

**DE NOVO CLASSIFICATION REQUEST FOR
MASIMO CORPORATION SAFETYNET OPIOID SYSTEM**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Monitor for opioid induced impairment of oxygenation. A monitor for opioid induced impairment of oxygenation is a device that uses sensor hardware and software algorithms to detect desaturations of arterial oxygen saturation resulting from opioid overdose.

NEW REGULATION NUMBER: 21 CFR 868.2250

CLASSIFICATION: Class II

PRODUCT CODE: QVT

BACKGROUND

DEVICE NAME: Masimo SafetyNet Opioid System

SUBMISSION NUMBER: DEN200011

DATE DE NOVO RECEIVED: February 17, 2020

SPONSOR INFORMATION:

Masimo Corporation
52 Discovery
Irvine, CA 92618

INDICATIONS FOR USE

The Masimo SafetyNet Opioid System is intended to monitor and alarm when a patient may be experiencing an opioid induced impairment of oxygenation.

The Masimo SafetyNet Opioid System is indicated for the non-invasive continuous monitoring of individuals 15 years and older for the identification of when they may be experiencing a substance induced impairment of oxygenation (e.g., opioid induced respiratory depression (OIRD) caused by oral or injectable opioids) in hospital and home environments.

LIMITATIONS

The Masimo SafetyNet Opioid Halo System is contraindicated for the monitoring of opioid users on supplemental oxygen greater than 2.0 L/min.

Obstructive sleep apnea (OSA) can increase the risk of false OIRD alarms by causing oxygenation instability trends that can be mistaken as OIRD.

The Masimo SafetyNet Opioid System is not designed to detect apnea. Do not use the Masimo SafetyNet Opioid System as an apnea monitor.

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

DEVICE DESCRIPTION

The Masimo SafetyNet Opioid System (device) is a system intended for noninvasively and continuously monitoring opioid users 15 years and older to identify substance induced impairment of oxygenation that can lead to opioid induced respiratory depression (OIRD) caused by oral or injectable opioids in hospital or home use environments. The device functions using a pre-determined notification escalation policy that provides the ability for the user to receive alerts and to establish a network of emergency contacts who can be contacted based on the level of alert/alarm as determined by the device. These emergency contacts are notified after previous notifications sent to the device user do not resolve the desaturation condition. As a final action, the device can notify Emergency Medical Service (EMS) dispatch to trigger a wellness call. If assistance is needed or the device user does not respond, the dispatch will request that EMS (i.e., ambulance service) be sent to the device user's location.



The device consists of the following components:

- **Bedside Station** – Device component that communicates monitoring data wirelessly from the medical technologies to provide visual/audible alerts. The Bedside Station is paired by Bluetooth (BLE) with the Sensor. It also provides visual indication of its status (including connectivity) and audible alarms. The Hub is line powered (AC/DC power supply).
- **Masimo Sensor** - Wireless wearable pulse oximetry sensor that provides the monitoring data. The Sensor is a headless, battery-powered pulse oximeter that is worn on the wrist by the device user and transmits photoplethysmogram derived data to the Hub or App by BLE for transmission to the SafetyNet Cloud server. The measurements are taken by a wire connected, adhesive, wrap-style probe applied to the finger. The Sensor contains the oximetry technology (Masimo SET pulse oximetry, K183697) for the device.

- Masimo SafetyNet Opioid App - Software application installed on a smart device that provides the graphical user interface to display live monitoring data (e.g., pulse rate (PR), pulse waveform) and alarm condition status. The App is installed on a smart mobile device and wirelessly communicates with the SafetyNet Cloud server (by Wi-Fi or Cellular data).
- Opioid Halo - Software that runs continuously to provide real-time detection of the severe OIRD risk based upon changes or patterns in oxygenation biomarker data (peripheral oxygen saturation (SpO2), pulse rate (PR), perfusion index (Pi)) found to be consistent with published understanding of physiological effects of OIRD.
- Notification Escalation Policy – Policy that is used to add levels of awareness through the notification of the device user, emergency contact, or contracted Emergency Responders. The Level 1-3 alarms are triggered on the Bedside Station and App. The Level 2 and 3 alarms also trigger text notifications to the device user entered emergency contacts and the Level 3 alarm will trigger a wellness call to the device user by an Emergency Medical Service dispatch.

Table 1: Summary of Alarm Levels

Notification Level	Alarm Trigger	Visual Alarm	Audible Alarm	Emergency Contact	Emergency Dispatch
Level 1	Early signs of unstable oxygen levels or low oxygen levels.	Yes	Yes	No	No
Level 2	Medically meaningful or very unusual signs of unstable oxygen levels or sustained low levels of oxygen.	Yes	Yes	Yes	No
Level 3	Extremely unusual signs of unstable oxygen levels or a long period of low levels of oxygen or an extreme drop in your oxygen level.	Yes	Yes	Yes	Yes

- Masimo SafetyNet Cloud - A server accessed over the internet that gathers and stores measured data communicated wirelessly from a Bedside Station. The Cloud software processes transmitted data and enforces the notification escalation policy based upon the data received.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY

The device includes previously cleared components (K183697) that are in direct contact with the skin during use. The finger probe and single-use sensor are categorized as surface contacting (intact skin) devices with prolonged contact in accordance with ISO 10993-1 referenced by the FDA guidance document, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". The components were subjected to biocompatibility testing in accordance ISO 10993-1. The following tests were conducted to assess

biocompatibility of the device for the surface, intact skin contacting components for prolonged duration:

- Cytotoxicity
- Sensitization
- Irritation

All tests passed. The results demonstrated the biocompatibility of the device.

SHELF LIFE/REPROCESSING/STERILITY

The device is provided non-sterile and is not intended to be sterilized by the device user. The Bedside Station is reusable, and the Sensor includes both reusable (Masimo Chip sensor attached to wrist that wirelessly communicates with the Bedside Station) and single-use disposable components (finger-wrap sensor that measures blood oxygen information). The labeling provides cleaning and low-level disinfection procedures for the Bedside Station and reusable Sensor components.

The Centroid O2 sensor has a shelf life of 1 year based on the adhesive used on the sensor. Shelf life was assessed by testing strength of the adhesive over time.

ELECTRICAL, THERMAL, AND MECHANICAL SAFETY, ELECTROMAGNETIC COMPATIBILITY, & WIRELESS COEXISTENCE

Electrical, thermal, & mechanical safety and electromagnetic compatibility testing has been performed and complies with the following standards for use in hospital and home healthcare settings:

- IEC 60601-1-2 4th Edition, Medical Electrical Equipment – Part 1-2: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Electromagnetic Disturbances - Requirements And Tests
- IEC 60601 1: 2005 + CORR. 1:2006 + CORR. 2:2007 + AM1:2012: Medical electrical equipment, Part 1: General requirements for basic safety and essential performance
- IEC 60601-1-11: 2010 Medical Electrical Equipment – Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in a home healthcare environment
- The Sensor was previously tested for requirements of IEC 60601-1-2:2014+AMD1:2020 and AIM 7351731:2017 - Medical Electrical Equipment and System Electromagnetic Immunity Test for Exposure to Radio Frequency Identification Readers for RFID.

Wireless co-existence testing has been done to verify that the subject device will not have degraded performance that might be associated with wireless coexistence in a shared wireless environment in the intended use environment. Testing was conducted to meet

recommendations of the FDA Guidance, “Radio-Frequency Wireless Technology in Medical Devices (2013).”

SOFTWARE & CYBERSECURITY

Software documentation including management of cybersecurity was provided in accordance with the FDA Guidance Document, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices,” (issued May 11, 2005) for a Major Level of Concern (LOC). A Major LOC is deemed appropriate as malfunction of the device software or a latent design flaw in the device software may lead to erroneous information or a delay in the delivery of appropriate medical care, which would likely result in serious injury or death.

HUMAN FACTORS TESTING

Human factors and usability risks were evaluated and acceptably mitigated in accordance with FDA Guidance, “Applying Human Factors and Usability Engineering to Optimize Medical Device Design (2016)”. The testing included lay persons as well as those who engage in illicit opioid use and was conducted to support the acceptability of the human factors and usability risks. Testing included a risk-based approach which considered the expected intended use of the device and analyzed the tasks to determine those that were device use-related. The device use-related tasks were categorized based upon risk to establish critical device use-related tasks. Formative activities were conducted in the development of the user interfaces of the device to ensure they were effective for the intended population, which includes home device users (lay operators). Knowledge Task Assessment and Simulate Use testing was conducted to determine the completion of the critical device user tasks did not result in any unacceptable human factors and usability risks. The results of the human factors and usability testing supported the acceptability of the human factors and usability risks. There were no unacceptable residual risks that required further modifications of the design or the user interface to mitigate risks to acceptable levels.

PERFORMANCE TESTING - BENCH

Non-clinical bench testing was performed on the device to provide verification of the pulse oximeter monitoring functions and general instrument functions (e.g., input/output interfaces). Additionally, bench performance testing using a pulse oximeter simulator was completed to demonstrate that the device can communicate through a wireless connection to enable communication with the Sensor.

SUMMARY OF CLINICAL INFORMATION

Clinical Performance Validation Summary

Clinical testing was performed to support the clinical benefits of the Masimo SafetyNet Opioid System. To support performance in the improved detection of opioid induced respiratory depression (OIRD), 40,322 data segments from 641 study participants (opioid

use-cases, 135 prescription home opioid (i.e., naïve, chronic), 242 hospitalized opioid, and 264 illicit opioid) using Masimo SET pulse oximetry for classification were analyzed. The results support the increased specificity in the detection of OIRD as compared to a traditional pulse oximeter with a fixed threshold alarm. See summary of the overall sensitivity and specificity below.

Table 2: Summary of the Overall Sensitivity and Specificity

Subject Type	Data Segments			Benchmark		Halo – Level 1		Halo – Level 2		Halo – Level 3	
	Used	Cases	OIRD	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Overall	40322	641	130	99.2%	80.6%	100.0%	93.9%	100.0%	97.5%	79.2%	99.5%
Naïve	3640	58	2	100.0%	87.4%	100.0%	97.8%	100.0%	99.3%	100.0%	100.0%
Chronic	44781	77	13	100.0%	80.2%	100.0%	95.7%	100.0%	98.4%	100.0%	99.6%
Hospital	319401	241	98	99.0%	79.9%	100.0%	93.2%	100.0%	97.2%	75.5%	99.5%
Illicit	264	264	17	100.0%	83.4%	100.0%	85.8%	100.0%	93.5%	82.4%	99.6%

The data from 936 cases that included the same 641 opioid users and an additional 295 sleeping non-opioid users supported the improved reduction of non-actionable alarm as compared to a fixed threshold pulse oximeter (benchmark). See summary of alarm reductions below:

Table 3: Summary of the Alarm Reductions

Subject Type	Used Subjects	Benchmark	Halo – Level 1		Halo – Level 2		Halo – Level 3	
		Alarms	Alarms	% Reduction	Alarms	% Reduction	Alarms	% Reduction
Overall	936	33415	8366	75.0%	3663	89.0%	1097	96.7%
Naïve	58	2196	217	90.1%	81	96.3%	5	99.8%
Chronic	77	4991	756	84.9%	347	93.0%	145	97.1%
Hospital	242	25928	7212	72.2%	3119	88.0%	923	96.4%
Illicit	264	141	87	38.3%	55	61.0%	15	89.4%
Sleeping Non-opioid users	295	159	94	40.9%	61	61.6%	9	94.3%

The dataset collected on 17 illicit opioid rescue cases also supported the responsiveness of the Halo alarms, despite their increased specificity. The responsiveness was measured by calculating the time from opioid injection to alarm (TFO) and time from alarm to intervention (TTI).

Table 4: Summary of the Timing Data

Subject Type	Used	Benchmark		Halo – Level 1		Halo – Level 2		Halo – Level 3	
		TFO (min.)	TTI (min.)	TFO (min.)	TTI (min.)	TFO (min.)	TTI (min.)	TFO (min.)	TTI (min.)
Illicit	17	3.14	2.69	3.42	2.40	4.60	1.22	4.80	1.06

To evaluate effect of positive SpO2 bias in detection of OIRD that could be due to dark skin pigmentation, data from 264 illicit users were analyzed by comparison of sensitivity and specificity between the user's data and modified data with a hypothesized 2% positive bias (see summary of sensitivity and specificity below). Results demonstrate no

clinically significant effect on performance due to use of Halo software and reliance on trends in data.

Table 5: Sensitivity and Specificity of Illicit users using original and modified datasets

Version	Level 1		Level 2		Level 3	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Opioid Halo on Illicit Users data	100%	85.8%	100%	93.5%	82.4%	99.6%
Opioid Halo on Illicit Users data with additional 2% SpO2 bias	100%	88.7%	100%	95.1%	82.4%	99.6%

SpO2 Performance Validation Summary

SpO2 performance validation study was conducted on Masimo Radius PPG sensors by enrolling healthy male and female volunteer subjects with varying levels of skin pigmentation, characterized by the Massey scale (1-10). Subjects with Massey 1-3 were categorized as Light, and Massey 4-10 were categorized as Dark. A total of 26 subjects were enrolled in the study and subjected to induced hypoxia to target SpO2 levels down to 70%. Data from 13 subjects categorized as Light and 9 subjects categorized as Dark were analyzed. Data from 4 subjects were excluded due to incomplete desaturation profiles. See summary of results below for subjects overall and comparison between subjects categorized as Light and Dark.

Table 6: SpO2 Performance Summary

Measurement A_{RMS} Values for Radius PPG Sensors	
SpO2 Accuracy Range (%)	A_{RMS} (%)
90-100	1.73
80-90	1.80
70-80	1.73
70-100	1.75

Table 7. SpO2 performance between Light and Dark subjects

Group	No. Subjects	Bias	MAB	Prec.	A_{RMS}	LOA	Npairs
Light	13	0.05	1.48	1.79	1.79	[-3.46 3.56]	449
Dark	9	0.03	1.34	1.74	1.75	[-3.39 3.45]	313

Pediatric Extrapolation

There are differences in respiratory physiology in pre-pubescent children as compared to older children and adults, such as differences in respiratory control and lung mechanics as well as a higher metabolic requirement of oxygen. An important difference includes oxygen carrying capacity and the physiological response to hypoxemia, which can be more pronounced in younger children. Therefore, taking these concepts into account

along with leveraging clinical data from adult study participants, this device can be effectively used in opioid users as young as 15 years of age.

LABELING

The labeling (User Manual) provides a complete listing of contraindications, warnings, and precautions to help ensure safe and effective use of the device system. There is also a summary of the testing, both clinical and non-clinical, to support the performance of the device system in the anticipated device use populations and environments to help device users understand expected performance.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a monitor for opioid induced impairment of oxygenation and the measures necessary to mitigate the risks

Identified Risks to Health	Mitigation Measures
False negative leading to delayed treatment	Clinical performance data Non-clinical performance testing Software validation, verification, and hazard analysis Labeling
False positive based on other medical conditions or poor algorithm performance leading to unnecessary early intervention or response	Clinical performance data Non-clinical performance testing Software validation, verification, and hazard analysis Labeling
Software malfunction that causes an algorithm error	Software validation, verification, and hazard analysis
Delayed or incorrect treatment due to use-related error or overreliance on device	Usability assessment Labeling
Adverse tissue reaction	Biocompatibility evaluation
Sensor induced injury	Electrical, thermal, and mechanical safety testing
Failure to function as intended due to electromagnetic and wireless radio frequency interference	Electromagnetic compatibility testing Wireless coexistence testing

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the monitor for opioid induced impairment of oxygenation is subject to the following special controls:

- (1) Clinical performance data under anticipated conditions of use must demonstrate that the device performs as intended and include the following:

- (i) Comparison to a clinically relevant reference method to demonstrate and support the accuracy and level of sensitivity and specificity for detection of opioid induced impairment of oxygenation;
 - (ii) Demonstration of the consistency of the output and representativeness of the range of data sources and data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment;
 - (iii) Performance reported in clinically significant and distinct subpopulations and intended use environments;
 - (iv) For devices using algorithms based on machine learning, the clinical validation must be completed using a dataset that is separate from the training dataset; and
 - (v) Simulated use testing of hardware and sensors to characterize accuracy and precision across the intended use population
- (2) Software description, verification, and validation based on comprehensive hazard analysis must be performed. Software documentation must include:
- (i) Full characterization of technical parameters of the software, including any algorithm(s);
 - (ii) Specification of acceptable incoming sensor data quality control measures; and
 - (iii) Justification for the validity of the algorithm(s) (e.g., clinical relevance/importance of decision threshold).
- (3) Non-clinical performance data must demonstrate that the device performs as intended under anticipated conditions of use. Testing must include:
- (i) Performance testing of sensor hardware to characterize sensor accuracy and precision; and
 - (ii) Compatibility testing of sensors with other hardware and software components of the device.
- (4) Usability assessment must be provided to demonstrate that intended device users can safely and correctly use the device.
- (5) All components of the device that contact the skin must be demonstrated to be biocompatible.
- (6) Performance testing must demonstrate the electromagnetic compatibility (EMC), wireless coexistence, electrical safety, thermal safety, and mechanical safety of any hardware components and sensors of the device.
- (7) Labeling must include the following:
- (i) A summary of the clinical validation data, including relevant characteristics of the included subpopulations and use environments in the clinical study, and performance metrics, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each of the subpopulations, use environments, and opioid types;

- (ii) Principles of sensor operation, including warnings for how to avoid interfering with sensor readings;
- (iii) Information for preventing an overdose, recognizing signs of an overdose, and treating an overdose;
- (iv) Warnings identifying that the device is not designed to differentiate between the target condition (e.g., opioid-induced respiratory depression) and other conditions that may cause a false reading (e.g., obstructive sleep apnea);
- (v) Warnings against overreliance on the device; and
- (vi) A warning regarding the need for supervised use with awareness of effective countermeasures (e.g., naloxone) in case of an overdose.

BENEFIT-RISK DETERMINATION

The risks of the device include frequent unnecessary interventions or delayed treatment due to inaccurate detection of opioid induced impaired oxygenation or failure of communication between device components. Unnecessary interventions (“false positive”) may result in desensitization (i.e., alarm fatigue) of device users and caregivers and overburdening of EMS. Delayed treatment (“false negative”) may result in death. Additional risks include overdose through overreliance on the device and injury to the device user at the sensor application site.

The benefits of the device include reduction in non-actionable alarms compared to monitoring with traditional pulse oximetry, more focused and improved detection of oxygen desaturation associated with opioid induced respiratory depression, and quicker detection and treatment of an opioid overdose. During the clinical validation study, data collected from prescription home (i.e., naïve, chronic), hospitalized, and illicit opioid users using Masimo SET pulse oximetry was analyzed for improved specificity and reduction in non-actionable alarms. The analysis found equivalent sensitivity as a system with a higher specificity in the detection of OIRD as compared to a pulse oximeter with a fixed threshold alarm. The analysis of the data also found a significant reduction in non-actionable alarms (i.e., 76% for Level 1, 89% for Level 2, and 96.7% for Level 3) from a standard fixed threshold alarm pulse oximeter. Analysis of study data also found an improved PPV with comparable NPV as compared to the benchmark (pulse oximeter) for all alarms levels and opioid user groups. The PPV values were higher for the naïve and illicit user groups, where opioid use may be more directly related to the reason for the instability in their biometric data markers. Although the PPV for the hospital and chronic opioid users were significantly higher than the benchmark, they were lower than those for the naïve and illicit opioid user groups. This is likely due to the presence of other health factors that can cause instability in the biometric data markers.

Since end-tidal CO₂ monitoring and respiratory rate along with SpO₂ thresholds below 90% were not included in the clinical studies, there are remaining uncertainties on level of evidence available to develop a reference standard that can serve as ground truth to denote severe OIRD, though critical data were available to lead to development of a sufficiently rigorous ground truth comparator. Furthermore, for in-hospital patients who may be experiencing other physiologic perturbations not related to OIRD, it is uncertain what other data was available for the clinical experts to lay ground truth of an OIRD event. Finally, the uncertainty related to the benefit of the Masimo SafetyNet Opioid system is associated mainly with the device user’s willingness to

adhere to the use of the device and the responsiveness of those who are notified of an alarmable condition. The device user may also misuse the device by increasing their opioid dose resulting in an overdose, a concern that labeling mitigations are targeted to address.

Patient Perspectives

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

Benefit/Risk Conclusion

The risks of frequent non-actionable alarms and delayed detection of overdose are mitigated based on the performance of the Halo software and notification escalation policy. Though the sensitivity of Level 3 alerts (to alert for a wellness call/EMS dispatch) was lower than for the comparator (SpO2 alerts set at <90%) for illicit and hospital device users, device performance for Level 1 and 2 alerts (100% sensitivity) mitigates the lower performance. Importantly, there are no available alternatives to monitor for OIRD, especially for the out-of-hospital populations. For in-hospital use, the device will add specificity to the standard of care (SpO2 set to alert <90%). Based upon these supporting performance data, the benefit-risk profile of the Masimo SafetyNet was found to be favorable, considering the opportunity to detect a life-threatening condition and provide alarms and communications targeted at lifesaving measures. While the device is not without risks, the inherent risks associated with device operation and performance are further mitigated through the special controls found above. The benefit risk profile also takes into account the significance of the ongoing opioid epidemic and the increasing numbers of overdose related deaths.

In conclusion, the probable benefits outweigh the probable risks for the Masimo SafetyNet Opioid 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 Masimo SafetyNet Opioid System is granted and the device is classified as follows:

Product Code: QVT

Device Type: Monitor for opioid induced impairment of oxygenation

Regulation Number: 21 CFR 868.2250

Class: II