

**DE NOVO CLASSIFICATION REQUEST FOR
NEUROLUTIONS IPSIHAND UPPER EXTREMITY REHABILITATION SYSTEM**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Electroencephalography (EEG)-driven upper extremity powered exerciser. An EEG-driven upper extremity powered exerciser is a non-invasive prescription device intended for rehabilitation by driving movement or exercise of an impaired upper extremity in response to the detection of purpose oriented electrical activity produced by the patient's brain.

NEW REGULATION NUMBER: 21 CFR 890.5420

CLASSIFICATION: Class II

PRODUCT CODE: QOL

BACKGROUND

DEVICE NAME: Neuroolutions IpsiHand Upper Extremity Rehabilitation System

SUBMISSION NUMBER: DEN200046

DATE DE NOVO RECEIVED: July 23, 2020

SPONSOR INFORMATION:

Neuroolutions, Inc.
1101 Pacific Ave, Suite 300
San Cruz, California 95060

INDICATIONS FOR USE

The Neuroolutions IpsiHand Upper Extremity Rehabilitation System is indicated as follows:

The Neuroolutions IpsiHand Upper Extremity Rehabilitation System is indicated for use in chronic stroke patients (≥ 6 months post-stroke) age 18 or older undergoing stroke rehabilitation, to facilitate muscle re-education and for maintaining or increasing range of motion in the upper extremity.

LIMITATIONS

The sale, distribution, and use of the Neuroolutions System are restricted to prescription use in accordance with 21 CFR 801.109.

The Neuroolutions System is contraindicated for use in patients having any of the following conditions:

- Severe spasticity or rigid contractures in the wrist and/or digits that would prevent the Neuroolutions Handpiece from being properly fit or positioned for use.
- Skull defects due to craniotomy or craniectomy.

The safety and effectiveness of Neuroolutions System therapy has not been evaluated in the following patient populations:

- Patients with Dementia, or who are too cognitively impaired to understand tasks
- Patients with severe, *receptive aphasia* who have difficulty understanding written or spoken language, or who are unable to follow written instructions
- Patients with severe *unilateral* visual inattention (neglect) that would visually limit use of the Tablet

The Neuroolutions System should be used with caution in patients with nerve or sensory impairment that may limit or interfere with the patient's ability to sense pain in response to potential pressure points on the Neuroolutions Handpiece.

As with use of any medical device, there are risks associated with treatment using the Neuroolutions System. Some patients may experience any of the following adverse events during use of the device.

- Fatigue, discomfort and/or headache associated with device use
- Skin redness or pressure point(s) associated with the mechanical hand exerciser

Durability testing has not been completed beyond 6-months, persistence of benefits beyond 6-months post device use are currently unknown.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Neuroolutions IpsiHand Upper Extremity Rehabilitation System (a.k.a. Neuroolutions System or IpsiHand System) detects goal-oriented brain activity using non-invasive EEG electrodes to allow a stroke patient to perform therapeutic exercises that they would otherwise not be able to perform, due to their impairment.

The Neuroolutions System shown in the figure below, consists of the Neuroolutions Handpiece, a Tablet computer, and a Biometric Headset.



Neuroolutions Handpiece



Tablet



Biometric Headset

Using a standard Windows Tablet as the patient interface, the System translates brain signals from the Biometric Headset into movement of the motor-driven Handpiece worn over the patient's hand and wrist. The motion of the Handpiece, in turn, opens and closes the patient's impaired hand. The combined action of these System components allows the stroke patient to perform physical therapy exercises that they would otherwise not be able to perform, due to their impairment. The Biometric Headset, which contains dry electroencephalographic (EEG) sensors, receives electrical signals from the motor or pre-motor cortex, predominantly of the unaffected hemisphere of the patient's brain, and in doing so, detects the patient's intentions to move their affected hand. These intentions to move are translated into motor movements of the Handpiece using software that drives a linear actuator contained inside of the Handpiece. The Handpiece opens and closes the hand using a 3-finger pincer grip mechanism designed to emulate the movement of grasping an object using the two forefingers and thumb in a grasping motion (one degree of freedom).

The device functions as powered exercise equipment for the patient's hand using three separate modes: the main mode of therapy is referred to as the brain-computer interface (BCI) or 'thought' mode in which the patient's hand is opened or closed by the powered orthosis based on brain signals received from the Biometric headset; the second mode is referred to as a 'volitional' mode in which a patient actively opens and closes their hand with the System enabling independent range of motion; the third is a continuous passive motion (CPM) mode in which the System simply moves the patient's hand passively through a comfortable range of motion in a repetitive fashion.

The Neuroolutions System is designed for use in clinic or home settings as part of prescribed rehabilitation therapy.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

Only the Biometric Headset and Neuroolutions System Handpiece are considered patient-contacting components of the System. The sponsor tested ^{(b) (4)} samples each of the loop

straps, orthosis padding, headset top foam padding and headset ear pad covers, which are patient-contacting throughout the therapy. However, the orthosis housing, EEG electrode components, plastic components of the finger tray and thumb rest, chargers, and the polycarbonate components of the biometric headset were not tested, as these components are in contact with the skin for a brief period and represent a low risk. The tablet was also not tested for biocompatibility, as it is an off-the-shelf consumer electronics device that is in contact with the patient only when initiating or updating the therapy program, thus posing a low risk for biocompatibility issues.

The biocompatibility evaluation for the Biometric Headset and Neuroolutions System Handpiece was conducted in accordance with the International Standard ISO 10993-1: 2009 “Biological Evaluation of Medical Devices Part-1: Evaluation and Testing Within a Risk Management Process”. The Biometric Headset and Neuroolutions System Handpiece are categorized as a surface device in limited (< 24 hours) contact of the skin. Assessment of the device included the following tests:

- Cytotoxicity (ISO 10993-5:2009)
- Sensitization Test (ISO 10993-10:2010)
- Intracutaneous Reactivity (ISO 10993-10:2010)

The inner rings passed sensitization and irritation testing but demonstrated some cytotoxicity. It appears likely that the Silver/Silver Chloride (manufactured from (b) (4) fine silver) that is deposited on the Acrylonitrile Butadiene Styrene (ABS D100) base material for the inner sensor electrode is the cause for the failure. This appears to be a low risk and was determined to be acceptable. All other components met the prespecified acceptance criteria for all tests.

SHELF LIFE/REPROCESSING/STERILITY

The Neuroolutions System is not provided sterile and is not intended to be sterilized prior to use. The device consists of the following reusable components: a handpiece, a tablet, and a headset. Cleaning and disinfection methods were validated in accordance with AAMI TIR12:2010 (Designing, testing, and labeling reusable medical devices for reprocessing in health care facilities: A guide for device manufacturers). Testing was performed by Nelson Labs to demonstrate low-level disinfection of the Neuroolutions System when used by different patients in a clinic setting (multiple patient use), and during factory reprocessing performed by Neuroolutions, Inc. Validated cleaning and disinfection instructions have been provided for each of the three components.

The risk of contamination, particularly when the device is used between multiple patients in clinic use, is also ameliorated by the use of a legally marketed disposable protective cover that is worn as a barrier between the patient’s skin and the Neuroolutions Handpiece.

ELECTROMAGNETIC CAPABILITY & ELECTRICAL SAFETY

The Neuroolutions System was tested according to the following FDA-recognized consensus standards:

- IEC 60601-1:2005 (Modified to be equivalent to (AAMI/ANSI ES60601-1:2005/(R)2012 and C1:2009/(R)2012 and, A2:2010/(R)2012) “Medical Electrical Equipment; Part 1: General requirements for basic safety and essential performance.” Results demonstrated that the device is compliant to this standard.
- IEC 60601-1-2:2014 "Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance-Collateral Standard: Electromagnetic disturbances - Requirements and Tests."
- IEC 60601-1-11:2015 “Medical electrical equipment: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.”

Wireless

The Neuroolutions System includes the following wireless technologies operating in the ISM band and has been evaluated against ANSI/AAMI/IEC 60601-1-2 (4th edition) for immunity and emissions appropriate for the healthcare and home environment.

- Wi-Fi 802.11 b/g/n 2.4GHz
- Bluetooth 2.1 2.4GHz

Although the sponsor provided wireless compatibility testing, they did not provide wireless coexistence testing. Thus, the sponsor added a General Precaution warning in the labeling explaining that the device may be susceptible to interference from common radio frequency (RF) devices and added a section in the troubleshooting to address such issues.

Battery testing

Evaluation of the product to IEC 60601-1:2005 + A1:2012 included review of 3rd party testing of sub-components such as the rechargeable lithium ion Handpiece battery to IEC 62133 Edition 2.0 2012-12.

SOFTWARE

The sponsor provided documentation acceptable for software and firmware with a “Moderate” Level of Concern (LoC), as outlined in the FDA guidance document “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.” issued May 11, 2005. The primary risk to patients is delay of treatment due to software/firmware malfunction or failure.

SUMMARY OF CLINICAL INFORMATION

A total of three separate clinical investigations were performed to evaluate the safety and effectiveness of the Neuroolutions System. The first study (QRS-0008) was completed and the results published in Bundy et al. 2017, Contralesional Brain-Computer Interface Control of a Powered Exoskeleton for Motor Recovery in Chronic Stroke Survivors. The second study (QRS-0012) was completed, and the third study (QRS-0013) was on-going at the time of submission,

with preliminary analyses provided. Additionally, a meta-analysis was performed to provide further interpretation of the outcomes of these clinical investigations which utilized subject self-controls.

A. Treatment of Chronic Stroke with IpsiHand, Clinical Study (QRS-0008)

This feasibility study tested whether a powered hand orthosis driven by a brain-computer interface (BCI), using neural activity from the unaffected cortical hemisphere, could affect motor recovery in chronic hemiparetic stroke survivors. The study was a prospective, non-randomized, self-controlled study performed in two phases at one investigational site. Phase 1 was conducted to determine the feasibility of recording ipsilateral (contralesional) motor commands and to demonstrate the ability to use the signals to control a computer, and Phase 2 was intended to determine if the BCI-system can be used to impact rehabilitation. Rehabilitation was assessed by examining changes in commonly used functional motor scores.

Ten chronic (≥ 6 months) hemiparetic (Modified Ashworth Scale of 1+ or less of elbow flexion in the affected upper extremity) stroke survivors utilized the BCI IpsiHand System at home for 12 weeks. During this time, data was collected before, during, and upon completion of use of the Neuroolutions IpsiHand System.

Subjects had a statistically significant improvement in the Action Research Arm Test (ARAT) of a mean ^{(b) (4)} points (from (b) (4) at baseline to (b) (4) at exit). A difference of ^{(b) (4)} points represents the Minimal Clinically Important Difference (MCID) in chronic stroke survivors. Six of the 10 subjects showed a difference exceeding the ARAT MCID. Secondary outcome measures including Canadian Occupational Performance Measure (COPM), Motricity Index, and grip strength also significantly improved.

No patient injury or adverse events have been reported in any subject; and only minor fatigue was reported in one (1) subject and was self-limiting.

B. IpsiHand Device Use in Stroke Patients to Assess Functional Motor Outcomes, Clinical Study (QRS-0012)

The study was a prospective, non-randomized, self-controlled study performed in two phases at two (2) investigational sites. The protocol allowed for enrollment of up to 20 adult (at least 18 years of age) stroke survivors who sustained a cerebrovascular accident (CVA) six (6) or more months prior to the date of screening and who had moderate functional impairment of the right or left upper extremity as evidenced by screening assessments.

The goal of the study was to assess whether a motor-activity based BCI system (Neuroolutions IpsiHand System) would provide rehabilitative benefits for stroke survivors. Forty-two subjects were evaluated against the inclusion/exclusion criteria, and those 31 who met those criteria were assigned to Group 1 or Group 2. The study was carried out in two phases. In Phase 1, each participant (Group 1 and Group 2) completed up to three (3) sessions for recording EEG signals, by wearing a research-grade EEG Headset with EEG electrodes in place. The signals were recorded with BCI software. If the participant's EEG signals were adequate for controlling a BCI

mediated hand orthosis, the participant continued on to Phase 2. Of the 31 enrolled subjects, 7 did not meet the Phase 1 EEG criteria and 24 progressed to Phase 2, which evaluated whether a BCI system can be used to impact stroke rehabilitation. In Phase 2, each subject (Group 1 and Group 2) was issued a BCI-mediated hand orthosis and advised to use the device daily at home, a minimum of five out of seven consecutive days per week for a total of 12 weeks. Each subject had a motor assessment at 4 weeks, 8 weeks, and 12 weeks of device use. Based on progress achieved during the first 12 weeks of device use (if a subject achieved a 2-point improvement on UEFM from 8 to 12 weeks), clinical discretion, and other variables, some subjects agreed to continue using the Neuroolutions System at home for up to 36 weeks. Seventeen subjects completed the study protocol, and 12 completed the 6-month durability visit.

All eligible subjects underwent the same assessments, except that Group 1 subjects completed functional MRI imaging (fMRI) to obtain structural, diffusion tensor imaging (DTI), resting state (rs) and task-based (tb) fMRI at the following specific time-points during Phase 2:

- Prior to using home BCI therapy to establish a baseline
- 12 weeks of home BCI therapy device use

All subjects were followed for an initial period of 12 weeks. Subjects who achieved motor progress, as evidenced by results of their motor assessments throughout their participation, were allowed to continue using the device at home for up to 36 weeks, or until progress plateaued (plateau was indicated by 'less than 2 points of Fugl Meyer change at the 12-week visit'). A total of eight subjects who qualified to continue with the study past 12 weeks, declined to continue for a number of reasons including personal/scheduling conflicts, or a desire to return to previous therapy.

The Fugl-Meyer - Upper Extremity (UEFM) was administered at baseline, during use of the device, and post treatment to assess motor impairment and functional movement of the affected upper extremity as related to the impact of BCI therapy.

From baseline to 12 weeks, patients (n=17) demonstrated a mean improvement of (b) (4) with a standard deviation (SD) of (b) (4) (two sided, one-sample t-test, p-value < 0.0001).

Twelve of the 17 subjects who completed at least 12-weeks of device use also completed a durability visit 6-months post device use. The mean improvement was (b) (4) points on the ARAT assessment at 12 weeks with a SD of (b) (4) (two-sided, one-sample t-test, p-value (b) (4)). The mean change from baseline to completion was (b) (4) (n=17). The mean change in motricity at 12 weeks for the study analysis (n=17) was (b) (4) points with a SD of (b) (4) (p < .0001). The mean increase in gross grasp was (b) (4) pounds with a SD of (b) (4). The mean change in AMAT scores was (b) (4) points (SD (b) (4) and p < .0001).

The only adverse events reported were one case of minor fatigue, discomfort (including headache) reported with device use following heart surgery and one case of skin redness indicative of a pressure point on the patient's thumb, which was resolved with re-emphasized training on thumb positioning.

C. Chronic Stroke Rehabilitation with Contralesional Brain Computer Interface, Preliminary Clinical Study Report (QRS-0013)

The third clinical investigation evaluating the Neuroolutions System is currently being conducted with the approval of the Washington University IRB, located in St. Louis, MO. The clinical study (preliminary report provided in QRS-0013, Rev. B) is a prospective, non-randomized, self-controlled crossover study performed in two phases at one investigational site (St. Louis, MO).

Phase 1 of the study investigated the feasibility of recording electroencephalogram (EEG) signals from the affected and unaffected brain hemispheres and was intended to demonstrate the possibility of using these signals to control the motor output of a robotic hand orthosis (Handpiece). Phase 2 was the home use portion of the study, which assessed if the BCI system could be used to impact stroke rehabilitation. Subjects were enrolled into either Group 1 (additional fMRI assessment and range of motion (ROM) exercises, crossover group) or Group 2 (no fMRI or ROM).

Group 1 subjects underwent 12 weeks each of device use and the ROM Home Exercise Program (24 weeks total). For the first 12 weeks, half of the subjects used the Neuroolutions IpsiHand System before the ROM home exercise program, and half of the subjects used the Neuroolutions IpsiHand System after the ROM home exercise program. For the second 12 weeks, the subjects switched the treatment regimen regarding use of the investigational device before or after the ROM home exercise program.

The preliminary report presented results from 13 chronic hemiparetic stroke survivors who utilized the Neuroolutions System in BCI-mode at home for 12- weeks. Three of the subjects are actively participating in the crossover portion (second treatment regimen) of the study. During the study, the clinical specialist collected data before, during, and upon completion of device use.

Based on this preliminary statistical analysis, from baseline to 12 weeks, on the patients who completed 12 weeks of therapy (n=12) demonstrated a mean improvement of (b) (4) with a SD of (b) (4) (two-sided, one sample t-test, $p < 0.0001$)

The results of Phase 1 of the study support the feasibility of recording EEG signals from the unaffected (contralesional) hemisphere and suggest that these signals can be used to control the motor output of a robotic hand orthosis (Handpiece). The results of Phase 2 of the study suggest that brain-controlled movement of the affected hand, through use of the Neuroolutions IpsiHand System, can positively impact rehabilitation by improving motor function.

To interpret the therapy outcomes of the Neuroolutions IpsiHand System relative to a control intervention, an independent meta-analysis including studies published from 2000 to June 2020 was conducted of serial changes in terms of upper limb motor function for chronic stroke patients treated with standard rehabilitation care (as measured by Fugl-Meyer Upper Extremity Assessment, FM-UE). Analysis shows the effect size computed from serial differences, in terms of FM-UE assessment from a total (b) (4) patients, ranges from (b) (4) to (b) (4) with an average change in FM-UE of (b) (4). Although small, this estimated average improvement can be hypothesized to originate from the training effect, or placebo effect, as some chronic stroke

patients treated with regular rehabilitation care will exhibit an improvement after periods of inactivity. Importantly, this small improvement is far below the Minimal Clinically Important Difference (MCID) scores for the FM-UE, which has been defined as an increase of 5.25 points from baseline in those patients in the chronic phase of stroke. The findings of this meta-analysis conclude that chronic stroke survivors do not demonstrate a clinically meaningful improvement in their motor function when receiving standard of care alone, as evidenced by the Fugl-Meyer assessment.

To date, there has been no patient injury or adverse events reported in any subject.

Pediatric Extrapolation

The Neuroolutions IpsiHand Upper Extremity Rehabilitation System is indicated for patients age 18 and older. For medical devices, the FD&C Act defines patients before their 22nd birthday as pediatric patients. In this De Novo request, complete data from patients between 28-79 (mean age 57.9) were used to support the use of the device in adult patients. It was appropriate to indicate the device for individuals 18 and older because patients aged 18 to 21 do not carry additional differences or risks relative to the patient population studied, incidence of stroke and hemiparesis is present in the transitional adolescent population (pediatric sub-population) of 18-21 years of age, and this device has a likely benefit for this group.

LABELING

The labeling (User Manual) meets the requirements of 21 CFR Part 801.109 for prescription devices.

The labeling for providers and patients includes information describing the data collected with regard to the durability of the effects of device use. Namely, providers and patients are made aware that 6-month durability data were collected in a small cohort and the permanency of these gains beyond that window remain unknown.

Information in the labeling for providers and patients also describes the data collected with regard to the proportion of users that attained a clinically meaningful increase in the Fugl-Meyer with device use. Namely, 33.3% of patients who used the device as directed did not achieve a clinically meaningful increase in Fugl-Meyer score during the 12-week trial of device use. It is important that providers and patients be made aware that not all patients will experience a clinically meaningful benefit from device use.

The labeling includes instructions explaining how users can navigate the software application to use the different modes of the device (Brain-Computer Interface, Volitional, and Continuous Passive Motion). Instructions for use includes information on fitting the device to the patient, how the device operates, and the typical sensations experienced during treatment.

The labeling also outlines the cleaning for home use and clinical use.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the electroencephalography (EEG)-driven powered exerciser and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Device provides ineffective treatment, leading to worsening condition	Clinical performance testing Software verification, validation, and hazard analysis Wireless compatibility testing
Unintended motion leading to injury	Software verification, validation, and hazard analysis
Thermal injury including burns and shock	Electromagnetic compatibility (EMC) testing Electrical safety testing Battery safety testing Labeling
Adverse tissue reaction	Biocompatibility evaluation Labeling
Cross contamination, leading to infection or adverse tissue reaction	Reprocessing validation Labeling
Pain or discomfort including: <ul style="list-style-type: none"> • Headache • Fatigue • Skin redness 	Labeling Clinical performance testing

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the electroencephalography (EEG)-driven powered exerciser is subject to the following special controls:

- (1) Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Testing must capture any adverse events observed during clinical use and must demonstrate that the EEG signal can be translated into intended motion.
- (2) Software verification, validation, and hazard analysis must be performed.
- (3) Performance data must demonstrate the electromagnetic compatibility, electrical safety, battery safety, and wireless compatibility of the device.
- (4) The device components that contact the patient must be demonstrated to be biocompatible.
- (5) Performance data must validate the reprocessing instructions for the reusable components of the device.
- (6) Labeling must include:
 - (i) Instructions on fitting the device to the patient;
 - (ii) Information on how the device operates and the typical sensations experienced during treatment; and
 - (iii) Reprocessing instructions.

BENEFIT-RISK DETERMINATION

The risks of the device are based on data collected in the clinical studies described above. Namely, the studies included adverse events such as pain or discomfort due to headache and fatigue as well as adverse tissue reaction if the device was not positioned properly. Known risks for skin contacting devices include issues of biocompatibility, and when intended for multi-patient use, there is a known risk of cross contamination. With devices of this type, malfunction due to electromagnetic interference or software faults can also pose risks such as thermal injury, unintended motion, or inability to treat due to device failure. None of the above are serious and all can be resolved quickly and easily by discontinuing use or adjusting the device.

The probable benefits of the device are also based on data collected in the clinical studies as described above. Improvements include improved upper extremity function as measured by the Action Research Arm Test (ARAT) and the upper extremity Fugl-Meyer (UEFM) score, results that were statistically significant and clinically meaningful. There were also statistically significant improvements in Motricity Index and grip strength and a self-scored subjective measure of each subject's ability to use their affected arm in functional tasks. Improvements were observed in pinch strength, Modified Ashworth Scale and Active Range of Motion (AROM).

Sources of uncertainty in the benefits included the effect of concomitant use of Botox by some study participants, small sample sizes with an open label study design that does not control for the placebo effect, and limited follow up time to establish durability of treatment effect. The first was addressed using subgroup analysis showing that when the data were combined across studies there was a larger mean UEFM improvement in Botox patients ((b) (4) pts) than in non-Botox patients ((b) (4) pts). The small sample size and lack of placebo control was addressed by pooling data and citing historical controls. Due to the limited follow up time, the sponsor includes in the labeling information on the durability of the treatment effect.

PATIENT PERSPECTIVES

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

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

The Neuroolutions IpsiHand Upper Extremity Rehabilitation System is indicated for use in chronic stroke patients (≥ 6 months post-stroke) age 18 or older undergoing stroke rehabilitation, to facilitate muscle re-education and for maintaining or increasing range of motion in the upper extremity.

The probable benefits outweigh the probable risks for the Neuroolutions IpsiHand Upper Extremity Rehabilitation System. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Neuroolutions IpsiHand Upper Extremity Rehabilitation System is granted and the device is classified as follows:

Product Code: QOL

Device Type: Electroencephalography (EEG)-driven upper extremity powered exerciser

Regulation Number: 21 CFR 890.5420

Class: II