DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

June 22, 2017

toSense, Inc.
Susan Pede
VP, Operations
4225 Executive Square
Suite 570
La Jolla, California 92037

Re: K160899
Trade/Device Name: CoVa Monitoring System 2
Regulation Number: 21 CFR 870.2300
Regulation Name: Cardiac Monitor (Including Cardiotachometer and Rate Alarm)
Regulatory Class: Class II
Product Code: MWI, DSB, FLL
Dated: June 9, 2017
Received: June 12, 2017

Dear Susan Pede:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-

related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

for Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K160899

Device Name
CoVa Monitoring System 2

Indications for Use *(Describe)*

The CoVa Monitoring System 2 is intended for adult patients under the direction of a licensed medical professional or by clinical personnel trained in its proper use. It is intended to record, store, and transmit the following physiological data: i) heart rate including heart rate variability; ii) respiration rate; iii) thoracic impedance; iv) estimated stroke volume; v) estimated cardiac output; and vi) posture. It displays these physiological data, along with ECG and impedance waveforms, to the licensed medical professionals and/or clinical personnel. The information should be integrated into the context of all clinical data to make determinations of patient status.

The CoVa Monitoring System 2 is indicated for patients with fluid-management disorders managed by regular use of diuretics, and/or suffering from a disease or medical condition characterized by an increase in fluid, such as kidney failure, heart failure, and/or edema caused by a chronic disease (e.g. heart failure) normally treated with a diuretic.

The following are contraindications for the CoVa Monitoring System 2:

• The System is not defibrillator-proof. Thus its Sensor should be removed from a patient before using an external defibrillator.
• The System includes magnetically active materials, and thus should not be used by patients undergoing a procedure involving magnetic resonance imaging (MRI).

• The System should not be used by patients diagnosed with severe cardiac arrhythmias.

• The System should not be used by critically ill patients.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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510(k) Summary

Date Prepared	June 21, 2017
Name	toSense, Inc. 9333 Genesee Ave. Suite 260 San Diego, CA 92121
Contact Person	Matthew Banet, Ph.D. Chief Scientific Officer matt.banet@tosense.com (619) 733-4968
Trade Name	CoVa™ Monitoring System 2 (referred to herein as 'CoVa™ 2')
Common Name	Mobile patient monitoring system, cardiac monitor
Classification Name	Patient Physiological Monitor (without arrhythmia detection or alarm); Impedance Plethysmograph
Classification Regulations	21 CFR 870.2300 (MWI), 21 CFR 870.2770 (DSB), 21 CFR 880.2910 (FLL)
Predicate Devices	CoVa™ Monitoring System (referred to herein as the 'CoVa™ 1') Manufacturer: toSense, Inc. Number: K142087 Clearance Date: May 1, 2015 CardioDynamics BioZ Dx (referred to herein as the 'BioZ monitor') Manufacturer: CardioDynamics Number: K070156 Clearance Date: September 26, 2007
Description	toSense's CoVa™ 2 features a body-worn Sensor, Gateway, and Web-based System. The Sensor has the same mechanical form factor and functionally equivalent electronic systems as the CoVa™ 1 Sensor. Both Sensors perform measurements by non-invasively sensing and processing single-lead electrocardiogram (ECG) and thoracic bioimpedance (TBI) waveforms. The Sensor in CoVa™ 2, like that in CoVa™ 1, uses these two waveforms to measure heart rate (HR), heart rate variability (HRV), respiration rate (RR), and thoracic impedance (TI). The specifications for these measurements, calculated using the rank-regression method, are included in the 510(k) Summary for K142087. Embedded software within the CoVa™ 2 Sensor has been modified to also estimate stroke volume (SV) and cardiac output (CO) from the ECG and TBI waveforms. Additionally, both Sensors measure skin temperature (TEMP) and posture using, respectively, a temperature sensor and accelerometer. The Sensor has a form factor similar to a conventional necklace, with the electronics built into its

strands and base. To make a measurement, a pair of customized disposable Electrodes—each featuring two electrode regions—snaps into a magnetic interface on the backside of the base and then attaches to the patient's chest. The Sensor is typically used for measurement periods less than 5 minutes but can also be used for longer periods (e.g. several hours).

Using a Bluetooth™ transceiver, the Sensor wirelessly transmits measurement information from the patient to a Gateway, such as a tablet computer or mobile phone running the Android operating system. These systems receive information from the Sensor, and then forward it to the Web-based System through either a local-area network (e.g., network based on 802.11), or a wide-area cellular network (e.g. AT&T). The Web-based System displays information and can forward it to a third-party system through a web-services interface.

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The following are contraindications for CoVa™ 2:

- The System is not defibrillator-proof. Thus its Sensor should be removed from a patient before using an external defibrillator.
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- The System should not be used by patients diagnosed with severe cardiac arrhythmias.
- The System should not be used by critically ill patients.

We note that unlike CoVa™ 1, CoVa™ 2 is not contraindicated for patients with implanted cardiac devices, such as pacemakers and/or implanted cardio-defibrillators (ICDs). This contraindication was removed based on detailed clinical studies with the intended-use population that detected no interference between the Sensor and the implanted cardiac devices.

Summary of Substantial Equivalence

We have identified CoVa™ 1 and the BioZ monitor as predicate devices for CoVa™ 2. The BioZ monitor also serves as an acceptance-standard device for measuring SV and CO in CoVa™ 2's clinical trials, as described below.

Each indication for use and measurement assigned to CoVa™ 2, other than estimates of SV, CO and display of information (including ECG waveforms), is also assigned to CoVa™ 1. CoVa™ 2's estimates of SV and CO, and its display of that information along with ECG and TBI waveforms, is performed in a similar manner by the BioZ monitor. The proposed intended-use population for

CoVa™ 2 is also aligned with that of both CoVa™ 1 and the BioZ monitor.

CoVa™ 2's Sensor and the BioZ monitor both use an impedance-based technology to estimate SV and CO. The Sensor makes impedance measurements with four Electrodes disposed in a relatively local area on the chest, just above the heart. The BioZ monitor makes similar impedance measurements with eight electrodes: four are disposed on each of the patient's sides, just above the hips, while the other four are disposed on each side of the patient's neck.

The CoVa™ 2 Sensor and BioZ monitor use similar equations to estimate SV from the TBI waveform. Both equations use input parameters —specifically left ventricular ejection time (LVET), a baseline impedance (Z_0), and a maximum acceleration or velocity of blood leaving the left ventricle [$(dZ(t)/dt)_{max}$]— extracted from the TBI waveform using various signal-processing techniques. Both equations also utilize a parameter called a 'volume conductor' (Vc) calculated from biometric parameters to calculate SV. For the CoVa™ 2 Sensor, the SV calculation is optimized for TBI waveforms measured in a localized area on the chest using the four electrodes described above. We believe its SV estimation differ slightly from that used in the BioZ monitor, the exact form of which is an unpublished trade secret. In both the CoVa™ 2 Sensor and the BioZ monitor, CO is determined from the product of SV and HR, with HR calculated from the ECG waveform.

We have validated CoVa™ 2's measurements of SV and CO with a clinical study focused on its intended-use population. This study compared the CoVa™ 2 Sensor (the test device) to cardiac MRI (c-MRI, the reference device), and the BioZ monitor (the acceptance-standard device). These studies indicate that agreement between the test and reference devices was better than agreement between the acceptance-standard and reference devices for both CO and SV.

The CoVa™ 2 Sensor, the CoVa™ 1 Sensor, and the BioZ monitor use similar impedance-based technologies to measure TI and RR. We validated the CoVa™ 2's measurements of TI and RR with bench tests that are performed during manufacturing with each new hardware and software release. These bench tests ensure that the CoVa™ 2 Sensor's measurements of TI and RR are equivalent to those made by the CoVa™ 1 Sensor. We note that, for the CoVa™ 1 Sensor, clinical trials using human subjects and FDA-cleared reference devices were used to validate its measurements of TI and RR. The clinical trials indicated that measurements of TI and RR made by the Sensor are substantially equivalent to those made by the reference devices.

The CoVa™ 2 Sensor and the CoVa™ 1 Sensor use standard technologies to measure ECG waveforms and to calculate HR and HRV. Both Sensors also use: i) tri-axial accelerometers to measure the patient's motion-related properties, such as posture; ii) thermal sensors to measure TEMP; and iii) Bluetooth™ wireless transceivers to send numerical and waveform information to a gateway device. Both the CoVa™ 1 and CoVa™ 2 Gateways use a cellular transmitter or, alternatively an 802.11 radio, to send information to a Web-based System.

We note that along with CoVa™ 2's benefits, there are some risks associated with measuring SV and CO values from a patient, and then wirelessly transmitting them to a remote clinician. In particular, a patient sending measurements from home may not have the benefit of a visible clinical evaluation, and the accuracy and variability of CoVa™ 2's measurement, without such context, could lead to erroneous treatment decisions. For this reason, our Indications for Use state that CoVa™ 2 *estimates* SV and CO, and that once transmitted to a remote clinician, this information should be integrated into the context of all clinical data to make determinations of a patient's status. Based these and other reasons, we do not believe core technologies used in CoVa™ 2 raise any new

questions of safety or effectiveness.

Clinical Testing

To evaluate CoVa™ 2's new measurements of SV and CO, we performed a clinical study on human volunteer subjects. This study is referred to herein as 'Clinical Study 3 – CoVa™ 2'. During it measurements were made with both a test device (CoVa™ 2) and an acceptance-standard device (the CardioDynamics BioZ, or 'BioZ monitor'). The BioZ monitor is also a predicate device for CoVa™ 2. Measurements from both devices were then compared to those from a gold-standard reference device (GE Medical Systems Discovery MR 450 cardiac MRI, or 'c-MRI'). Both the acceptance-standard and reference devices were cleared by the Agency.

The study was conducted on 4 separate days over a period spanning 2 months; typically, about 10-15 subjects were tested each day the study was conducted. To determine reference SV and CO values, images were collected at the above-mentioned site, and then analyzed off-site by Precision Image Analysis ('PIA'), based in Kirkland, WA.

Following guidance from the Agency, we designed Clinical Study 3 – CoVa™ 2 as a non-inferiority trial to show that, when compared to the reference device, the test device was non-inferior to the acceptance-standard device. In total, 60 volunteer subjects (33M, 27F) participated in the study, with 6 subjects excluded because they displayed severe arrhythmias while being measured with the test device. Of the 54 subjects included in the final analysis, 26 (15M, 11F) had medical conditions including fluid-management disorders managed by regular use of diuretics, recent cardiac surgery, and/or a diagnosis of chronic disease (e.g. obstructive pulmonary disease, cardiomyopathy, edema, or kidney disease). These subjects were within our intended-use population, and thus were separately analyzed as an intended-use sub-group. The remaining 28 subjects in Clinical Study 3 – CoVa™ 2 were healthy volunteers without any of the above-mentioned conditions.

Each subject participating in the study was first measured with the reference device, followed by the test and acceptance-standard devices. Subjects were first situated on a gurney, and asked to maintain a supine position for at least 5 minutes. They remained supine while placed in the MRI tube (and under the MRI magnet), and were measured for a period of about 30 minutes with the reference device. Once measurements were complete, subjects remained in the supine position while they were transferred from the MRI tube to the gurney, where measurements were taken with test and references devices over two separate 5-minute periods. The measurement order of the test and acceptance-standard devices was randomized based on the Study ID.

The objective of the clinical study was to show that agreement between the test and reference devices for both SV and CO was as good or better than agreement between the acceptance-standard and reference devices. 'Agreement', as used herein, was determined from the 95% limits of agreement between measurements made by the two devices, as calculated from the bias and standard deviation of differences between recorded paired values. Results for Clinical Study 3 – CoVa™ 2 are summarized below in Tables 1 (SV results) and 2 (CO results):

Table 1 – SV Measurements from Intended-use Sub-group

Parameter	Test Device vs. Reference Device (SV)	Acceptance-Standard Device vs. Reference Device (SV)
bias	1.6 mL	11.6 mL
standard deviation	15.1 mL	25.6 mL

mean (from reference device measurements)	67.1 mL	67.1 mL
95% LOA	-28.1 mL, +31.2 mL	-38.5 mL, +61.7 mL
percentage error*	44.1%	74.8%

Table 1: Summary of results from Clinical Study 2 – CoVa^{TM} 2 for SV (* percentage error is (1.96 × standard deviation)/mean).

Table 2 – CO Measurements from Intended-use Sub-group		
Parameter	**Test Device vs. Reference Device (CO)**	**Acceptance-Standard Device vs. Reference Device (CO)**
bias	0.3 L/min	0.6 L/min
standard deviation	1.0 L/min	1.5 L/min
mean (from reference device measurements)	4.52 L/min	4.52 L/min
95% LOA	-1.8 L/min, +2.3 L/min	-2.3 L/min, +3.6 L/min
percentage error*	43.4%	65.0%

Table 2: Summary of results from Clinical Study 2 – CoVa^{TM} 2 for CO. (* percentage error is (1.96 × standard deviation)/mean).

Tables 1 and 2 indicate that for both CO and SV, agreement between the test and reference devices was better than agreement between the acceptance-standard and reference devices. Sources of error include the measurement error of the reference device, and the fact that the measurements with the three devices were taken at different times, during which values of SV, HR, and CO may have changed. In particular, anxiety brought on by the close confines of the MRI chamber may increase the values of these parameters.

Additionally, we performed a follow-on analysis using means-square error (MSE) of both the test and acceptance-standard devices as applied to the intended-use sub-group. In this analysis, which is summarized in the tables below, the MSE was calculated using standard techniques as applied to measurements made by the test, acceptance-standard, and reference devices. Tables 3 and 4, below, show the average and standard deviations of the MSE for each subject in the intended-use sub-group, along with the 95% confidence interval calculated from these values.

These results indicate that measurements of the test device are superior to those of the acceptance-standard device. We calculate the p-values for superiority as 0.0021 (for SV) and 0.02 (CO).

Table 3 – SV Measurements from Intended-use Sub-group		
Parameter	**Test Device vs. Reference Device (SV)**	**Acceptance-Standard Device vs. Reference Device (SV)**
Average MSE	222.4 mL	763.6 mL
Standard Deviation of MSE	67.1 mL	151.5 mL

95% Confidence Interval	84.1, 360.6 mL	451.6, 1075.7 mL

Table 3: Summary of MSE error analysis from Clinical Study 2 – CoVa™ 2 for SV.

Table 4 – CO Measurements from Intended-use Sub-group		
Parameter	**Test Device vs. Reference Device (CO)**	**Acceptance-Standard Device vs. Reference Device (CO)**
Average MSE	1.1 L/min	2.6 L/min
Standard Deviation of MSE	0.3 L/min	0.5 L/min
95% Confidence Interval	0.4, 1.7 L/min	1.5, 3.8 L/min

Table 4: Summary of MSE error analysis from Clinical Study 2 – CoVa™ 2 for CO.

Performance Testing

Electrical and mechanical components of CoVa™ 2 are functionally identical to those of CoVa™ 1. CoVa™ 1 was tested and met the requirements of the relevant sections of the following performance standards:

IEC 60601-1 Standard: Medical Electrical Equipment - Part 1: General Requirements for Basic Safety and Essential Performance (2005)

IEC 60601-1-2 Standard: Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance, Collateral Standard: Electromagnetic Compatibility (2007)

60601-1-6 Standard: Medical Electrical Equipment - Part 1-6: General Requirements for Basic Safety and Essential Performance, Collateral Standard: Usability; and IEC 62366 Standard: Medical Devices – Application of Usability Engineering to Medical Device

60601-2-27 Edition 3.0 2011-03 Medical Electrical Equipment - Part 2-27: Particular Requirements for the Basic Safety and Essential Performance of Electrocardiographic Monitoring Equipment

ISO 80601-2-56 Medical electrical equipment – Part 2-56: Particular Requirements for Basic Safety and Essential Performance of Clinical Thermometers for Body Temperature Measurements

These tests were not repeated for CoVa™ 2.

Conclusion

CoVa™ 2 has been tested and found to comply with recognized performance, safety, and electromagnetic compatibility standards for medical devices. Clinical studies indicate its measurements are substantially equivalent to those made by its predicate devices.

Based on the above, we believe CoVa™ 2 is as safe and effective as its predicate devices.