low V <sub>T</sub> , O <sub>2</sub>	5	3	6%
	<b>Deaths</b>			
	Death (while device not in use)	2	2	4%
	Death (while device was in use)	2	2	4%
	Pain - not device related	2	2	4%
	Nausea	2	2	4%
	Autonomic Dysreflexia	3	2	4%
	Ulcer	2	2	4%
	Elevated Temperature	3	2	4%
	Redness or Swelling	4	2	4%
*	Difficulty Eating with Device	1	1	2%
	Dizziness	1	1	2%
	Atelectasis	1	1	2%
	PEG Tube displaced	1	1	2%
	Excess Gas / Bloating	3	1	2%
	Pressure Sore	1	1	2%
	Blood with Exsufflation	1	1	2%

\*device related event

*Capnothorax*

The most commonly occurring adverse event was air tracking into the pleural cavity caused by CO<sub>2</sub> used to inflate the abdomen during surgery, e.g. a capnothorax. This event is related to the electrode implantation procedure.

No compromised pulmonary gas exchange or hemodynamic instability was reported due to the capnothorax. One patient was treated with a chest tube for two days and required an extension of hospitalization by an additional 5 days. Another patient required treatment with a chest tube for less than a day, but required no additional days of hospitalization. A third patient was treated with a chest tube and remained hospitalized for an additional day of observation. All other patients with capnothorax were treated with a chest tube for less than 24 hours.

The incidence of pneumo/capnothoraces observed during implantation of the NeuRx DPST<sup>TM</sup>, RA/4 is similar to that associated with other laparoscopic procedures. While this complication is common, it is usually not clinically serious, and is acceptable within the context of the procedure and the patient population. This adverse event is specifically addressed in the firm's training program. Procedural instructions specifically reference the incidence of capnothorax (21 of 50 patients or 42%) and discuss the cause, incidence, preventive measures, diagnosis (chest x-ray after completion of the procedure) and treatment of capnothorax.

*Aspiration and upper airway obstruction:*

The study also documented 11 incidents of aspiration affecting 3 patients. All of the aspirations occurred during pacing. These instances occurred early in the study. The first patient to report aspiration had two episodes. This was noted by one of the caregivers who observed food particles during routine suctioning. There were no symptoms reported during these episodes. Another patient had 8 of the 11 reported episodes of aspiration. These events were attributable to a misuse of the Passy-Muir valve. No respiratory distress, hypoxemia or pneumonia, were reported. The first patient mentioned above was put on antibiotics by their pulmonologist although no microbiological cultures were collected and no fever was reported.

The incidences of upper airway obstruction occurred with patients who fell asleep with capped tracheostomy. The patients were reminded to use a Passy Muir valve while sleeping.

*Localized Infection:*

Two patients developed localized infections that required treatment. These infections were associated with the diaphragm leads at the epigastric site. The first patient was treated with a short course of antibiotics, and externalization of the wires after which the infection resolved. The second patient developed a localized wound infection at the epigastric site and was successfully treated with oral antibiotics.

*Broken wires and anode and external equipment failure:*

In 10 incidents with 7 patients, the lead wire has been cut or broken at or near the skin surface due to manipulation by the patient's caregiver. In these cases, the lead was repaired / replaced at an office visit. Additional patients have experienced a break of the lead wire at the connector, which in all cases was fixed at the patient's home. There were three cases in which the anode lead broke resulting in complete cessation of system function and the need to return to mechanical ventilation until corrected. In all three cases, a surface anode was temporarily substituted, allowing the patient to continue to use the device, until the anode lead could be re-terminated into the connector block. No wire breaks have occurred in the leads going to the diaphragm motor point. In no case was the patient required to return to the operating room for device repair. A modification was made to the device design in May of 2007 to address this breakage issue. Eleven (22%) of the reported patients were implanted after this modification. None of these patients reported broken external leads or anodes in 7.7 cumulative years of implant time.

Breakage of external components (patient cables or stimulator connectors) has occurred. If the breakage resulted in an inability to use DPS because no backups were available or suitable, this was considered an adverse event and was classified as an "External Equipment Failure".

In one case, both external stimulators failed causing the patient to be returned to mechanical ventilation until replacements could be provided. The reason for the failure has been addressed in hardware and labeling modifications.

*Spasms:*

Five patients reported muscle spasms in the arms and legs as a result of diaphragm stimulation. This occurred initially when the stimulation was initiated or it was a persisting problem that was controlled by reducing the level of stimulation on one or more channels. All five affected patients were able to continue the use of the device and went on to full-time pacing.

*Pain / Discomfort with stimulation:*

Three patients reported temporary pain or discomfort with the stimulation. The pain/discomfort was controlled by either permanently or temporarily reducing the level of stimulation on one or more channels. In some instances, stimulation elicited referred pain, particularly to the shoulder, or in the abdomen. This was eliminated in some cases through reduction in parameter settings.

*Increased Secretions:*

Three patients complained of increased respiratory secretions, that were subsequently reduced with continued use of the device. In an informal survey 59% of patients responding reported fewer secretions, with 50% of caregivers reporting less suctioning.

*Low Tidal Volume ( $V_T$ ) / Oxygen ( $O_2$ ) Desaturation*

Two patients identified low tidal volumes and oxygen desaturation during their conditioning sessions. These patients were returned to mechanical ventilation when shortness of breath or discomfort were identified. These patients eventually paced full-time with the device.

One additional patient reported a low tidal volume and oxygen desaturation, possibly attributable to a scorpion bite while pacing. Upon treatment for the scorpion bite the patient was able to return to pacing with no additional effects.

*Difficulty Eating with Device:*

One patient reported difficulty eating and drinking. The patient was not using a Passy Muir valve at the time. The instructions for use of the NeuRx DPST<sup>TM</sup>, RA/4 recommend the use of a Passy Muir (one way breathing) valve to allow the patient to eat or drink during stimulation until coordination between swallowing and breathing is established.

*Death:*

A total of 4 deaths were reported during the course of this study. Two of the deaths occurred while the patient was being mechanically ventilated and not paced. In one case the patient was found lifeless during the night; in another case the patient died of cardiac arrhythmia and subsequent cardiac failure.

Two deaths occurred during use of the NeuRx DPST<sup>TM</sup>, RA/4. One patient was observed to lose

consciousness while the device was functioning. A second patient died of septic shock due to urosepsis and was using the NeuRx DPS™, RA/4 prior to a hypotensive arrest. No device malfunction was observed.

Autopsies were not performed, but the deaths do not appear to be device related and the causes of death are not unexpected in this patient population.

*Pneumonia*

Three patients developed pneumonia or respiratory tract infection during the clinical trial requiring treatment with oral or IV antibiotics. Patients with pneumonia were mechanically ventilated during the course of their pneumonia and resumed pacing after the incident cleared, typically in one to two weeks. Two of the patients had a history of recurrent pneumonias prior to use of the NeuRx DPS™, RA/4, with one of those patients continuing to experience recurrent pneumonia and respiratory tract infections post-implantation.

Pneumonia is a common occurrence among patients with chronic spinal cord injury receiving prolonged mechanical ventilation. In these patients, diseases of the respiratory system are the leading cause of death (22% of all deaths), with pneumonia accounting for 71% of these deaths. Although the current study with the NeuRx DPS™, RA/4, was not explicitly designed to compare the risk of pneumonia with the device against that of alternate therapies (particularly mechanical ventilation), the study's results in this regard are broadly consistent with reported experience with these patients: pneumonias were observed, but not with an exceptionally high incidence given the patient population.

IX. SUMMARY OF PRECLINICAL STUDIES

**Biocompatibility:**

As this device is a long term implant, ISO 10993 recommends cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, subacute toxicity, genotoxicity and implantation testing. The following testing was conducted (note that subacute testing is covered by implantation testing and systemic toxicity):

**Biocompatibility Testing**

Test	Description	Results
Cytotoxicity	MEM Elution Test	Grading from 1-4 was used. The test sample article graded 0 while the positive controls graded 4.
Sensitization	Guinea Pig Maximization Test	The test criteria of grades 1 or better are presumed to be due to sensitization. The grading was 0 for all experimental articles and 1, 2 or 3 for the positive controls.

Test	Description	Results
Intracutaneous Reactivity	ISO Method of Intracutaneous Reactivity Test	The average reaction was not appreciably greater than the reaction to the blank.
Systemic Injection Test	ISO Method of Systemic Injection Test	There was not a significant difference in biological reactivity between test groups and their corresponding negative controls.
Pyrogen Test	Material Mediated Rabbit Pyrogen Test	The individual temperature rise of each individual rabbit was below the test criteria of 0.5 degrees C. The test material was demonstrated to be non-pyrogenic.
Implantation Test	Thirty Day Muscle Implantation Test	The results indicate that the negative control and test article mean scores are in the same overall Toxicity rating (Not exceeding 1).
Implantation Test	Twenty-Six Week Muscle Implantation Test	The results indicated that the negative control and the test article mean scores were in the same overall toxicity rating.
Mutagenicity	Ames Assay Test	As none of the tester strains treated with the test article extract showed mean revertant frequencies greater than two fold when compared to the concurrent negative control, the test article was considered non-mutagenic.

All test results indicate the device is biocompatible.

### **Environmental and Mechanical Testing:**

#### **Temperature and Humidity Cycle Testing:**

The device may be used in a variety of environmental conditions, including use in a shower room or in an ambient dry environment. Consequently, tests were performed to simulate the

environmental temperature and humidity conditions expected to be experienced by the External Stimulator.

To test temperature and humidity tolerance the device was preprogrammed, turned on, and subjected to the following sequence of humidity and temperature variations:

#### Cycle 1: Cold/Dry Environment to Hot/Wet Environment

Simulation of transition from outside/dry winter environment into a hot shower room:

25° C @ 50% RH, initial conditions  
5° C @ 30% RH, 120 minute slew  
5° C @ 30% RH, 180 minute soak  
50° C @ 90% RH, 120 minute slew  
50° C @ 90% RH, 180 minute soak  
5° C @ 30% RH, 120 minute slew  
5° C @ 30% RH, 180 minute soak  
25° C @ 50% RH, 90 minute slew

The pulse output (pulse width and amplitude) was verified at least once on each channel during the last 60 minutes of each “soak” interval. At the end of the final interval the unit was fully evaluated and met the acceptance criteria below.

#### Cycle 2: Hot/Dry Environment to Cold/Wet Environment

Simulation of transition from high temperature low humidity environment into a low temperature/high humidity environment:

25° C @ 50% RH, initial conditions  
50° C @ 10% RH, 120 minute slew  
50° C @ 10% RH, 180 minute soak  
5° C @ 75% RH, 120 minute slew  
5° C @ 75% RH, 180 minute soak  
50° C @ 10% RH, 120 minute slew  
50° C @ 10% RH, 180 minute soak  
25° C @ 50% RH, 90 minute slew

The pulse output (pulse width and amplitude) was verified at least once on each channel during the last 60 minutes of each “soak” interval. At the end of the final interval the unit was fully evaluated and met the acceptance criteria below.

#### Acceptance Criteria

Any disruption of output must return to predetermined acceptance values at the time of testing, without user intervention.

Any audible alarms must resolve automatically following the disruption. Additionally, the “High Lead Impedance” alarm must sound when the cable is removed upon completion of the test.

## Results

These tests demonstrated the acceptable operation of the device (the External Stimulator) through a range of environmental conditions.

### **Vibration testing:**

As the device is to be used by a person in a powered wheelchair, testing was performed to demonstrate the acceptable operation of the device when exposed to vibrations.

The device was preprogrammed, turned on, and subjected to 15 minutes of 2.1 Gp-p of 20 – 200Hz random vibration on each of three axes (back, side and end).

The pulse output (pulse width and amplitude) was observed on a channel during vibration. If the patient cable detached, it was noted, reattached and the test continued for the remaining duration. At the end of the final axis testing, the unit was fully evaluated and met the predetermined acceptance criteria referenced above.

### **Mechanical Strength Testing**

Data indicate the electrode Teflon insulation and Prolene (polypropylene suture) core retain their strength during simulated long-term exposure studies. Samples at simulated six month, 1, 2, 3, 4, 5, and 10 year exposures in phosphate buffered saline maintained strength characteristics not significantly different from unaged (time 0) samples.

## **Software**

Two NeuRx DPS™, RA/4 components contain software: the Clinical Station and the Stimulator. The software for each component runs independently and was validated with a predefined software validation procedure.

### **Clinical Station:**

The software for the Clinical Station has several functions. It provides for multi-mode functionality of the device. The three operating modes are described below: stimulator, programmer and surgical mapping modes.

#### STIMULATOR MODE

The Stimulator operating mode emulates the functionality of the NeuRx DPS™, RA/4 External Pulse Generator. When the Clinical station is in this mode, it has the abilities of the stimulator.

#### PROGRAMMER MODE

The Programmer operating mode automatically uploads the current parameter values from a connected stimulator. It also automatically downloads display parameters to the connected stimulator, as they are modified.

#### SURGICAL MAPPING MODE

The Surgical mapping operating mode provides intra-operative stimulation and sensing of stimulated response. This mode provides twitch or burst stimulation and displays the abdominal pressure response. The pressure response is received from the solid state pressure transducer. This transducer is placed laparoscopically to detect pressure changes which are used to optimize the placement of the electrodes.

**Stimulator:**

The stimulator operates continuously under software control. The software processes the parameter data and generates the required timing in real-time.

**Sterilization:**

The implantable portions of the device are sterilized by ethylene oxide (EO). The Sterility Assurance Level is  $10^{-6}$ . The validation was performed in conformity with recommendations contained in ANSI/AAMI/ISO 11135:1994.

Ethylene Oxide and Ethylene Chlorohydrin residual testing was conducted, in accordance with ANSI/AAMI/ISO 10993, Part 7. The residuals are within the recommended limits for implanted devices.

**Electromagnetic compatibility:**

Electromagnetic Compatibility testing was performed on this device.

Testing of the NeuRx DPS™, RA/4 was completed according to:

- EN60601-1-2 36.201.1/EN 55011 Radiated Emissions,
- EN60601-1-2, 36.202.2/EN 61000-4-2 Electrostatic discharge immunity, EN60601-1-2, 36.202.3/EN 61000-4-3 Radiated Electromagnetic Field Immunity, EN 60601-1-2, 36.202.6/EN 61000-4-6 Conducted RF immunity for I/O,
- EN 60601-1-2, 36.202.8/EN 61000-4-8. Magnetic Field Immunity

In each case, the device passed the standardized test.

As the NeuRx DPS™, RA/4 is intended for out of the hospital transport, testing for the higher electric field immunity level of 20 V/m was performed. This testing was done in a shielded room with the frequency broadcast from 26MHz to 1 GHz, with both horizontal and vertical antenna polarization. No deviation to the selected operation modes was observed during this testing.

**Animal Studies**

The following animal studies were performed. The first dog study was designed to demonstrate a "proof of concept". The rat study was performed to assess tissue encapsulation. The second dog study was conducted with the vacuum probing device used during the surgical procedure.

Purpose	Animal	Number	Results
Demonstration that this procedure could produce the same maximum tidal volumes as phrenic nerve cuff electrodes	Dogs	7 dogs, 32 intramuscular electrodes	The tidal volume induced 167% of the ventilation required for basal metabolic needs without fatiguing the diaphragm.
To study the nature of tissue encapsulation surrounding the	Rats	4 electrodes in each Rat. 3 rats to a group	No encapsulation of the implanted electrode was observed.

Purpose	Animal	Number	Results
implanted electrode			
Test new vacuum probing device	Dogs	2 dogs, device placed in multiple diaphragmatic locations for 1 to 5 minutes	Exposure damage at 5 minutes is minimal and limited to area of application.

X. SUMMARY OF CLINICAL INFORMATION

The clinical study of this device is detailed below.

**Objectives**

The objective of this study was to assess the ability of the NeuRx RA/4 to provide clinically acceptable tidal volume during diaphragm pacing while maintaining an acceptable safety profile.

**Study Design**

The study was a prospective, non-randomized, multi-center study utilizing a historical control.

**Enrollment**

50 patients were enrolled in this study at 5 investigational sites beginning in the year 2000.

**Patient Population**

The inclusion and exclusion criteria were as follows:

**Inclusion:**

- Age 18 years or older
- Cervical spinal cord injury with dependence on mechanical ventilation
- Clinically stable following acute spinal cord injury
- Bilateral phrenic nerve function clinically acceptable as demonstrated with EMG recordings and nerve conduction times
- Diaphragm movement with stimulation visible under fluoroscopy
- Clinically acceptable oxygenation on room air (>90% O2 saturation)
- Hemodynamically stable
- No medical co-morbidities that would interfere with the proper placement or function of the device
- Committed primary caregiver
- Negative pregnancy test in females of child-bearing potential
- Informed consent from patient or designated representative

**Exclusion:**

- Co-morbid medical conditions that preclude surgery
- Active lung disease (obstructive, restrictive or membrane diseases)
- Active cardiovascular disease
- Active brain disease
- Hemodynamic instability or low oxygen levels on room air
- Hospitalization for, or a treated active infection, within the last 3 months

- Significant scoliosis or chest deformity
- Marked obesity
- Anticipated poor compliance with protocol by either patient or primary caregiver.
- Currently breastfeeding

### **Study Endpoints:**

The study primary endpoint was to assess the ability of the NeuRx DPS™, RA/4 to provide clinically acceptable tidal volume for at least four continuous hours of pacing. For a male patient, the tidal volume that is required to meet the basal metabolic requirement ( $V_{T-bmr}$ ) was defined at 7ml/kg body weight. For a female patient, the  $V_{T-bmr}$  was defined as 6ml/kg body weight. The safety endpoint was to qualitatively assess the adverse event reports and compare these to a similar patient population. Secondary endpoints include reduction of dependence on mechanical ventilation and surgical implementation site independence.

## **1. Methods**

### **1.1 Inclusion pre-screening:**

Candidates were patients with high spinal cord injury resulting in dependence on mechanical ventilation. They were required to have intact phrenic nerves bilaterally, below the level of the spinal cord injury, and were additionally required to be in otherwise generally good health.

### **1.2 Surgery**

Surgery was completed in four phases: exposure, mapping, implantation, and routing.

**1.2.1.** The *exposure* consisted of the setup for the standard four port laparoscopy to visualize the diaphragm. During this phase, any abdominal adhesions were released and any gastrostomy tube tubes were replaced or removed if needed.

**1.2.2.** The next phase consisted of the *mapping* of the diaphragm on a grid pattern for response to twitch stimuli. Locations on each hemi-diaphragm were stimulated with each site recorded on a grid that is overlaid on the laparoscopic video display. The magnitude of the abdominal pressure change, to the applied stimuli, was recorded at each location. The primary electrode site was identified as the location in each hemi-diaphragm associated with maximal pressure change. A secondary electrode site was identified as either a backup to the primary site or at a location in each hemi-diaphragm that recruited another phrenic nerve motor point region (e.g. anterior, lateral, or posterior) of the diaphragm at a similar magnitude.

**1.2.3.** Once the primary and secondary electrode sites were identified in each hemi-diaphragm the *implantation* phase began. An intramuscular electrode was introduced into the abdominal cavity with the electrode delivery instrument. The electrode was inserted into the diaphragm at an angle so that the electrode lead travelled parallel to the plane of the diaphragm prior to exit, following which the delivery instrument was withdrawn. The electrode was then tested to assure the desired response to twitch stimuli was achieved and the procedure was repeated for the remaining electrodes. If the response was not adequate when tested, the electrode was withdrawn and another implanted. In all, four electrodes were implanted.

**1.2.4.** Electrode leads were then *routed* to the percutaneous exit site. The indifferent electrode (or anode) was routed from the percutaneous exit site. The electrodes were then

retested to make sure that all of the connections had been made properly. An EKG strip was recorded with all four electrodes active to be sure there was no capture of the cardiac rhythm. The port incisions were then closed and the patient was transferred to recovery.

### **1.3 Reversal of Disuse Atrophy & Conditioning**

At one to two weeks post surgery, the patient returned to the hospital for the initiation of stimulation. Each electrode was characterized over the range of stimulus parameters using the Clinical Station. After initiation of stimulation, tidal volumes were recorded with a calibrated Wrights Spirometer and oxygen saturation was monitored with a pulse oxymeter. It should be noted that the tidal volumes were measured with the patient's tracheotomy, which in most cases is a cuff-less tracheal tube. This means that tidal volumes recorded (and subsequently reported below in the results) with the Wrights Spirometer were lower than the actual inspired air volume due to air leaks around the patients stoma and through their upper airway. An EKG rhythm strip was recorded at maximal stimulus parameters to assure that there was no capture of the cardiac waveform. Initial parameter settings were determined and the RA/4 External Stimulator was programmed. Initial conditioning sessions were performed while the patient was at the hospital to assure the patient and their caregivers understood and were comfortable with the operation of the DPS.

The patient returned home and logged his/her use of the NeuRx DPST<sup>™</sup>, RA/4 and the improvement in tidal volume as determined with the Wrights Spirometer. Pulse oximetry and a rank scale indication of respiratory effort were recorded along with any comments with each use of the DPS. The clinical team assessed the patient's progress on a weekly basis during the initial weeks, reviewing the log sheets and making any changes to parameters as necessary. Log sheets were maintained until the patient had reached, or was capable of, full time use. Electrodes were characterized again at 3, 6, and 12 month intervals post surgery, if the patient had not reached a steady-state plateau or full time use of the system.

### **1.4 Chronic Use**

Once the patient had achieved full time use of the DPS or was using it at a level that was consistent with their desired level of activity, they were free to use the system as desired. The DPS includes two external stimulators, two patient cables, extra batteries and percutaneous connector site tapes. Additional supplies (batteries, cables, and percutaneous connector tapes) were supplied as needed.

## **2. Description of Enrolled Subjects**

Patients in this study group have all suffered from high spinal cord injury and were full-time dependant on positive pressure mechanical ventilation prior to enrollment. The age of enrolled patients was from 18 to 74 years of age. The time since injury for enrolled patients ranged from three months to twenty-seven years. The male enrollment of 74% (gender ratio of thirty-seven males to thirteen females) is fairly consistent with the national database statistics concerning spinal cord injury in which 81.2% of affected individuals are identified as male. The predominant cause of injury was motor vehicle accidents (40%), followed by sports injuries (40%) and all others (20%). The demographic information is summarized in Table 1, below. Table 2 contains information on the level of injury in implanted patients.

Table 1: Demographics (n=50)

	Average	Stdev	Min	Max
Age (years)	36	16	18	74
Weight (kg)				
Males (n=37)	83	16	57	127
Females (n=13)	59	13	40	84
Time Since Injury (years)	5.6	6.9	0.2	26.9

Table 2: Level of Spinal Injury

Level of Injury	# of Patients	Percent of Total
C1	3	6%
C1/C2	14	28%
C2	24	48%
C2/C3	1	2%
C3	3	6%
C3/C4	3	6%
C4	1	2%
C4/C5	1	2%

Basal metabolic requirements (BMR) and positive pressure mechanical ventilator settings for the implanted patients are given in Table 3.

Table 3: Metabolic Requirement and Mechanical Ventilation settings (n=50)

	Average	Stdev	Min	Max
Basal Metabolic Requirement (ml)				
Male (7ml/kg)	578	109	399	889
Female (6ml/kg)	355	79	240	504
Tidal Volume (ml)				
Male	1025	233	400	1500
Female	837	341	170	1500
Minute Ventilation (liters / min)				
Male	12	3	6	21
Female	10	4	4	18

### 3. Results

#### 3.1 Summary

Fifty patients have been implanted with the NeuRx DPS™, RA/4 at five clinical sites. Overall, these patients account for over 83 years of active implant time with an average follow-up of 1.7 ± 1.4 years (median = 1.4, range 0.2 – 7.7).

Study objectives: The primary study endpoint is to assess the ability of the NeuRx DPS™, RA/4's to provide clinically acceptable tidal volume for at least four continuous hours of pacing. For a male patient, the tidal volume that is required to meet the basal metabolic requirement ( $V_{T-bmr}$ ) is defined as 7ml/kg body weight. For a female patient, the  $V_{T-bmr}$  is defined at 6ml/kg body weight. See table 4 for a summary of the results.

Table 4: Summary Results

Category	NeuRx DPS	
	#	% of Total
<b>Success</b>	<b>48</b>	<b>96%</b>
<i><math>V_T &gt; \text{Basal Req.}, \text{Continuous use} &gt; 4 \text{ hrs}</math></i>	48	96%
<b>Partial Success</b>	<b>1</b>	<b>2%</b>
<i><math>V_T &gt; \text{Basal Req.}, \text{max use} &lt; 4 \text{ hrs}</math></i>	1	2%
<b>Failure (never paced)</b>	<b>1</b>	<b>2%</b>
<b>TOTAL</b>	<b>50</b>	<b>100%</b>

The summary results given in Table 4 show the NeuRx DPS™ RA/4 achieving a success rate of 96% where success is defined as ongoing use > 4 hours with tidal volumes greater than basal requirements. One patient was able to achieve tidal volumes greater than basal requirements during initial conditioning but had to suspend conditioning because of a malfunctioning baclofen pump. At the time of the submission, the patient has only recently restarted conditioning. This patient is listed as a “partial success”, as this subject is currently conditioning they can not be strictly listed as either a full success or a failure. One enrolled patient was never able to achieve diaphragmatic pacing. Subsequent to this subject’s failure to pace, the study criteria were modified to include fluoroscopic confirmation of diaphragm excursion as a criterion for study inclusion.

Overall, a total of 48 patients out of 50 patients enrolled have been able to pace for longer than four consecutive hours while achieving tidal volumes greater than their basal metabolic requirements. At the end of the study period, a total of 44 patients were actively using the device. Four patients died in the course of the study (see discussion of adverse events, below).

The length of the conditioning phase was variable. It ranged from 1 week for 18-20 year olds on mechanical ventilation for less than 1 year, to 14 weeks for 40-50 year olds on a ventilator for greater than 5 years.

### 3.2 Adverse Events

Please see the table and description of adverse events in Section VIII.

## XI. RISK/PROBABLE BENEFIT ANALYSIS

The NeuRx DPS™, RA/4 is intended for use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but who lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4

continuous hours a day. It is intended for use only in patients 18 years of age or older.

Alternative systems and procedures for people with high spinal cord injury include mechanical ventilation, another diaphragm pacing device previously approved by FDA for use in patients with high spinal cord injury, and non-invasive ventilatory assistance devices including NPPV (CPAP or BiPAP), pneumobelt, and a rocker bed.

Mechanical ventilation requires the patient to be connected (usually through a tracheostomy tube) to a ventilator which supplies positive pressure to inflate the lungs and allows for respiration. Ventilators are connected to external power sources and in many cases have internal battery back-up for transportation, outside activities and for use in the event of power failure. While they can be used outside the home, they are cumbersome and require that the patient be connected to the device at all times.

Spinal cord injury patients also have access to an existing FDA approved diaphragmatic pacing device. The intended use of this approved device is similar to the intended use of the NeuRx DPST<sup>™</sup>, RA/4. However, it differs from the NeuRx DPST<sup>™</sup>, RA/4 in that it is connected to the phrenic nerve in the neck or thorax rather than in the muscle of the diaphragm.

Patients on full-time mechanical ventilation may still tolerate some time off mechanical ventilation with support of some form of non-invasive ventilation. NPPV in the form of CPAP or BiPAP requires a mask or nasal occlusion device and is variably tolerated. The devices can cause skin and nasal mucosal irritation. A pneumobelt requires the patient remain in the sitting position, while the rocker bed requires the supine position, limiting mobility. All the devices for non-invasive ventilation require either a battery operated or electrical power source. NPPV and the pneumobelt potentially provide more mobility than mechanical ventilation.

The safety profile of the NeuRx DPST<sup>™</sup>, RA/4 was explored in a study of 50 patients with high spinal cord injuries and stimulatable diaphragms. The most frequent adverse event attributable to this device was capnothorax. The capnothorax occurred as a consequence of the surgical implantation procedure. Forty two percent of the patients enrolled in the clinical study experienced this complication in association with implantation of the electrodes in the diaphragm. While no patients experienced compromised pulmonary gas exchange or hemodynamic instability as a result of the capnothorax, affected patients required treatment with a chest tube, for up to two days in one patient, and an extended hospital stay of 5 days, in one patient. Synapse Biomedical Inc. has addressed this risk in the labeling and training procedure provided with this device.

Eleven incidents of aspiration and 3 incidents of upper airway obstruction occurred in 3 patients. All episodes of aspiration occurred during pacing and most were associated with failure to use the Passy Muir valve while eating or sleeping as instructed. None of the episodes were clinically significant. The incidences of upper airway obstruction occurred with patients who fell asleep with capped tracheostomy. The patients were reminded to use a Passy Muir valve while sleeping.

The other adverse events attributable to the device have been short term concerns such as local implantation site infection. Other serious events such as pneumonia and death have occurred in patients while using the device but there is no reason to associate these adverse events with the use of the device. Pneumonia is considered one of the most frequent conditions reported in this patient population.

In the same study of 50 patients with stable, high spinal cord injuries, 96 % of patients were able to achieve clinically acceptable tidal volume for at least four continuous hours of pacing per day with the NeuRx DPST<sup>TM</sup>, RA/4. Use of the device for periods greater than four continuous hours a day occurred after a period of diaphragmatic conditioning that ranged from one week to several months. This suggests that the use of the NeuRx DPST<sup>TM</sup>, RA/4 in patients with high spinal cord injuries and stimlatable diaphragms may allow these patients to be removed from the ventilator for at least 4 hours a day, provided that a mechanical ventilator is available at all times (as recommended in the labeling).

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

#### XII. PANEL RECOMMENDATION

This HDE was not presented to the the FDA Anesthesiology and Respiratory Therapy Devices Advisory Committee.

#### XIII. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the NeuRx DPST<sup>TM</sup>, RA/4 will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on June 17, 2008.

#### XIV. APPROVAL SPECIFICATIONS

Directions for use: See Physician's Labeling.

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

Postapproval Requirements and Restrictions: See Approval Order.