EVALUATION OF AUTOMATIC CLASS III DESIGNATION (DE NOVO) FOR PROTEUS PERSONAL MONITOR INCLUDING INGESTION EVENT MARKER

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> Ingestible Event Marker - An ingestible event marker is a prescription device used to record time-stamped, patient-logged events. The ingestible component links wirelessly through intra-body communication to an external recorder which records the date and time of ingestion as well as the unique serial number of the ingestible device.

NEW REGULATION NUMBER: ***880.6305***

CLASSIFICATION: ***II***

PRODUCT CODE: ***OZW***

BACKGROUND

DEVICE NAME: ***PROTEUS PERSONAL MONITOR INCLUDING INGESTION EVENT MARKER***

510(K): ***K113070***

DATE OF 510(K) NSE DECISION: ***MAY 7, 2012***

DATE OF DE NOVO PETITION: ***MAY 14, 2012***

PETITIONER CONTACT:
PROTEUS BIOMEDICAL, INC.
2600 BRIDGE PARKWAY, SUITE 101
REDWOOD CITY, CA 94065
Phone: 650-632-4031
Fax: 650-362-1860

PETITIONER'S RECOMMENDED CLASSIFICATION: ***II***

INDICATIONS FOR USE

The Proteus Personal Monitor is a miniaturized, wearable data-logger for ambulatory recording of heart rate, activity, body angle relative to gravity, and time-stamped, patient-logged events, including events signaled by swallowing the Ingestion Event Marker (IEM) accessory. The Proteus Personal Monitor enables unattended data collection for clinical and research applications. The Proteus Personal Monitor may be used in any instance where quantifiable analysis of event-associated heart rate, activity, and body position is desirable.

LIMITATIONS

Prescription-use only

Caution: Do not wear (the Patch) during magnetic resonance imaging (MRI), cautery, and external defibrillation procedures.

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

DEVICE DESCRIPTION

The Proteus Personal Monitor, also called the "Patch", is a body-worn sensor that collects physiological and behavioral metrics including heart rate, activity, body angle and time-stamped user-logged events generated when a user marks an event by swallowing an Ingestion Event Marker (IEM) or by manually pressing an event marker button on the Patch. The Patch stores and wirelessly sends the IEM data to a general computing device.

The Proteus Personal Monitor Including Ingestion Event Marker system is comprised of three main subsystems; (1) the ingestion event marker (IEM), (2) the data recorder (Patch), and (3) the Proteus software.

1. Ingestion Event Marker (IEM)

The grain-of-sand sized IEM is designed to communicate the time-stamped confirmation of IEM device ingestion as a unique identifier to the Proteus Personal Monitor worn on the skin. The ingestion signal is communicated via volume conduction communication also known as intra-body communication. The IEM is attached to an inert pharmaceutical excipient tablet for ease of handling and swallowability.

2. Proteus Personal Monitor (Patch)

The Proteus Personal Monitor (Patch) receives, stores, and wirelessly sends ingestion confirmation data to a general computing device.

3. Software

The Proteus software is used to pair the Patch with a mobile computing device. The software organizes and displays ingestion events.

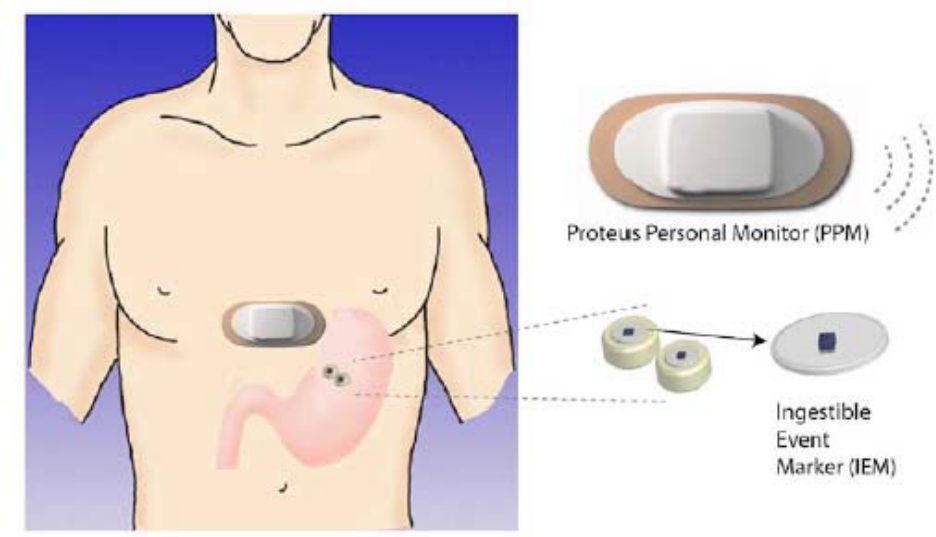

Figure 1: An overview of the Proteus Personal Monitor System – IEM (attached to an inert tablet carrier) and Patch, plus a display screen on a paired computing device (not pictured). Magnified view of IEM with attached excipient skirt is also displayed in graphic.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS (IEM)

The petitioner conducted a series of tests to demonstrate that the patient-contacting components of the Proteus Personal Monitor demonstrated acceptable performance for its intended purpose, which included the tests indicated below.

ISO 10993-5 CYTOTOXICITY TESTING
ISO 10993-10 IRRITATION TESTING
ISO 10993-11 SYSTEMIC TOXICITY TESTING

Given the results of the biocompatibility testing, the petitioner conducted additional animal testing to assess materials toxicity, which included the following tests summarized in Table 1 below.

TABLE 1. PRE-CLINICAL SAFETY TESTING

	Testing Performed	Results
Chemical Characterization	HPLC And Spectroscopic Analysis Of Concentrated Device Extracts	No Unintended Compounds Detected Above Stringent ICH Reporting Threshold For Drug Impurities
Copper (Cu) Toxicity	Risk Assessment By Gradient Corp (Metal Toxicology Experts)	No Risk Of Cu Toxicity With Realistic Exposure
Cytotoxicity	Quantitative Studies With Physiologic Device Extracts	Realistic Exposure Levels Are Non-Cytotoxic

IN VIVO STUDIES

The petitioner also performed forty-two (42) in-vivo studies, including rodent, canine and porcine models, to characterize device performance and safety. Porcine and canine animal models are frequently used in gastrointestinal (GI) device testing, and were chosen because of the similarities of their GI anatomy to that of a human. Efforts were made to include a wide range of body size in the non-clinical experiments, with body weight ranging from 25 to 95 kg. The purpose of this inclusion criterion is to provide an opportunity to investigate the potential effects of body size on the performance of the system. Canine testing was also performed to validate that device egestion occurred as well as additional rodent testing and literature review to assess toxicology of materials. A summary of the studies conducted are provided in Table 2.

TABLE 2. PERFORMANCE AND SAFETY TESTING

	Testing Performed	Results
Mechanical safety	Excretion and GI injury studies in canines	Ingested IEMs reliably excreted Supra-normal doses of IEMs do not inflict any clinically significant injuries
Electrical safety	Tissue stimulation in canines	No abnormal ECG morphology or arrhythmia
In vivo toxicity	14-day rat oral gavage study with physiologic device extracts	No evidence of toxicity in any dosing groups, including max dose group (equivalent to 30,000 IEMs/day), based upon clinical observations, hematology, serum chemistries and histopathology.
	Canine oral toxicology study	No evidence of IEM toxicity, based upon clinical observations and GI tract histopathology. No changes in blood levels of IEM inorganic materials following exposure.
	Rodent oral toxicology study	No evidence of IEM toxicity—even in highest dosing group, which received the weight-adjusted equivalent of 30,000 IEMs/day—based upon clinical observations, hematology, coagulation tests, blood chemistries, necropsy, and comprehensive histopathology.
	IEM copper (Cu) human health assessment, general use	Practical-use scenario (15 IEMs ingested simultaneously, daily or twice-daily) poses no risk of copper toxicity. Extreme-use scenario (30 IEMs ingested simultaneously, daily) poses no risk of systemic toxicity, but transient, non-systemic gastric upset could result at this dose. This concentration dependent effect

		would be mitigated by intake with a meal.
	IEM copper human health assessment, chronic use in a compromised population (renal transplant patients)	Post-operative renal transplant patients are not at greater risk than the normal population from Cu toxicity associated with chronic ingestion of four IEMs/day. There is no scientific basis to believe that the physiological response to Cu in IEM-enabled medicines will differ from the physiological response to Cu in food.
	Quantitative cytotoxicity	Corroborates conclusion of IEM Cu human health assessment.
	Additional chemical characterizations	No unintended compounds detected above reporting threshold for new drug substances, a stringent standard that was adapted for analysis of the IEM device.

ELECTROMAGNETIC COMPATIBILITY (EMC) AND ELECTRICAL SAFETY

Electromagnetic compatibility and electrical safety testing were performed to FDA recognized standards. All applicable tests passed.

TABLE 3. EMC AND ELECTRICAL SAFETY TESTING

Testing Category	Test Descriptions	Reference	Results
Electrical safety testing	Power input	IEC 60601-1, Sub-clause 7.1	Not applicable, because the unit is internally powered
	Limitation of voltage and/or energy	IEC 60601-1, Sub-clause 15 b	Not applicable, because the unit is internally powered
	Protective earthing, functional earthing and potential equalization	IEC 60601-1, Sub-clause 18 f	Not applicable, because the unit is internally powered and has a non-conductive enclosure
	Earth leakage current	IEC 60601-1, Sub-clause 19.4 f	Not applicable, because the unit is internally powered
	Enclosure leakage current	IEC 60601-1, Sub-clause 19.4 g	Not applicable, because the unit is internally powered and has a non-conductive enclosure
	Patient leakage current	IEC 60601-1, Sub-clause 19.4 h.6	Passed, 0 µA measured

	Patient leakage with mains voltage on F-type isolated applied parts	IEC 60601-1, Sub-clause 19.4 h.6	Passed, 0 µA r.m.s measured
	Patient auxiliary current	IEC 60601-1, Sub-clause 19.4 j	Passed, maximum of <1 µA r.m.s measured
	Dielectric voltage withstand	IEC 60601-1, Sub-clause 20.4	Passed
	Reversed battery connection	IEC 60601-1, Sub-clause 56.7	Not applicable; battery is not user-accessible
	Overflow, spillage, leakage, cleaning	IEC 60601-1, Sub-clause 44	Passed
	Creepage distances and air clearances	IEC 60601-1, Sub-clause 57.10	Passed
EMC testing	Group 1 Class B – Radiated emissions	per EN 60601-1-2, EN 55011 (CISPR 11)	Passed
IEM EMC testing	Electromagnetic compatibility (EMC)	IEC 60601-1-2:2007 6.2.3 Radiated RF electromagnetic fields Part 4-3: Testing and measurement techniques – Radiated, radio-frequency, electromagnetic field immunity test	Passed

ADDITIONAL DEVICE CHARACTERIZATION AND PERFORMANCE TESTING

The sponsor performed testing to characterize the performance of the ingestible disc antenna used in the IEM (Table 4) and simulation testing signal reception performance of the Patch data recorder (Table 5).

TABLE 4. INGESTIBLE DISC ANTENNA TESTING

Test Description	Result
Mechanical strength – immersion in SGF for 10 minutes at 37°C	(b) (4)
Residual solvent of the disc material	
Friability – immersion in SGF (10 mins) then SIF at 37°C	
Electrical properties of disc	

TABLE 5. DATA RECORDER TESTING

Test	Test Description	Result
High Frequency (HF) Signal Chain Performance Test	A "body simulation" network was interposed between the signal source and the Data Recorder	The passband is substantially flat between 10Hz and 80Hz
Low Frequency (LF) Signal Chain Performance Test	A patient simulator was attached to the inputs and the amplitude of the output was measured by an oscilloscope	The passband is substantially flat between 2Hz and 100Hz
Accelerometer Performance Tests	Rotating the accelerometer with respect to gravity -- Acceleration measurement from a subject during a steady walk	Measured values agreed well with the applied values R^2 =.99 -- The acceleration traces appear to be of a subject walking.
ECG Performance Testing	The algorithm was tested against all 48 test files from the MIT-BIH arrhythmia database. -- The PROMITTER substudy was conducted on the Proteus campus and enrolled 5 healthy volunteer subjects	The Median was 99.7% detection with a 5.9% standard deviation -- ECG results and accuracy was 99.4% for chest location and 99.2% for xyphoid location
Respiratory Rate Performance Testing	R-wave amplitude is modulated by the respiratory cycle, a stationary subject was instructed to breath regularly at a rate of 6 breaths/min	Device measurement result of 6 breaths/minute

MAGNETIC RESONANCE (MR) COMPATIBILITY

No testing has been conducted to demonstrate whether the device is MR compatible. The labeling has included a Caution that the user should not wear the Patch during magnetic resonance imaging (MRI).

SOFTWARE

The petitioner provided a description of software development processes, software hazard analysis and device system performance testing. The Patch software was reviewed in K093976 in conformance with FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 11, 2005.

SUMMARY OF CLINICAL INFORMATION

The Proteus system has been used by > 250 patients who participated in >3,800 cumulative days of system use involving >11,500 cumulative IEM ingestions as summarized in Tables 6 and 7 below. The studies characterized the safety and performance of the Proteus system. The safety of the system was characterized by recording all patient adverse events (AEs) noted during the study whether device related or not. The key measures of system performance (positive detection accuracy (PDA) and negative detection accuracy (NDA)) characterize the ability of the system to properly detect and register IEM ingestions.

The cumulative average of PDA across all conducted studies is 97.2% (95% CI). The cumulative average of NDA across all conducted studies is 100% (95% CI).

TABLE 6. RESULTS OF HUMAN CLINICAL TESTING

Cumulative Clinical Experience	N		
Number of subjects wearing the Proteus Personal Monitor (Patch)	254		
Number of subjects ingesting IEM	219		
Number of subject/days	3,811		
Number of IEM ingestions	11,655		
No unanticipated adverse device effects, no severe adverse events related to or possibly related to Proteus Personal Monitor System			
Non-serious AEs--92% mild, 8% moderate			
Adverse Event (AE) – Ingestible Sensor		Rate as % of subjects	Rate as % of ingestions
At least one AE	0	0	0
At least one severe AE	0	0	0
Discontinued due to AE	0	0	0
Adverse Events			
Nausea/vomiting	4	1.8%	0.0%
Related	1	0.5%	0.0%
Constipation	2	0.9%	0.0%
Anxiety	1	0.5%	0.0%
Asthma attack	1	0.5%	0.0%
Abdominal cramping	1	0.5%	0.0%
Non-cardiac chest pain	1	0.5%	0.0%
Bitter taste in mouth	1	0.5%	0.0%
Adverse Event – PPM (510(k) cleared component)			
Localized skin irritation and inflammation	45	17.7%	NA
Discontinued due to skin irritation	7	2.8%	NA

TABLE 7. SUMMARY OF HUMAN CLINICAL TESTING

Overall System Performance	
219 subjects of 254 subjects, inclusive of PPM-only users (IEM ingestion) 11,655 ingestions 3810 subject-days of system utilization Maximum daily ingestion: 34 IEMs Maximum system utilization: 42 days	99.3% Detection accuracy 100% Correct identification No SAEs / UADEs related to system

LABELING

Labeling includes all information required for the safe and effective use of the device as outlined in 801.109, including a detailed summary of the non-clinical and clinical testing pertinent to use of the device and the maximum number of daily device ingestions.

RISKS TO HEALTH

Table 8 below identifies the risks to health that may be associated with use of Ingestible Event Markers and the measures recommended to mitigate these risks.

TABLE 8. RISK/MITIGATION MEASURES

Identified Risks	**Recommended Mitigation Measures**
Adverse tissue reaction	Biocompatibility Testing Labeling (dose limits)
Systemic toxicity	Toxicology Testing Labeling (dose limits)
Electromagnetic incompatibility	Electromagnetic Compatibility Testing Wireless testing Labeling
Electrical safety issues	Electrical Safety Testing Labeling
Electrical/Mechanical failure	Non-clinical Performance Testing
Failure to mark event	Non-clinical Performance Testing Clinical Evaluation
Failure to excrete	Animal Testing
Usability	Human Factors Testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the Proteus Personal Monitor including Ingestion Event Marker is subject to the following special controls:

1. The device must be demonstrated to be biocompatible and non-toxic;

2. Non-clinical, animal and clinical testing must provide a reasonable assurance of safety and effectiveness, including device performance, durability, compatibility, usability (human factors testing), event recording, and proper excretion of the device;

3. Appropriate analysis and non-clinical testing must validate electromagnetic compatibility (EMC) performance, wireless performance, and electrical safety; and

4. Labeling must include a detailed summary of the non-clinical and clinical testing pertinent to use of the device and the maximum number of daily device ingestions.

BENEFIT/RISK DETERMINATION

The Benefit/Risk Determination for the Proteus Personal Monitor finds that although the benefits realized by the use of the device system are small, the risks posed by the device system are also small and pose little to no risk to the patient when Special Controls are met and are outweighed by the benefits of the device system.

CONCLUSION

The de novo petition for the Proteus Personal Monitor including Ingestion Event Marker is granted and the device is classified under the following:

Product Code: OZW
Device Type: Proteus Personal Monitor including Ingestion Event Marker
Class: II
Regulation: 21 CFR 880.6305